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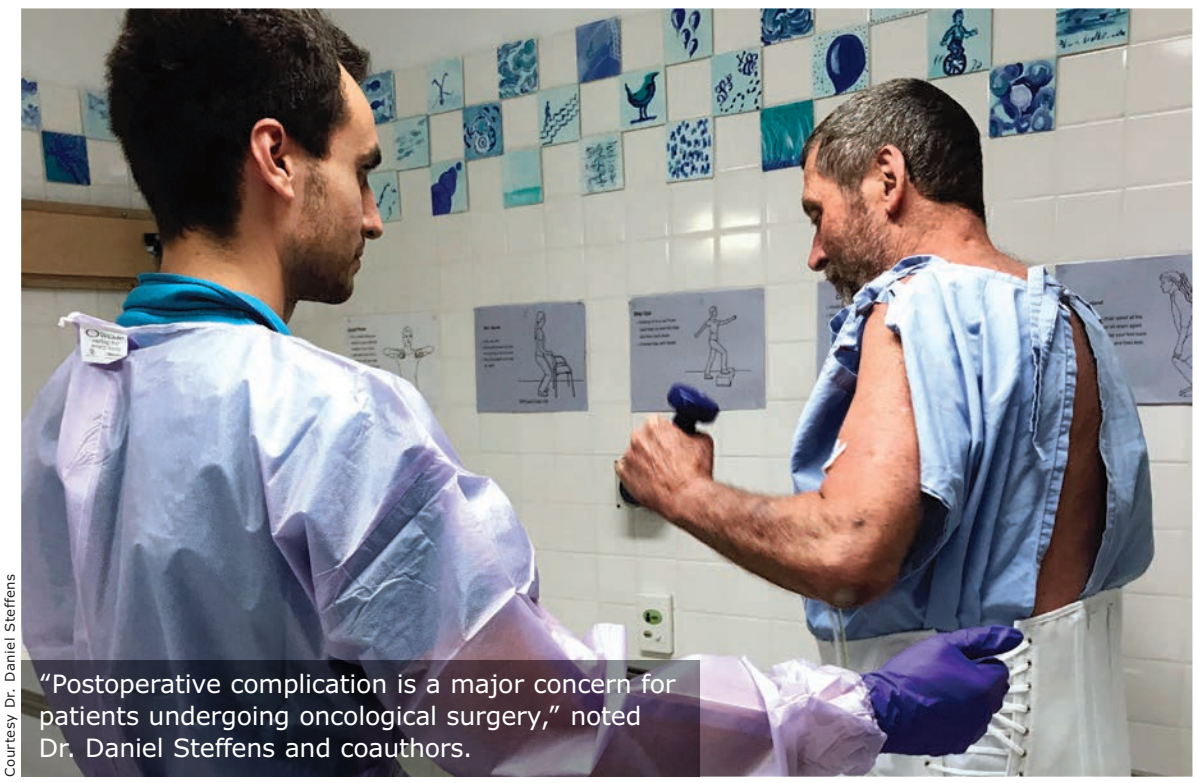
CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Courtesy Dr. Daniel Steffens

"Postoperative complication is a major concern for patients undergoing oncological surgery," noted Dr. Daniel Steffens and coauthors.

Preoperative exercise cuts postop lung resection complications

BY BIANCA NOGRADY
Frontline Medical News

Patients undergoing surgery for lung cancer may benefit from a program of preoperative exercise, with a systematic review suggesting it reduces postoperative complications and duration of hospital stay.

The review and meta-analysis, published in the February British Journal of Sports Medicine, looked at the impact of preoperative exercise in patients undergoing surgery for a range of cancers.

Their review of 13 interventional trials, involving 806 patients and six tumor types, found the postoperative benefits of exercise were evident only in patients undergoing lung resection.

Data from five randomized controlled trials and one quasirandomized trial in lung cancer patients showed a significant 48% reduction in postoperative complications, and a significant mean reduction of 2.86 days in hospital stay among patients undergoing lung resection, compared with controls.

"Postoperative complication is a major concern for patients undergoing oncological surgery," wrote Daniel Steffens, PhD, from the Surgical Outcomes Research Centre at the Royal Prince Alfred Hospital, Sydney, and his coauthors. They suggested the benefits for patients undergoing lung resection were significant

CANCER SURGERY PATIENTS HELPED // *continued on page 5*

OSA may provide cardioprotection

Cardiac troponin-I levels lower in sleep apnea patients

BY MADHU RAJARAMAN
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ The presence of obstructive sleep apnea (OSA) may have a protective effect in patients with acute coronary syndromes, according to researchers.

In a study of 127 patients presenting with acute coronary syndromes (ACS), median peak cardiac troponin-I (cTn-I) values were significantly higher in patients without obstructive sleep apnea, compared with OSA patients (10.7; interquartile range: 1.78-40.1, vs. 3.79; IQR: 0.37-24.3, respectively; $P = .04$). The findings were published Feb. 5 in the journal *CHEST*®.

The study comprised 89 OSA patients and 38 non-OSA patients who were admitted to a hospital for acute coronary syndromes. The OSA group had a median apnea-hypopnea index (AHI) of 32, while the non-OSA group had a median AHI of 4.8. There was no significant difference between the two groups in gender, age, or cardiovascular risk factors such as hypertension, diabetes mellitus, body mass index, dyslip-

PEAK CTN-I LEVELS LOWER IN OSA // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Turning Up the Heat on ICU Burnout

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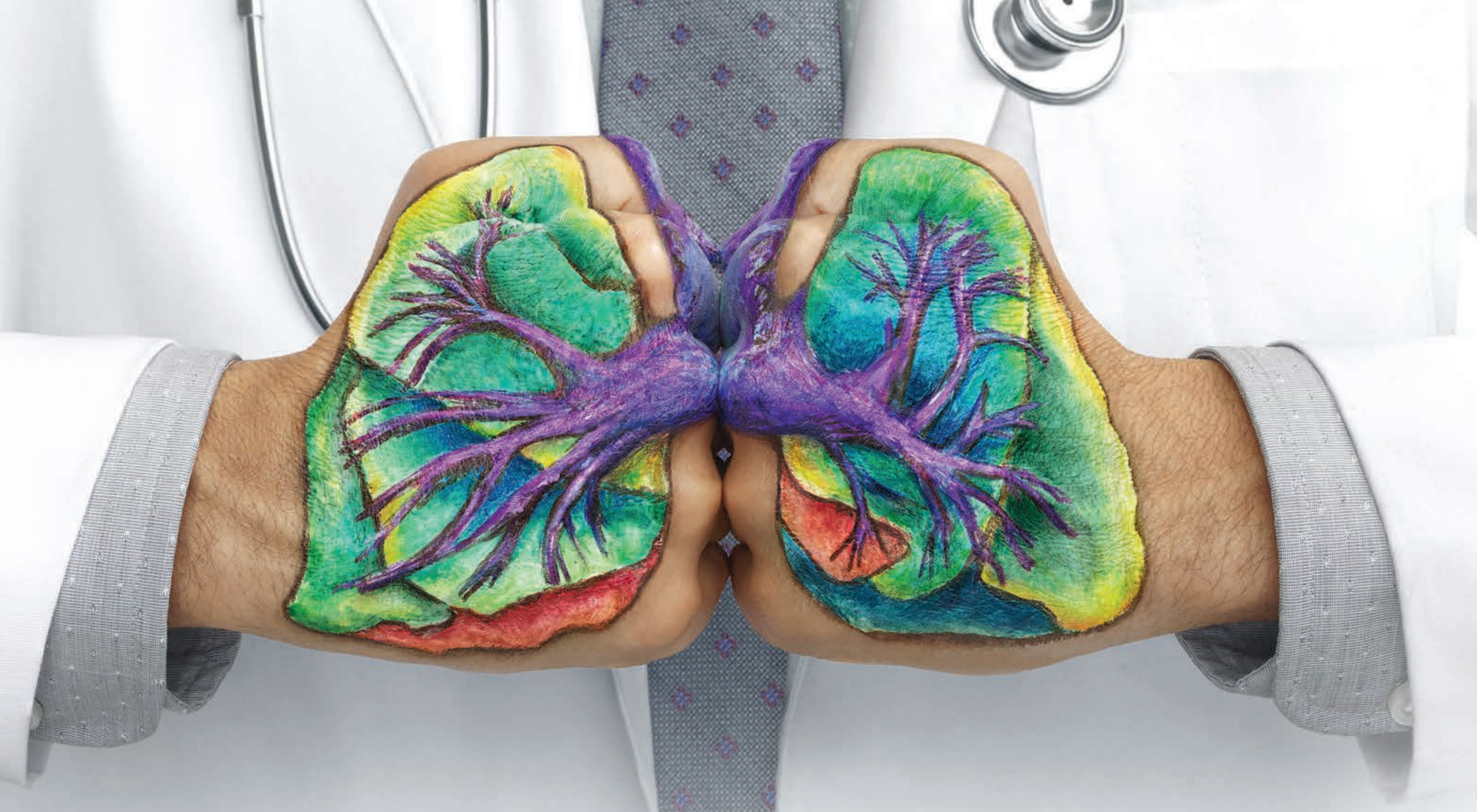

Indication

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

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

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

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

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

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

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

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

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

Genentech

A Member of the Roche Group

WE WON'T BACK DOWN FROM IPF

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

STUDIED IN A RANGE OF PATIENTS

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

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

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

COMMITTED TO PATIENTS

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

WORLDWIDE PATIENT EXPERIENCE

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

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

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

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

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

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

References: 1. Data on file. Genentech, Inc. 2016. **2.** Esbriet Prescribing Information. Genentech, Inc. January 2017. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083–2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011; 377(9779):1760–1769.

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

IPF=idiopathic pulmonary fibrosis.

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

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[2]

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

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[2]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

Fluarix Quadrivalent effective in very young

BY IAN LACY
Frontline Medical News

Fluarix Quadrivalent was highly effective against moderate and severe flu strains in very young children, in a phase 3 observer-blinded randomized trial of 12,018 children, presented at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

"Fluarix Quadrivalent, at the 0.5-mL dose in young children 6 to 35 months of age, demonstrated efficacy of 63.2% against moderate to severe influenza and 49.8% against any severity influenza disease," said Leonard Friedland, MD, director of scientific affairs and public health, Vaccines North America, GlaxoSmithKline.

ilacy@frontlinemedcom.com

SOURCE: D-QIV-004.

Cancer surgery patients helped

// continued from page 1

enough that exercise before surgery should be considered as standard preoperative care.

"Such findings may also [have impacts] on health care costs and on patients' quality of life, and consequently, have important implications for patients, health care professionals and policy makers."

The exercise regimens in the lung cancer studies mostly involved aerobic exercise, such as walking, and breathing exercises to train respiratory muscles, as well as use of an exercise bicycle. The exercises were undertaken in the 1-2 weeks before surgery, with a frequency ranging from three times a week to three times a day.

The authors noted that trials involving a higher frequency of exercise showed a larger effect size, which suggested there was a dose-response relationship.

There was little evidence of benefit in other tumor types. Two studies examined the benefits of preoperative pelvic floor muscle exercises in men undergoing radical prostatectomy and found significant benefits in quality of life, assessed using the International Continence Society Male Short form. However, the authors pointed out that the quality of evidence was very low.

One study investigated the effects of preoperative mouth-opening exercise training in patients undergoing surgery for oral cancer and found enhanced postoperative quality of life in these patients, but the researchers did not report estimates.

These findings may also have impacts "on health-care costs and on patients' quality of life, and consequently, have important implications for patients, health-care professionals, and policy makers," noted Dr. Daniel Steffens and colleagues, in their paper.

For patients undergoing surgery for colon cancer, colorectal liver metastases, and esophageal cancer, there was no benefit of exercise either in postoperative complications or duration of hospital stay. In all these studies, the authors rated the quality of evidence as "very low."

"Despite the evidence suggesting that exercise improves physical and mental health in patients with cancer, there are only a limited number of trials investigating the effect of preoperative exercise on patients' quality of life," the authors wrote. "Therefore, the effect of preoperative exercise on quality of life at short-term and long-term postoperation should be explored in future trials."

No conflicts of interest were declared.

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SOURCE: Steffens D et al. Br J Sports Med. 2018 Feb 1. doi: 10.1136/bjsports-2017-098032.

House cleaning linked to lung function decline

BY BIANCA NOGRADY
Frontline Medical News

House cleaning is bad for women's lung health, according to a study that has found accelerated decline in lung function among women regularly engaged in cleaning activities.

The longitudinal population-based cohort study, published online Feb. 16 in the American Journal of Respiratory and Critical Care Medicine, looked at the lung health of 6,230 people who were followed for more than 20 years as part of the European Community Respiratory Health Survey.

Analysis based on questionnaires about cleaning practices revealed that women who were responsible for cleaning at home or who worked as professional cleaners showed significantly greater declines in maximum forced vital capacity (FVC) and maximum forced expiratory volume in 1 second (FEV_1), compared with women who said they did not regularly clean.

Female occupational cleaners showed a mean FEV_1 decline of 22.4 mL/year, women who cleaned regularly at home showed a mean decline of 22.1 mL/year, while those who reported no cleaning activities had an 18.5 mL/year decline in FEV_1. For FVC, declines were 15.9 mL/year, 13.1 mL/year, and 8.8 mL/year, respectively. By comparison, the decline in FEV_1 among smokers who smoked at a rate of more than 20 pack-years was 27.2 mL/year, and their decline in FVC was 20.7 mL/year.

"FVC is an outcome of particular interest as survival in asymptomatic adults without a chronic respiratory diagnosis or persistent respiratory symptoms has been shown to be associated with FVC rather than airway obstruction as defined by the lower than normal FEV_1/FVC ratio," wrote Øistein Svanes, a PhD candidate in the department of clinical science at the University of Bergen (Norway) and his coauthors.

However, there was no association between cleaning practices in men – either professional or domestic – and accelerated lung function decline. The authors suggested that the exposures experienced by men who worked as cleaners may have been different from the exposures experienced by women. They also noted that the small numbers of male cleaners meant the study wasn't powered to pick up greater declines in lung function.

The study also showed a significant association between use of cleaning products and decline in lung function. Women who used sprays or other cleaning agents at least once a week showed significantly greater declines in FEV_1 and FVC, compared with women who didn't use cleaning products. Again, this effect was not significant in men.

"One possible mechanism for the accelerated decline in cleaners is the repetitive exposure to low-grade irritative cleaning agents over time, thereby causing persistent changes in the airways," the authors wrote. "Repeated exposure could lead to remodelling of the airways, thereby over time causing an accelerated decline in FVC and FEV_1."

The analysis found no significant increases in the incidence of chronic airway obstruction among regular cleaners, nor among those who used cleaning products. The authors noted that, while previous studies had suggested an increase in chronic obstructive pulmonary disease among occupational cleaners, their study reported relatively few cases of COPD.

While the prevalence of asthma was slightly higher in the two groups of women exposed to regular cleaning (12.3% and 13.7%, versus 9.6%), adjustment for asthma in the analysis did not change the associations. This suggests that the declines in lung function seen in regular cleaners were not mediated by cleaning-related asthma, the researchers noted.

They also noted that the women who reported not engaging in any cleaning may represent a particular socioeconomic group, but adjustment for socioeconomic status did not alter the associations.

The European Community Respiratory Health Survey is supported by the European Union, the European Commission, and the Medical Research Council. No conflicts of interest were reported.

chestphysiciannews@chestnet.org

SOURCE: Svanes Ø et al. Am J Respir Crit Care Med. 2018 Feb 16. doi: 10.1164/rccm.201706-1311OC.

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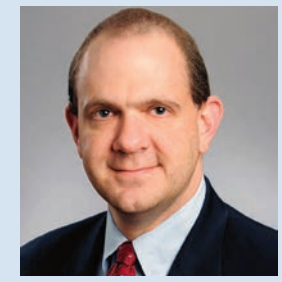

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Peak cTn-I levels lower in OSA // *continued from page 1*

idemia, and smoking.

The cohort was part of the Continuous Positive Airway Pressure (CPAP) in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea (ISAACC) study, a prior randomized, controlled trial that evaluated the effect of CPAP treatment on new cardiovascular events in patients with an episode of ACS and OSA, reported Alicia Sánchez-de-la-Torre, PhD, of the respiratory department at Hospital Universitari Arnau de Vilanova and Santa Maria in Catalonia, Spain, and her coauthors.

These findings "suggest that patients with higher AHI are significantly more likely to have low cTn-I levels than patients without evidence of OSA, which could imply that patients with elevated AHI, particularly those with severe OSA, may experience less severe myocardial injury," the authors noted.

Respiratory polygraphy was performed in the first 24-72 hours after hospital admission, and patients with an AHI of at least 15 events per hour were considered to have OSA. Those with an AHI less than 15 events per hour were included in the non-OSA group.

The OSA patients were randomized to conservative or CPAP treatment. An obstructive apnea "episode" was defined as a complete cessation of airflow for 10 seconds or longer, and an episode of hypopnea was defined as a reduction in airflow for at least 10 seconds associated with a greater than 4% decrease in arterial oxygen saturation.

Blood samples were collected from patients every 6 hours until two consecutive cTn-I measurements showed a decrease, with the highest measurement considered the peak cTn-I value.

Peak cTn-I value was significantly higher in non-OSA patients than in OSA patients. Median infarct size, measured by calculating the area under the cTn-I curve, was significantly different between the two groups (451 for non-OSA patients vs. 143 in OSA patients; $P = .049$), wrote Dr. Sánchez-de-la-Torre and her colleagues.

As cTn-I levels decreased, there was a trend toward increased OSA severity ($P = .058$). In the multivariable linear regression model used to assess OSA severity, patients with severe OSA had 61% lower cTn-I levels than non-OSA patients, the authors noted.

"The effects of chronic hypoxia in individual organ systems are not well understood. While chronic sustained hypoxia as seen with COPD may lead to pulmonary hypertension, chronic intermittent hypoxia (CIH) as seen predominantly in sleep apnea has been attributed to causing widespread effects ranging from systemic hypertension to metabolic dysfunction and systemic inflammation," noted Krishna Sundar, MD, FCCP. "Despite these associations, an increased risk of major cardiovascular events from untreated OSA is yet to be definitively established."

"The effects of chronic hypoxia in individual organ systems are not well understood," said Dr. Krishna Sundar.

In this article, a protective effect from OSA on myocardial ischemic events is demonstrated in a group of 127 consecutively admitted patients with acute coronary syndrome (ACS). While it is interesting that a high proportion of those admitted for ACS had OSA, there were no significant differences in the age, sex, BMI, usage of antihypertensive or antiplatelet agents, presence of hypertension, DM, dyslipidemia or smoking status between those with and without OSA. "OSA appeared to confer a protective effect on the size of myocardial injury with those having higher AHI values demonstrating lower peak cardiac troponin values," said Dr. Sundar, who is an associate clinical professor of pulmonary, critical care and sleep medicine at the University of Utah.

"An effect of age (mean age in this study being 64 years) and BMI (mean being 27) on the occurrence of preconditioning effects of OSA is not excluded given deleterious effects of untreated OSA on infarct size in other studies on obese or younger patients with ACS. Further understanding of molecular effects of chronic hypoxia exposure (high altitude, chronic lung disease, OSA) is required before the complex and often contradictory effects of chronic hypoxia can be affirmed as being protective or deleterious," added Dr. Sundar, who is also medical director of the Sleep-Wake Center at the University of Utah and a member of *CHEST Physician*'s editorial advisory board.

According to the study's authors, their findings "suggest that patients with higher AHI are significantly more likely to have low cTn-I levels than patients without evidence of OSA, which could imply that patients with elevated AHI, particularly those with severe OSA, may experience less severe myocardial injury."

Limitations of the study include exclusion of patients with severe ACS, exclusion of sleepy subjects, and assessment of myocardial injury using cTn-I as a biomarker, without further data to determine infarct size.

"The possible role of OSA in cardioprotection should be explored in future studies," the authors concluded.

The authors disclosed relationships with ResMed, Spanish Ministry of Health, Spanish Respiratory Society, Catalonian Cardiology Society, and ALLER. No other disclosures were reported.

chestphysiciannews@chestnet.org

SOURCE: Chest. 2018 Feb 5;153[2]:329-38. doi: 10.1016/j.chest.2017.06.046.

Results demonstrate 'paradigm shift' in OSA research

Although this study cannot definitively establish a clinically meaningful protective effect, it does provide important "preliminary evidence supporting the concept of OSA-induced cardioprotection" and challenges existing research, according to an editorial by Doron Aronson, MD, of the department of cardiology at Rambam Medical Center, Haifa, Israel, and coauthors (CHEST. 2018 Feb 153[2]:295-7. doi: 10.1016/j.chest.2017.07.036).

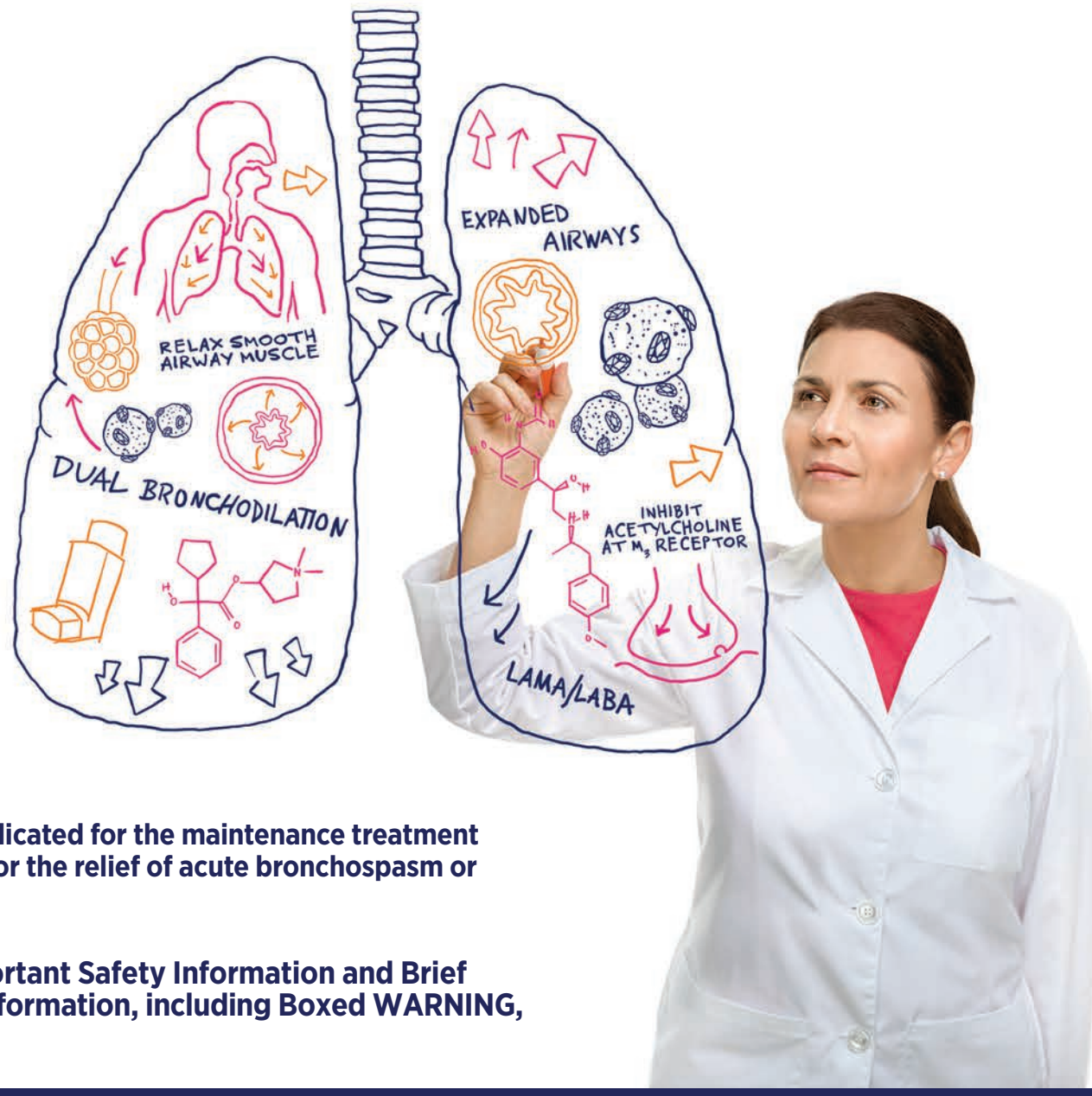
The results should be interpreted with caution, especially since accurate assessment of infarct size poses a challenge, they wrote.

"Myocardial infarct size is highly variable and is influenced by the duration of coronary occlusion, ST-segment elevation or non–ST elevation myocardial infarction, infarct location, residual antegrade infarct-related artery flow, collateral flow, the presence of non–culprit vessel coronary artery disease and myocardial metabolic demand," they wrote. "Without accounting for these variables in a small study, results may be affected by variation in the characteristics of the patients."

Though further study is needed, the findings may have "profound clinical implications regarding our therapeutic approach to patients with sleep apnea" if confirmed, the authors concluded.

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
- 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

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

2017 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 $AUC_{0\text{-}24}$, 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.

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.

‡**PINNACLE 1 & 2 Pivotal Trials:** Two 24-week efficacy and safety studies were conducted in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI 18 mcg/9.6 mcg BID compared with 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 also included an open-label active control.[1] Statistically significant results were also seen in Trial 2.[1,2] Secondary endpoints included change from baseline in peak FEV_1 at Week 24 for BEVESPI BID compared with 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 treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,2]

§**Separate Phase IIIb Trials (Study A & B):** Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Study B also included an open-label active control.[3] Inclusion criteria were consistent with the two 24-week pivotal trials.[1,3] Adverse events were numerically similar across treatment arms.[3] Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: 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 IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 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, 3270300, AZLP.

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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
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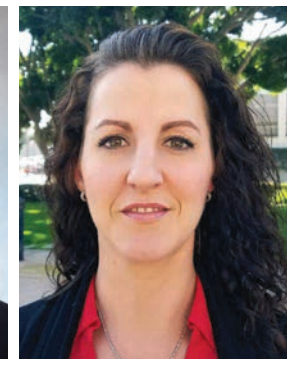
OSA Endotypes and Phenotypes: Toward Personalized OSA Care

BY ROBERT L. OWENS, MD; NAOMI DEACON, PHD; AND ATUL MALHOTRA, MD, FCCP



Dr. Owens is Assistant Clinical Professor of Medicine; Dr. Deacon is a Post-Doctoral Research Scholar; and Dr. Malhotra is Kenneth M. Moser Professor of Medicine and Chief, Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego.

Obstructive sleep apnea (OSA) contributes a major health burden to society due to its high prevalence and substantial neurocognitive and cardiovascular consequences. Estimates suggest that at least 10% of adults in North America are afflicted with OSA, making it probably the most common respiratory disease in the developed world (Peppard et al. *Am J Epidemiol.* 2013;177[9]:1006). Nasal CPAP is a highly efficacious therapy that has been shown to improve neurocognitive and cardiovascular outcomes. However, CPAP is not always well tolerated. Alternative therapies, such as oral appliances and upper airway surgery, have highly variable efficacy, and evidence of important clinical benefits are uncertain. Therefore, efforts are ongoing to determine optimal alternative strategies for therapy.

In order to treat any condition optimally, one needs to be able to predict who is at highest risk of developing the condition, then to assess the consequences if left untreated, and finally to be able to predict response to various treatment options. Currently, the OSA field is still in its early stages of our understanding. Clinically, we are often faced with patients who have varying presentations and manifestations, but, for reasons that are unclear. For instance, two individuals with the same body mass index may have very different clinical manifestations, one with severe OSA and one without any OSA. Similarly, two individuals with an apnea hypopnea index of 40 events per hour (ie, severe OSA) may have very different symptoms attributable to OSA, eg, one could be asymptomatic and the other could be debilitated from sleepiness. We and others have been making efforts to determine why these phenomenon occur. At present, the techniques to define mechanisms underlying OSA are labor-intensive, requiring one or two overnight experiments to gather meaningful data. Although we are gathering new insights based on these techniques, efforts are ongoing to simplify these approaches and to make assessment of pathophysiologic characteristics more accessible to the clinician (Orr et al. *Am J Respir Crit Care Med.* 2017 Nov 30. doi: 10.1164/rccm.201707-1357LE. [Epub ahead of print]).

We ultimately believe that a thorough analysis of a sleep recording combined with demographic data and other readily available clinical data (perhaps plasma biomarkers) may yield sufficient information for us to know why OSA is occurring and what interventions might be helpful for an individual patient. Currently, our use of the polysomnogram to derive only an apnea hypopnea index does not take full advantage of the available data. An apnea hypopnea index can be readily obtained from home sleep testing and does not truly provide much insight into why a given individual has OSA, what symptoms are attributable to OSA, and what interventions might be considered for the afflicted individual. By analogy, if the only useful data derived from an ECG were a heart rate, the test would rapidly become obsolete. Along these lines, if the only role for the sleep clinician was to prescribe CPAP to everyone with an AHI greater than 5/h, there would be little need or interest in specialized training. In contrast, we suggest that rich insights regarding pathophysiology and mechanisms should be gathered and may influence clinical management of patients afflicted with OSA. Thus, we encourage more thorough analyses of available data to maximize information gleaned and, ultimately, to optimize clinical outcomes.

Recent studies suggest that sleep apnea occurs for varying reasons, a concept that is now thought to be clinically important (Jordan et al. *Lancet.* 2014;383[9918]:736). We draw a crucial distinction between endotypes (mechanisms underlying disease) and phenotypes (clinical expression of disease). Important endotypes include compromised upper airway anatomy, dysfunction in pharyngeal dilator muscles, unstable ventilatory control (high loop gain), and low arousal threshold (wake up easily), among others. Important phenotypes of sleep apnea are emerging and still evolving to include minimally symptomatic OSA, OSA with daytime sleepiness, and OSA with major cardiometabolic risk, among others. Several important concepts have emerged regarding different OSA endotypes and phenotypes:

1 The mechanism underlying OSA may predict potential response to therapeutic interventions. For instance, the endotype of OSA with unstable ventilatory control (high loop gain) may respond to agents such as oxygen and acetazolamide, which serve to stabilize control of breathing. In patients with anatomical compromise at the level of the velopharynx, uvulopalatopharyngoplasty may be an effective intervention. For patients with multiple pathophysiologic abnormalities, combination therapy may be required to alleviate OSA (Edwards et al. *Sleep.* 2016;9[11]:1973).

2 Given that OSA has many underlying etiologies, efforts are underway to determine whether individuals with different risk factors for OSA develop their disease based on varying mechanisms. As an example, people with posttraumatic stress disorder (PTSD) may be at increased risk of OSA perhaps on the basis of a low threshold for arousal (Orr et al. *JCSM.* 2017, 13[1]: 57-63). Another example would be patients with neuromuscular disease who may be at risk of OSA primarily based on impaired pharyngeal dilator muscle function.

3 A new concept is emerging whereby endotypes of OSA may actually predict differing OSA phenotypes. In theory, loop gain-driven OSA may have different consequences from OSA driven by compromise of pharyngeal anatomy. To this point, data suggest that OSA in the elderly may not have as many consequences as OSA in younger people matched on severity of illness. OSA in the elderly has lower loop gain than OSA in younger people and is associated with less negative intrathoracic pressure at the time of arousal as compared with younger individuals with OSA (Kobayashi et al. *Chest.* 2010; 137[6]:1310). As such, the endotype of OSA in the elderly may explain why the clinical consequences are fewer than in the younger OSA counterparts.

4 The mechanism underlying OSA may be important in determining response to clinical interventions, such as nasal CPAP. Patients with a low arousal threshold may be prone to insomnia when placed on CPAP and could theoretically be poorly tolerant of therapy based on disrupted sleep architecture. Such patients may benefit from non-myorelaxant hypnotic therapy to consolidate sleep and improve CPAP adherence. In addition, patients with high loop gain (unstable ventilatory control) may be prone to develop central apneas when placed on CPAP therapy (Stanchina et al. *Ann Am Thorac Soc.* 2015;12[9]:1351). These patients may benefit from newer technologies, eg, auto or adaptive servo ventilation - ASV. High loop gain has also been shown to predict failure of upper airway surgery as a treatment for OSA by several groups (Li et al. *JCSM.* 2017;13[9]:1029). Such patients should, perhaps, undergo nonsurgical therapies for OSA.

We emphasize that some of the points being made are somewhat speculative and, thus, encourage further basic and clinical research to test our assumptions. Robust, multicenter clinical trials assessing hard outcomes will ultimately be required to change the current standard of care. Nonetheless, we believe that a more thorough understanding of OSA pathogenesis can help guide clinical care today and will be critical to the optimal treatment of afflicted individuals tomorrow.

CPAP adherence linked to reduced readmissions

BY ELI ZIMMERMAN
Frontline Medical News

Hospitalized patients with obstructive sleep apnea (OSA) who were nonadherent to continuous positive airway pressure (CPAP) treatment were more than three times as likely to be readmitted for complications, according to a study.

Since preventable causes of readmission like congestive heart failure, obstructive lung disease, and diabetes are connected to OSA, boosting adherence rates to sleep apnea treatment could be an effective way to mitigate these risks.

"Nonadherence to CPAP has been associated with increased chronic obstructive pulmonary disease (COPD) exacerbations, worsened insulin resistance, psychiatric illnesses, and

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Cost-effectiveness of CPAP adherence

The comorbidities associated with obstructive sleep apnea (OSA), such as heart failure, coronary artery disease, diabetes, and stroke, can be detrimental to patients' care and commonly lead to hospitalization. Not only are these diseases interfering with successful treatment, but financial penalties linked to 30-day readmissions have economic implications for hospitals as well. Increasing CPAP adherence, therefore, may be a low-cost tool to improve hospital outcomes. Dr. Truong and her colleagues find compelling data showing the association of CPAP adherence and reduced 30-day readmissions. However, more work is needed before we can fully back the idea that CPAP adherence will prevent readmissions. While many studies have shown associations between OSA and cardiovascular events, there are no large, randomized trials that show the cardiovascular benefit of CPAP. The current theory is that patients who are adherent to CPAP are more likely to be healthier individuals, which makes them less likely to exhibit the comorbidities that would cause readmissions. A large randomized trial is the next logical step, and with OSA costs estimated at $2,000 annually per patient, it is a step worth pursuing.

Lucas M. Donovan, MD, is a pulmonologist at the University of Washington, Seattle. Martha E. Billings, MD, is an assistant professor in the division of pulmonary and critical care medicine at the University of Washington, Seattle. They reported no conflicts of interest.

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lower urinary tract symptoms," wrote Kimberly K. Truong, MD, MPH, an internist at the University of California, Irvine, and her fellow investigators in a study published in the Journal of Clinical Sleep Medicine. That OSA is not only common and linked with other help problems but also can be treated readily with CPAP "makes it an important clinical and public health disease to target."

Investigators gathered data for 345 hospitalized

patients with OSA who were admitted to the VA Long Beach (Calif.) Healthcare System between January 2007 and December 2015.

Both the adherent and nonadherent groups were mostly white males. The 183 adherent patients were, on average, slightly older than the patients in the nonadherent group (66.3 vs. 62.3 years), while the nonadherent group had a larger proportion of African Americans (19.1%) than did the adherent group (10.4%).

"Nonadherence to CPAP has been associated with increased chronic obstructive pulmonary disease (COPD) exacerbations, worsened insulin resistance, psychiatric illnesses, and lower urinary tract symptoms," wrote Kimberly K. Truong, MD, MPH, and colleagues.

In an analysis of both groups, 28% of nonadherent patients were readmitted within 30 days of discharge, compared with 10.2% of those in the adherent group (*P* less than .001). Readmission rates were significantly higher for nonadherent patients brought in for all causes (adjusted odds ratio, 3.52; *P* less than .001), as were their rates of cardiovascular-related readmission (AOR, 2.31; *P* = .02).

The cardiovascular-related readmissions were most often caused by atrial fibrillation (29%), myocardial ischemia (22.5%), and congestive heart failure (19.3%) in the group who were not using CPAP. In this same group, urologic problems (10.7%), infections (8.0%), and psychiatric issues (5.3%) were the most common causes for hospital readmissions.

"Those with OSA and COPD are considered to have overlap syndrome and, without CPAP therapy, are at higher risk for COPD exacerbation requiring hospitalization, pulmonary hypertension, and mortality," according to the investigators.

Investigators were surprised to find that the rate of pulmonary-related readmissions was not higher among nonadherent patients, considering the shared characteristics of OSA and COPD.

While nonadherent patients had an adjusted rate of pulmonary-related readmissions of 3.66, the difference between nonadherent and adherent patients was not significant.

"Those with OSA and COPD are considered to have overlap syndrome and, without CPAP therapy, are at higher risk for COPD exacerbation requiring hospitalization, pulmonary hypertension, and mortality," according to Dr. Truong and her colleagues. "However, the number of patients with pulmonary readmissions was very small, and analysis did not reach statistical or clinical significance."

Given the single-center nature of the study, these findings have limited generalizability. The study may also have been underpowered to uncover certain differences between the two groups because of the small population size.

The investigators reported no relevant financial disclosures.

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SOURCE: K. Truong et al. J Clin Sleep Med. 2018;14(2):183-9.

OSA patients report sleeping better with dronabinol

BY BIANCA NOGRADY
Frontline Medical News

Obstructive sleep apnea patients reported sleeping better and experienced less apnea and hypopnea events after taking dronabinol, in a new study.

A paper published in the January edition of Sleep presents data from a phase 2, blinded, randomized controlled trial of the nonselective cannabinoid 1 and cannabinoid 2 receptor agonist, dronabinol, in 73 adults with moderate or severe obstructive sleep apnea (OSA). No approved drug treatments for OSA exist, and this study provides results "from the largest and longest randomized controlled trial to date of any putative drug treatment for OSA," the researchers wrote.

Patients were randomized to 2.5 mg dronabinol or 10 mg dronabinol daily for up to 6 weeks, or placebo. At the end of treatment, researchers saw significant increases in the apnea-hypopnea index 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 apnea-hypopnea index decreases were similar between the two dosages of dronabinol.

Questioning the apnea-hypopnea index

This study has found a small overall effect on the apnea-hypopnea index with treatment, but a strong beneficial effect on subjective sleepiness. In addition, participants who received the higher dose of the drug showed significant satisfaction with their therapy. It is therefore intriguing that there was no impact on objective wakefulness or sleep architecture with this treatment.

This suggests that perhaps sleepiness and subjective well-being may be improved without necessarily seeing major improvements in the apnea-hypopnea index, which calls into question our use of this index as a primary endpoint.

Sigrid C. Veasey, MD, is with the Center for Sleep and Circadian Neurobiology at the Perelman School of Medicine, University of Pennsylvania, Philadelphia. Her comments were taken from an accompanying editorial (Sleep. 2018 Jan 1. doi: 10.1093/sleep/zsy014). She reported no conflicts of interest.

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 apnea-hypopnea index, the increases seen in the placebo group were no longer significant, but the decreases from baseline seen in the treatment arms were greater.

This study provides results "from the largest and longest randomized controlled trial to date of any putative drug treatment for OSA," according to David W. Carley, PhD, of the University of Illinois at Chicago, and colleagues.

Dronabinol treatment was also associated with significant decreases, compared with placebo, in non-REM apnea-hypopnea index and REM apnea-hypopnea index.

Patients' self-reported daytime sleepiness, measured by the Epworth Sleepiness Scale, remained similar compared with baseline in those who received placebo and the

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2.5-mg/day dose of dronabinol, but decreased significantly by a mean of –2.3 points compared with placebo in those on the higher dose of dronabinol.

There were no significant changes from baseline in objective sleepiness, as measured by the maintenance of wakefulness test, in any of the study groups.

There were no significant changes from baseline in objective sleepiness, as measured by the maintenance of wakefulness test, in any of the study groups. Researchers also saw no significant changes in sleep architecture, oxygenation, or the duration of supine sleep in any of the study groups, although the patients on the higher dose of dronabinol showed a slight increase in REM sleep and those on placebo showed a slight decrease.

Younger patients and those with a greater preponderance of REM-related apnea/hypopnea, and shorter average event duration were both more likely to respond to treatment, but apart from these factors there were no other influences on likelihood of patients responding to dronabinol.

David W. Carley, PhD, of the University of Illinois at Chicago, and his coauthors noted that there was a great need for pharmacological treatments for obstructive sleep apnea because positive airway pressure – while effective – has poor long-term adherence rates.

"Based on a series of animal investigations, we proposed that drugs which dampen afferent vagal feedback to the medulla may be effective in stabilizing respiratory pattern generation and increasing activation of upper airway dilating muscles during sleep," they wrote.

One patient experienced diarrhea and vomiting that required admission to hospital, and 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. Overall, nearly 90% of patients reported at least one adverse event, but the rates did not differ significantly between the treatment and placebo arms.

The researchers noted that significantly higher satisfaction scores were seen among patients receiving the higher dose of dronabinol.

"All of these observations argue that dronabinol, at doses from 2.5 to 10 mg/day, is safe for use by medically stable patients with moderate or severe OSA," the authors wrote. "Participants also tolerated and adhered well to daily self-administration of dronabinol."

The National Institutes of Health; National Heart, Lung, and Blood Institute; and National Center for Advancing Translational Sciences funded the study. One author declared grants from the National Institutes of Health for the study, and patents related to treatment of sleep-related breathing disorders by cannabinoid drugs. He also holds stock in RespireRx Pharmaceuticals, which holds an exclusive license to these and other related patents.

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SOURCE: Carley D, et al. Sleep. 2018 Jan 1. doi: 10.1093/sleep/zsx184.

Adenotonsillectomy reduced hypertension in OSA subgroup

BY KATIE WAGNER LENNON
Frontline Medical News

Hypertensive children with obstructive sleep apnea (OSA) who underwent adenotonsillectomy experienced significant improvements in their blood pressure after surgery, according to a retrospective analysis.

This is one of the few studies to have ever examined whether adenotonsillectomy for children with OSA had any effects on blood pressure and was based on "one of the largest cohorts for evaluating postoperative BP changes in nonobese children with OSA," noted Cho-Hsueh Lee, MD, and colleagues. The report was published in JAMA Otolaryngology–Head & Neck Surgery. Among the previous studies that evaluated BP in children with OSA before and after having this surgery, the results varied, they added.

"Our subgroup analysis results revealed that hypertensive children with OSA had significant improvements in all BP measures after surgery," wrote Dr. Cho-Hsueh Lee and colleagues.

"Our subgroup analysis results revealed that hypertensive children with OSA had significant improvements in all BP measures after surgery," wrote Dr. Lee, of the department of otolaryngology at National Taiwan University Hospital in Taipei, and coauthors. "These findings highlight the need to screen children with OSA to determine their hypertensive status and appropriately treat these children to ease their OSA symptoms and potentially prevent future adverse cardiovascular outcomes."

The researchers analyzed the medical records of 240 nonobese children with clinical symptoms and polysomnography-confirmed OSA (having an apnea-hypopnea index of greater than 1) who underwent adenotonsillectomy. Prior to surgery, 169 patients (70.4%) of the patients were classified as nonhypertensive, while 71 (29.6%) were classified as hypertensive. The children had a mean age of 7.3 years, and 160 were males.

Patients participated in full-night polysomnography (PSG) before surgery and at 3-6 months after adenotonsillectomy in the National Taiwan University Hospital Sleep Center. Apnea episodes were defined as a 90% decrease in airflow for two consecutive breaths. Sleep center staff measured the study participants' systolic and diastolic BP in a sleep center using an electronic sphygmomanometer, in the evening, prior to the PSG study, and in the morning. Pediatric hypertension was based on the nocturnal BP measurement and was defined as having mean systolic and diastolic BP greater or equal to the 95th percentile for age, sex, and height.

"Postoperatively, hypertensive children had a significant decrease in all BP measures, including nocturnal and morning [systolic] BP. ... A total of 47 hypertensive patients (66.2%) became nonhypertensive after surgery," the researchers said.

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"Postoperatively, hypertensive children had a significant decrease in all BP measures, including nocturnal and morning [systolic] BP. ... A total of 47 hypertensive patients (66.2%) became nonhypertensive after surgery," the researchers said.

For patients who were hypertensive before surgery, the average nocturnal (before PSG) preop systolic BP was 114.3 mm Hg, versus 107.5 mm Hg after surgery. The mean nocturnal diastolic BP for this same group of patients decreased to 65.1 mm Hg from 74.3 mm Hg. Similarly, the average morning (after PSG) systolic BP and diastolic BP were 106.0 mm Hg and 64.4 mm Hg after these patients underwent adenotonsillectomy, compared with 111.8 mm Hg and 71.7 mm Hg prior to surgery, respectively.

The adenotonsillectomy didn't improve all patients' BP. For some who were nonhypertensive before surgery, blood pressure increased, with 36 (21.3%) of this group having become hypersensitive after surgery, the researchers acknowledged.

Overall, the cohort experienced significant improvements in several PSG measures, including the average apnea-hypopnea index, which decreased from 12.1 events per hour to 1.7. The total arousal index also declined, going from 6.1 events per hour to 4.2. In addition, the mean oxygen saturation improved from 96.8% to 97.7%.

The investigators described several limitations of the study, including their inability to collect patients' arterial stiffness, carotid intima thickness, and other cardiovascular measures beyond BP.

They recommended a follow-up study. "Although we observed improvements in BP measures within 6 months after surgery for hypertensive children with OSA, the long-term effects of surgery on BP remain uncertain," they explained.

The study was supported by grants from the Ministry of Science and Technology, Republic of China (Taiwan). The researchers disclosed no potential conflicts of interest.

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SOURCE: Lee, C-H et al. JAMA Otolaryngol Head Neck Surg. 2018 Feb 15. doi: 10.1001/jamaoto.2017.3127.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This pediatric study from Taiwan is important because it shows that hypertension is a significant issue in nonobese children and can be modulated by treatment for OSA. The only concern I have is that blood pressure normative reference data were adopted to Taiwanese children from the National High Blood Pressure Education Program working group in the United States. Our sleep clinic at Helen DeVos Children's Hospital often receives referrals from Pediatric Cardiology and Pediatric Nephrology for sleep studies for hypertensive patients. Hopefully, because of this publication, primary care providers will also consider OSA in their work-up for pediatric hypertension!

Radiation exposure in MICU may exceed recommended limit

BY ANDREW D. BOWSER
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ Patients admitted to medical intensive care units may be exposed to doses of radiation that are substantial and exceed federal annual occupational limits, according to results of a recent observational study.

These "substantial" radiation doses in some patients suggest that efforts are warranted to "justify, restrict and optimize" the use of radiological resources when possible, said Sudhir Krishnan, MD, of the Cleveland Clinic, and his coauthors.

"Although we were unable to assess or predict the potential long-term adverse effects of radiation exposure, judicious use of radiological resources is recommended," Dr. Krishnan and his colleagues wrote in the journal *CHEST*®.

The retrospective, observational study included 4,155 adult admissions to a medical intensive care unit (MICU) at an academic medical center in 2013. Investigators calculated the cumulative effective dose (CED) of radiation based on ionizing radiological studies for each patient.

With a median length of stay of just 6.4 days, a total of 131 admissions (3%) accrued a CED of radiation of at least 50 millisieverts (mSv), the annual limit recommended by the National Commission on Radiation Protection, and 47 of those patients (1%) accrued a CED of radiation of at least 100 mSv, the 5-year cumulative exposure limit, the authors reported.

These findings suggest that "MICU patients could be subjected to radiation doses in a matter of days that are equivalent to or more than [the] CED observed in patients with chronic diseases and patients with trauma," they wrote.

As hypothesized, patients with higher severity of illness scores (APACHE III scores) received a higher CED of radiation, according to the report. Using a multivariable linear regression model, investigators found that higher CED was predicted by higher APACHE III scores, sepsis, longer MICU stay, and gastrointestinal disorders and bleeding.

CT scans were the most common source of radiation exposure in patients who exceeded a 50 mSv of radiation, accounting for 49% of the total accrued dose, with interventional radiology accounting for 38%.

Despite concerns about "the statistical risk of latent radiogenic cancer," radiologic studies performed in the critically ill have the potential to reduce morbidity and mortality, the authors acknowledged. "This understandably shifts the risk-benefit ratio towards radiation exposure. However, complacency in this regard cannot be entirely justified," they wrote.

Of the patients in the study who were exposed to a CED of at least 50 mSv, 81% survived the hospital admission and could be subjected to even more radiation as a part of ongoing medical care, they noted.

"Robust tools for monitoring CED prospectively per episode of clinical care, counseling patients exposed to high doses of radiation, and prospective studies exploring radiogenic risk associated with medical radiation are urgently required," the authors said.

The investigators reported no significant conflicts of interest.

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SOURCE: Krishnan S et al. Chest. 2018 Feb 4. doi: 10.1016/j.chest.2018.01.019.

VIEW ON THE NEWS

Nirmal S. Sharma, MD, comments: This is a very valid study. I think radiation exposure in the ICU is too high. Previous studies have shown that doing imaging on demand has had similar outcomes to doing it daily. (Currently, across the country, chest x-rays are done daily for most patients in the ICU, who have a respiratory problem.) We tried using this model at the University of Alabama at Birmingham, but some physicians were not comfortable with it and had to revert to previous practices. We would need future studies to find out if the radiation exposures in survivors from the ICU results in increased incidence of malignancies at a later date.

FDA approves angiotensin II for shock patients

BY IAN LACY
Frontline Medical News

Angiotensin II has been approved for use in intravenous infusions to increase blood pressure in adults with septic or other distributive shock, the Food and Drug Administration announced.

Shock-related drops in blood pressure can restrict blood flow to vital organs and can result in organ failure and death. "There is a need for treatment options for critically ill hypotensive patients who do not adequately respond to available therapies," Norman Stockbridge, MD, PhD, director of the division of cardiovascular and renal products in the FDA's Center for Drug Evaluation and Research, said in a written statement.

The effectiveness of angiotensin II for treating critically low blood pressure was confirmed in a clinical trial of 321 patients who were in shock. A significant number of patients responded to angiotensin II treatment, compared with those given placebo. In combination with conventional treatments, angiotensin II increased blood pressure safely and effectively, according to the FDA statement.

The application for angiontensin II was received under Priority Review, which asks the FDA to take action on an application within 6 months if the agency determines that an approved drug would improve the safety and effectiveness of treating a serious medical condition.

The angiotensin II injections, which would be marketed as Giapreza by La Jolla Pharmaceutical Company if approved, can cause serious blood clots.

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Combo therapy does not improve outcomes for *A. baumannii*

BY HEIDI SPLETE
Frontline Medical News

Adding meropenem to colistin had no effect on clinical success in cases of severe *Acinetobacter baumannii* infections, based on data from 406 patients.

In a study published online in The Lancet Infectious Diseases, Mical Paul, MD, of Rambam Health Care Campus, Haifa, Israel, and colleagues randomized 198 patients to colistin alone and 208 to colistin plus meropenem (Lancet Infect Dis. 2018 Feb 15. doi: 10.1016/S1473-3099[18]30099-9).

The demographics were similar between the groups and approximately 77% of patients in each group were infected with *A. baumannii*.

The primary outcome was defined as clinical success 14 days after randomization; 79% (156) of the colistin-only patients and 73% (152) of the combination patients did not meet the criteria, the researchers said. In addition, no significant difference between the groups was noted in all-cause mortality at 14 days or 28 days, or for any other secondary outcomes including fever and time spent in the ICU.

The results highlight "the necessity of assessing combination therapy in randomized trials before adopting it into clinical use," the researchers said.

The study was not designed to examine the effect of the two types of therapy on bacteria other than *A. baumannii*, the researchers noted. However, based on the findings, "we recommend against the routine use of carbapenems for the treatment of carbapenem-resistant *A. baumannii* infections," they said.

The study was supported by EU AIDA grant Health-F3-2011-278348. Dr. Paul had no financial conflicts to disclose.

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SOURCE: Paul M et al. Lancet Infect Dis. 2018 Feb 15. doi: 10.1016/S1473-3099(18)30099-9.

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Perfusion-only scan rules out PE in pregnancy

BY ANDREW D. BOWSER
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ For pregnant women with suspected pulmonary embolism (PE), evaluation with low-dose perfusion scintigraphy may be preferable to computed tomographic pulmonary angiography (CTPA), according to authors of a recent retrospective study.

Pulmonary embolism causes 9% of maternal deaths in the United States, according to the authors of the study, which was published online in the journal *CHEST*®. While it's clear that perfusion scans yield lower radiation exposure than CTPA, to date, there has been only limited study of its diagnostic performance in women with suspected PE.

The negative predictive value was a particularly important endpoint to evaluate because pulmonary embolism is rare among pregnant women and most perfusion-only imaging is negative, according to the investigators.

The new study is believed to be the largest to date of perfusion-only imaging in this setting, according to first author Jean-Ju Sheen, MD, of the department of obstetrics and gynecology at Columbia University Medical Center, New York, and her coauthors.

The low-dose perfusion scan offered comparable diagnostic efficacy while potentially limiting radiation exposure, according to the authors of this single-center, retrosepctive cohort study.

The study included pregnant women (mean age, 27.3 years) who underwent imaging for pulmonary embolism at Montefiore Medical Center, New York, between 2008 and 2013. A total of 225 women underwent perfusion-only scans, while 97 underwent CTPA.

Chest pain and dyspnea were the most common symptoms for patients in both groups: 136 of the patients (60.4%) in the low-dose perfusion group reported chest pain versus 40 patients (41.2%) in the CTPA group. Additionally, approximately half of the patients in both groups had dyspnea.

Tachycardia was found in 43 of patients (44.3%) who underwent CTPA, compared with 77 of the patients (34.2%) who underwent the diagnostic test involving less radiation exposure.

Imaging was negative for PE in 198 of the patients (88.0%) who were scanned with low-dose perfusion, while 84 of patients (86.6%) who had CTPAs were negative for PE. For both groups of patients, the percentage who had indeterminate imaging was 9.3%. Only one study participant had a deep vein thrombosis at the time she presented with PE symptoms.

The primary end point of the study, negative predictive value, was 100% for the perfusion-only group and 97.5% for CTPA, according to the report. It was determined by a diagnosis of venous thromboembolism within 90 days of evaluation.


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Those "indistinguishable" negative predictive values suggest that low-dose perfusion scintigraphy performs comparably to CTPA, making it an appropriate first diagnostic modality for pregnant women who are suspected of having pulmonary embolism, wrote Dr. Sheen and her colleagues.

The negative predictive value was a particularly important endpoint to evaluate because pulmonary embolism is rare among pregnant women and most perfusion-only imaging is negative, the authors stated.

Of the women in the study, 252 (89%) of those who tested negative for PE – either by a low-dose perfusion scan or a CTPA – returned to the medical center for follow-up 90 days later.

Thromboembolic events occurred in two of the women who previously had a negative CTPA, but none occurred in patients who had been tested for PE with low-dose perfusion scan. The two thromboembolic events were detected in women who were no longer pregnant.

Ten patients in the study (3.1%) were treated for pulmonary embolism, the authors reported. The PE diagnoses were based on four positive low-dose perfusion scans and six positive CTPAs "in conjunction with clinical suspicion." These patients' most common symptoms were chest pain and dyspnea.

Only one of these patients had recently been diagnosed with a deep vein thrombosis.

When perfusion defects are found, they should be interpreted cautiously, particularly in asthmatic patients, the researchers noted.

"Segmental perfusion defects secondary to abnormal ventilation cannot be distinguished from PE without a ventilation scan," added the investigtors.

Three of the patients diagnosed with a PE had asthma. In a subanalysis of the 77 patients with asthma who participated in this study, the negative predictive values were 100% for both those who received a low-dose perfusion scan and those who received a CTPA. For patients in this subgroup, the negative rates of PE from low-dose perfusion scan and CTPA were 74.1% and 87.1%, respectively.

"Maternal-fetal radiation exposure should be of utmost importance when considering the choice of diagnostic test," the authors wrote. "When available, [a low-dose perfusion scan] is a reasonable first choice modality for suspected pulmonary embolism in pregnant women with a negative chest radiograph."

One study coauthor is on an advisory panel for Jubilant DraxImage, and another has a spouse who is a board member of Kyron Pharma Consulting.

The remaining authors, including Dr. Sheen, reported no conflicts of interest.

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SOURCE: Sheen JJ et al. Chest. 2018 Feb. doi: 10.1016/j.chest.2017.08.005.

VIEW ON THE NEWS

Nirmal S. Sharma, MD, comments: During pregnancy, all radiation is bad radiation, but when it was really needed, we did use this low-radiation perfusion scan quite a bit at my past institution. This article definitely shines light on the utility/validity of this technique because most centers still use a computed tomographic pulmonary angiography study in pregnant females (with shielding methods) if suspicion of pulmonary embolism is high. The downside to low-dose perfusion scintigraphy is that it cannot be used in patients with grossly abnormal chest x-rays.

If you are doing a low-dose perfusion scan alone, without ventilation studies, in subjects who have ventilation issues caused by severe parenchymal disease or an obstructive lung disease, such as asthma, interpretation becomes an issue. Such patients may have segmental and subsegmental perfusion defects caused by loss of ventilation.

For patients with COPD taking fluticasone furoate/vilanterol who need additional lung function improvement

LESS TO TAKE.
MORE TO TAKE IN.

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

COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroid; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

INDICATION

TRELEGY is for maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema, who are on fluticasone furoate and vilanterol (FF/VI) and need additional treatment of airflow obstruction or who are already taking umeclidinium and FF/VI. TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

IMPORTANT SAFETY 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. 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)

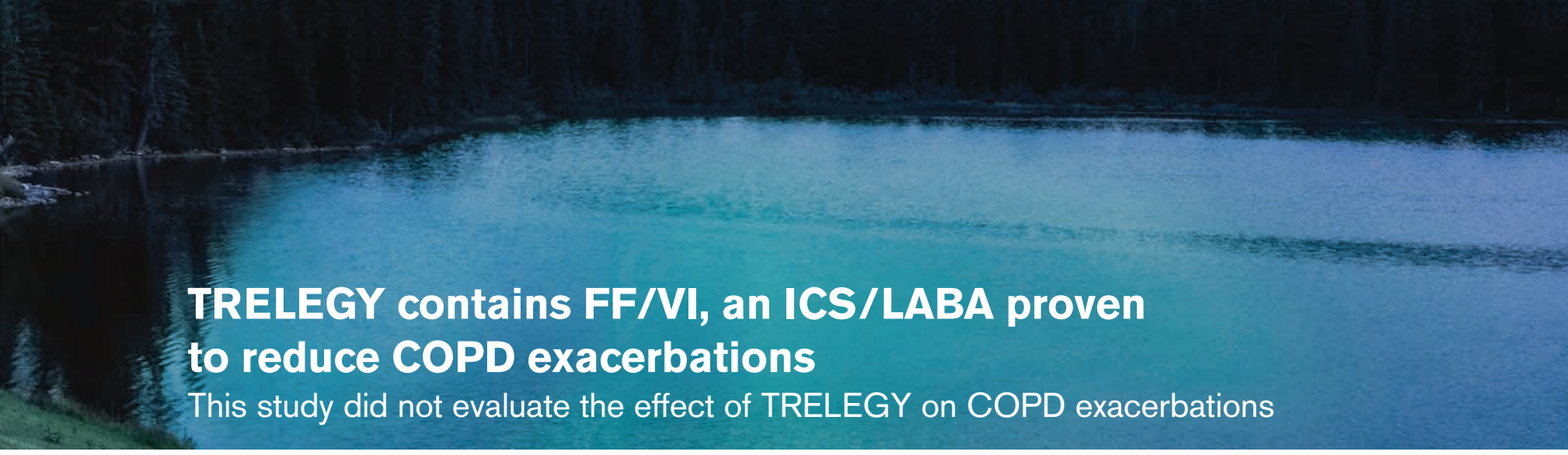
CONTRAINDICATIONS

- 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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Printed in USA. 831276R0 January 2018

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

Twitter content analysis reveals clinical opportunity

BY CHHAVI JAIN
Frontline Medical News

Social media communication around lung cancer is focused primarily on cancer treatment and use of pharmaceutical and research interventions, followed closely by awareness, prevention, and risk topics, according to an analysis of Twitter conversation over a 10-day period.

Although awareness and risk prevention tweets were likely to contain cues toward action, "messages focused on treatment, end of life ... were significantly less likely to integrate cues for personal activity," the investigators wrote. The report was published in Journal of the American College of Radiology.

"[These] findings suggest an opportunity to increase cues to action across all phases of the communication continuum," wrote Dr. Jeannette Sutton and her colleagues.

"Such findings suggest an opportunity to increase cues to action across all phases of the communication continuum," wrote Jeannette Sutton, PhD, of the University of Kentucky, Lexington, and her colleagues.

The investigators collected 1.3 million unique Twitter messages between Sept. 30 and Oct. 9, 2016, that contained at least one of six keywords commonly used to describe cancer: cancer, chemo, tumor, malignant, biopsy, and metastasis. They then drew a random, proportional stratified sample of 3,000 messages (12.5%) for manual coding from the 23,926 messages posted that included keywords related to lung cancer. Tweets were examined by user type (individuals, media, and organizations) to identify content and structural message features.

Message content was most frequently related to treatment (32.1%), followed by awareness (22.9%), end of life (15.5%), prevention and risk information (13.3%), active cancer-unknown phase (7.6%), diagnosis (6.1%), early detection (2.7%), and survivorship (1%), Dr. Sutton and her colleagues reported.

"The large volume of messages containing content about pharmaceuticals suggests that Twitter is also a forum for sharing information and discussing emerging treatments. Importantly, treatment messages were shared primarily by individuals, suggesting that this online user community jointly includes members of the public as well as medical practitioners and companies who have an awareness of emerging treatment approaches, suggesting an opportunity for online engagement between these various groups (e.g., Lung Cancer Social Media #LCSM community and related chats)," the investigators wrote.

The National Science Foundation supported parts of this research.

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SOURCE: Sutton J et al. J Am Coll Radiol. 2018 Jan. doi: 10.1016/j.jacr.2017.09.043.

Follow-up CTs nonsuperior to x-rays in NSCLC

BY NEIL OSTERWEIL
Frontline Medical News

MADRID – Computed tomography scans do not appear to be superior to plain old chest x-rays for follow-up of patients with completely resected non–small cell lung cancer (NSCLC), results of a randomized clinical trial suggest.

Among 1,775 patients followed out to 10 years with either a "minimal" protocol – consisting of history, physical exam, and periodic chest x-rays – or a "maximal" protocol – including CT scans of the thorax and upper abdomen, as well as bronchoscopy for squamous-cell carcinomas – there were no significant differences in overall survival at either 3, 5, or 8 years of follow-up, reported Virginie Westeel, MD, from the Centre Hospitalier Régional Universitaire of the Hôpital Jean Minjoz in Besançon, France.

"Most clinical practice guidelines recommend follow-up after resection for non–small cell lung cancer, including clinic visits with history and physical examination with chest x-rays every 6 to 12 months for 2 years and then yearly. This recommendation relies on expert opinion and small prospective series, but there [were] until now no randomized controlled trials to answer this question," she said at a briefing at the European Society of Medical Oncology Congress.

In hopes of finding that answer, Dr. Westeel and colleagues in the French Cooperative Thoracic Oncology Group conducted a clinical trial comparing the standard follow-up approach recommended in most clinical guidelines, as described by Dr. Westeel, with an experimental protocol consisting of history and exam plus chest x-ray, CT scans, and fiber-optic bronchoscopy (mandatory for squamous- and large-cell carcinomas, optional for adenocarcinomas).

Patients with completely resected stage I, II, and IIIA tumors, and T4 tumors with pulmonary nodules in the same lobe, were randomly assigned to follow-up with one of the two protocols.

In each trial arm, the assigned procedures were repeated every 6 months after randomization for the first 2 years, then yearly until 5 years.

After a median follow-up of 8.7 years, there was no significant difference in the primary endpoint of overall survival. Median OS was 123.6 months in the maximal protocol group, compared with 99.7 months in the minimal protocol group ($P = .037$)

The 3-, 5-, and 8-year survival rates for the maximal and minimal protocols, respectively, were 76.1% vs. 77.3%, 65.8% vs. 66.7%, and 54.6% vs. 51.7%.

Because there appeared to be a separation of the survival curve beginning around 8 years, the investigators performed an exploratory 2-year landmark analysis.

They found that, among patients who had a recurrence within 24 months of randomization, there was no difference in OS between each follow-up protocol. However, among those patients with no recurrence within 24 months of resection, the median OS was not reached among patients assigned to the maximal protocol versus 129.3 months for those assigned to the minimal protocol ($P = .04$).

Patients without early recurrence had higher rates of secondary primary cancers, and for these patients, early detection with CT-based surveillance could explain the differences in overall survival, Dr. Westeel said.

"Our suggestion for practice is that, because there is no survival difference, both follow-up protocols are acceptable. However, a CT scan every 6 months is probably of no value in the first 2 years," but yearly chest CTs to detect second primary cancers early may be of interest, she said.

Enriqueta Felip, MD, from Vall D'Hebron Institute of Oncology in Barcelona, who was not involved in the trial, commented that, while the study needed to be conducted, it was unlikely to change her clinical practice because of potential differences among patients with varying stages of NSCLC at the time of resection.

"I think it's an important trial,

FRONTLINE MEDICAL NEWS

"Most clinical practice guidelines recommend follow-up after resection for non–small cell lung cancer," said Dr. Virginie Westeel.

[but] tomorrow I will follow my patients with a CT scan," she said.

Dr. Felip was an invited expert at the briefing.

The study was supported by the French Ministry of Health, Fondation de France, and Laboratoire Lilly. Dr. Westeel and Dr. Felip reported no conflicts of interest relevant to the study.

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States show large disparities in lung cancer mortality

BY RICHARD FRANKI
Frontline Medical News

Mortality from lung cancer is expected to be close to 50 per a population of 100,000 in 2018, with the highest rate in West Virginia and the lowest in Utah.

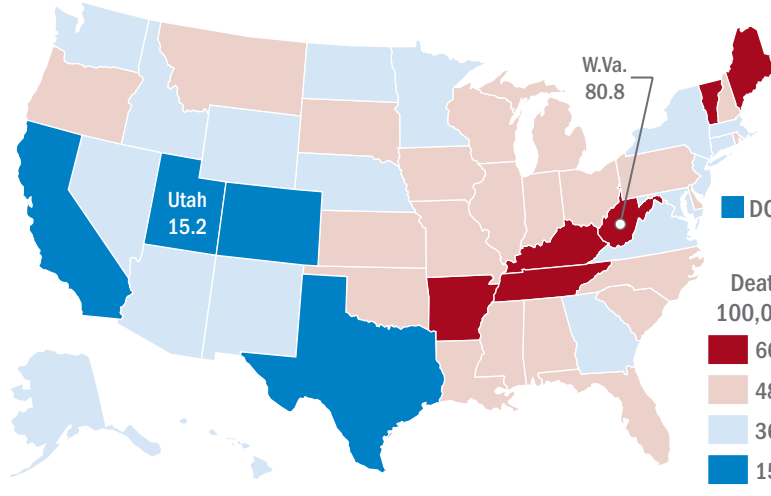
Approximately 154,050 deaths from lung cancer – three times as many as any other cancer – are predicted for the year in the United States by the American Cancer Society in its Cancer Facts & Figures 2018, based on analysis of 2001-2015 data from the National Center for Health Statistics. That figure is down from the 155,870 predicted for 2017, as the most recent trend (2011-2015) in the death rate has been a decline of about 2.3% per year for women and 3.8% per year for men, the ACS noted.

The expected number of deaths for 2018, coupled with a current population estimate of nearly 326 million, works out to an expected death rate of 47.3 per a population of 100,000. The Census Bureau estimates for the state populations and the deaths projected by the ACS produce expected death rates of 80.8 per 100,000 for West Virginia and 15.2 for Utah. Kentucky's rate of 79.3 is just behind West Virginia, but Colorado, the next-lowest state after Utah, has an estimated rate that's almost twice as high at 28.5.

Nationally, death rates for lung cancer were 53.8 per 100,000 for males and 35.4 for females for 2011-2015, and incidence rates were 73 per 100,000 for males and 52.8 for females for 2010-2014, the ACS reported.

Among racial and ethnic groups, in men, the mortality was highest for those who were both non-Hispanic and black (66.9 per 100,00) during 2011-2015. Of the racial and ethnic groups of women for the same period, white women had the highest death rate (39). Hispanic/Latino men (26.4) and Hispanic/Latino women (13.3) had the lowest deaths rates, according to the report.

Estimated lung cancer death rates for 2018



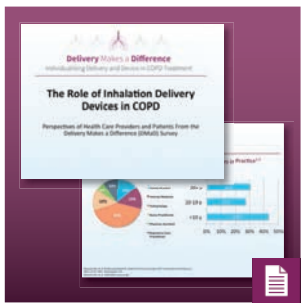
FRONTLINE MEDICAL NEWS

Note: Based on 2001-2015 mortality data from the National Center for Health Statistics.
Source: American Cancer Society

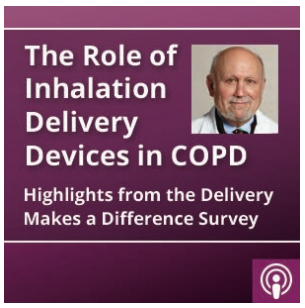
rfranki@frontlinemedcom.com

How can you help the 64% of patients who are unconcerned about proper device technique?[1]

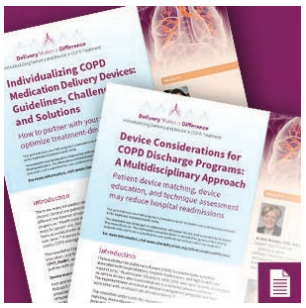
Explore **Delivery** Makes a **Difference**, an online program with a variety of educational resources.



A **slide presentation** with surprising results from the Delivery Makes a Difference (DMaD) surveys



A **podcast** highlighting health care provider *and* patient responses from the DMaD survey



Newsletters exploring how to improve inhalation-device use and steps aimed at reducing hospital readmissions

Videos explaining how to match a patient to an inhalation device and how to watch for common errors in inhalation-device technique

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The **Delivery** Makes a **Difference** initiative examines patient and provider perspectives on inhalation-device use and education in COPD.

Reference: 1. Hanania NA, Braman S, Adams SG, et al. The role of inhalation delivery devices in COPD: perspectives of patients and health care providers. Submitted manuscript.

This promotional, non-CME program is intended only for US health care professionals involved in the treatment of patients with COPD and is provided by Sunovion Pharmaceuticals Inc.

New multi-analyte blood test shows promise in screening for several common solid tumors

BY SHANNON AYMES
Frontline Medical News

Imagine a single blood test that would cost less than $500 and could screen for at least eight cancer types.

It's early days for the technology, called CancerSEEK, but the test had a sensitivity of 69%-98%, depending on the cancer type, and a specificity of 99% in a cohort of 1,005 patients with stage I-III cancers and 850 healthy controls, wrote Joshua D. Cohen of the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University, Baltimore, and his colleagues. The report was published in Science.

CancerSEEK tests for mutations in 2,001 genomic positions and eight proteins. The researchers examined a 61-amplicon panel with each amplicon analyzing an average of 33 base pairs within a gene. They theorized the test could detect between 41% and 95% of the cancers in the Catalog of Somatic Mutations in Cancer dataset. They next used multiplex-PCR techniques to minimize errors associated with large sequencing and identified protein biomarkers for early stage cancers that may not release detectable ctDNA.

The researchers used the technology to examine blood samples from 1,005 patients with stage I (20%), stage II (49%), or stage III (31%) cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast prior to undergoing neoadjuvant chemotherapy. Participants had a median age of 64 years (range of 22-93 years). The healthy controls did not have a history of cancer, chronic kidney disease, autoimmune disease, or high-grade dysplasia.

The sensitivity of the test ranged from 98% in ovarian cancer to 33% in breast cancer, but the specificity was greater than 99% with only 7 of 812 control participants having a positive result. "We could not be certain that the few 'false positive' individuals identified among the healthy cohort did not actually have an as-yet undetected cancer, but classifying them as false positives provided the most conservative approach to classification and interpretation of the data," the authors wrote.

When tumor tissue samples from 153 patients with statistically significant ctDNA levels were analyzed, identical mutations were found in the plasma and tumor in 90% (138) of all cases.

Based on cancer stage, sensitivity for stage I cancers was 43%, for stage II 73%, and for stage III 78%. Again, sensitivity varied depending on cancer type, with 100% sensitivity for stage I liver cancer and 20% sensitivity for stage I esophageal cancer.

When tumor tissue samples from 153 patients with statistically significant ctDNA levels were analyzed, identical mutations were found in the plasma and tumor in 90% (138) of all cases.

The protein markers in the CancerSEEK test might also be able to anatomically locate malignancies. Using machine learning to analyze patients testing positive with CancerSEEK, the results narrowed the source of the cancer to two possible anatomical sites in approximately 83% of patients and to one anatomical site in approximately 63% of patients. Accuracy was highest for colorectal cancer and lowest for lung cancer.

"We could not be certain that the few 'false positive' individuals identified among the healthy cohort did not actually have an as-yet undetected cancer, but classifying them as false positives" was most conservative.

As the study included otherwise healthy patients with known malignancies, the results need to be confirmed with prospective studies of incidence cancer types in a large population. Patients in the screening setting may have less advanced disease and other comorbidities that could impact the sensitivity and specificity of the CancerSEEK test, the researchers wrote.

The study was funded by multiple sources including grants from the National Institutes of Health. The authors reported various disclosures involving diagnostics and pharmaceutical companies.

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SOURCE: Cohen JD et al., Science. 2018 Jan 18. doi: 10.1126/science.aar3247.

What are the clinically relevant questions answered by this test?

Molecular panels are here to stay – and the GI community will in some shape or form be impacted, be it in performing diagnostic procedures on test-positive patients, or risk-stratifying patients prior to testing.

The conceptual challenge is that it is not about what any given test measures – various panels use separate combination of markers from epigenetics to DNA mutations as well as whole or truncated proteins – but how well a specific test with its somewhat arbitrarily chosen components and cutoffs performs. And, more importantly, what the clinical implications of positive or negative test results are. And no one knows that. At least for now.

A recent report in Science from a group from the Ludwig Center for Cancer Genetics at Johns Hopkins proposes a new cancer blood test based on a very systematic and thoughtful approach to include select mutations in cell-free DNA and circulating proteins associated with various solid organ tumors. For validation, they used healthy and advanced but nonmetastatic cancer cohorts. Through stringent controls and a series of validations, the authors present a range of sensitivities for the various cancer types with an impressive specificity. This is a technically very strong approach with many nifty and thoughtful additions to give this test a very promising first foray – did anybody watch CNN?

DR. JUNG

While not ready for prime time, which is a tall order for a first report, the authors dutifully point out the need for a prospective real life cohort validation. In the meantime, regardless of the outcome of this particular test, it is a repeated reminder that we need to stay abreast of the advances and the details of each molecular test, especially with a likely very diverse and distinct group of tests to choose from.

Many of us will be part of interpreting results and determining further management. Just as with hereditary cancer genetic panel testing, our technical ability may have stretched beyond our ability to fully understand the implications. Many questions will arise: What about true false positives? False negatives? Intervals? Can such tests replace other screening? How to choose any given test over the other? Should tests be combined or alternated? The tests will be technically refined and are here to stay – we need to get to work on finding answers to the clinically relevant questions.

Barbara Jung, MD, is the Thomas J. Layden Endowed Professor and chief of the division of gastroenterology and hepatology, University of Chicago.

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

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

AstraZeneca

Elderly at highest CV risk get short-statined

BY BRUCE JANCIN
Frontline Medical News

ANAHEIM, CALIF. – Adults older than age 75 years with known atherosclerotic cardiovascular disease are significantly less likely than younger patients to receive a high-intensity statin for secondary prevention, even though they actually tolerate statin therapy better, Michael G. Nanna, MD, said at the American Heart Association scientific sessions.

This was among the eye-opening findings from his analysis of data from the PALM (Patient and Provider Assessment of Lipid Management) Registry, a national registry that provides a snapshot of how cardiologists, primary care physicians, and endocrinologists in real-world community practice care for their patients with known atherosclerotic cardiovascular disease (ASCVD) or at high risk for it.

The analysis included 7,736 patients receiving care in 138 U.S. cardiology, primary care, and endocrinology practices, including 1,704 patients over age 75, 1,038 of whom had known ASCVD and thus were candidates for secondary prevention measures, explained Dr. Nanna, a second-year cardiology fellow at Duke University in Durham, N.C.

The impetus for this study was the dearth of information about what's going on in everyday clinical practice in terms of statin utilization and side effects in the elderly since release of the 2013 American College of Cardiology and American Heart Association cholesterol guidelines. Those guidelines highlighted the lack of randomized clinical trial data to support the use of statins in patients over age 75, who had typically been excluded from participation in the major studies.

The guidelines recommended moderate-intensity statin therapy for secondary prevention in the elderly, and didn't take a firm position regarding statins for primary prevention in older patients.

Bruce Jancin/Frontline Medical News

Dr. Michael G. Nanna said, "My dream is that studies like this will motivate folks to fund a randomized clinical trial looking at high-intensity statins in older adults."

What's happening in community practice

For primary prevention in the elderly, physicians appear to be extrapolating from their practice patterns in younger at-risk patients. Sixty-three percent of patients younger than age 75 at high risk for ASCVD were on a statin for primary prevention, as were an equal percentage of older patients. Moreover, 10.2% of older patients were on a high-intensity statin for primary prevention, a rate not significantly different from the 12.3% in younger at-risk patients.

Statin therapy for secondary prevention in the elderly was a different story. Older patients were significantly less likely to receive any statin for secondary prevention. And they were much less likely to get a high-intensity statin, by a margin of 23.5%-36.2%.

Indeed, in a multivariate regression analysis adjusted for patient demographics, diabetes, smoking, heart failure, body mass index, insurance type, income, and whether a patient saw a cardiologist, older patients with ASCVD were 42% less likely to receive a high-intensity statin than patients younger than age 75.

"It's interesting that older patients who have ASCVD are actually the group at highest risk of events, yet they're the least likely to receive a high-intensity statin," Dr. Nanna observed in an interview.

Of note, older patients were significantly less likely to report any side effect on a statin, by a margin of 41.3%-46.6%. They were also markedly less likely to report myalgias, by a margin of 23.3%-33.3%.

"One of the reasons why folks have shied away from treating older patients with statins, and especially with high-intensity statins, is the theoretical risk of more side effects and drug interactions. We didn't see that," Dr. Nanna said.

What's next

"My dream is that studies like this will motivate folks to fund a randomized clinical trial looking at high-intensity statins in older adults," Dr. Nanna said. "I think there are funding challenges because both rosuvastatin and atorvastatin are generic at this point. But I think it needs to be done."

Rumor has it, he added, that the first randomized trial of statin therapy in the elderly will be in the primary prevention setting. "That's an area where we're all essentially operating in an evidence-free zone," Dr. Nanna said.

Regeneron and Sanofi fund the PALM Registry. Dr. Nanna reported having no relevant financial disclosures.

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FDA approves implantable therapy for PAH

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration announced that it has approved an implantable system for treprostinil to treat adult patients with New York Heart Association (NYHA) Class I, II, and III pulmonary arterial hypertension.

This infusion system is implanted into a patient for intravenous delivery of treprostinil (Remodulin) and is designed to help supply blood to the lungs and keep a patient's blood pressure within a healthy range. The system comprises three parts: the pump, the programmer, and the catheter.

The Medtronic 8201 Implantable 80 cm Intravascular Catheter is inserted through a vein at the superior cavoatrial junction and connects the catheter to the Medtronic SynchroMed II 8637P Programmable Pump in a pump pocket placed beneath the abdominal skin. Then, the surgeon uses the Medtronic N'Vision 8840 Clinician Programmer with 8870 Application Card to program and review the pump's settings. Once programmed, the implantable system delivers the Remodulin injection from the pump reservoir, through the pump tubing, the catheter port, and the catheter to the intravascular delivery site. Finally, the pump stays permanently implanted and the health care provider uses a needle and syringe refill kit to refill the pump with Remodulin, as needed.

Read the full approval on the FDA's website.

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Try thrombolysis for caval extension of iliofemoral DVT

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – Caval extension of an acute iliofemoral deep vein thrombosis paradoxically portends better treatment outcomes than does thrombolysis of a DVT without involvement of the inferior vena cava, said Rabih A. Chaer, MD, professor of surgery at the University of Pittsburgh.

This finding from a retrospective analysis of the University of Pittsburgh experience might seem counterintuitive. After all, caval extension clearly indicates a greater clot burden. One possible explanation: Clearing a thrombus from a large vessel, such as the inferior vena cava (IVC), provides an added protective effect. Also, since the caval segments don't have valves – their flow is based upon negative pressure in the chest – they may not contribute as much to postthrombotic morbidity to the same extent as do thrombosed iliofemoral segments, Dr. Chaer speculated at a symposium on vascular surgery sponsored by Northwestern University.

In addition, patients with caval extension were treated more aggressively: 98% of them underwent pharmacomechanical thrombolysis with the Angiojet or another device as an adjunct to catheter-directed thrombolysis, compared with 82% of noncaval patients.

The impetus for Dr. Chaer and coinvestigators to review the Pittsburgh experience was a lack of clarity in the

Continued on page 38

ILLUMINATEOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

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

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

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

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Continued from page 36

literature as to the effect IVC thrombosis has on thrombolysis outcomes in patients with acute iliofemoral DVT. Even though caval thrombus extension is present in up to 22% of patients with iliofemoral DVT, current guidelines issued by the American College of Chest Physicians, the American Heart Association, and the Society for Vascular Surgery don't address the distinction between iliofemoral DVT with and without IVC extension in regard to the occurrence of postthrombotic syndrome (PTS), the most common complication of DVT.

The incidence of PTS in patients whose iliofemoral DVT is treated

Bruce Jancin/Frontline Medical News

Dr. Rabih A. Chaer said lack of clarity in the literature led to the review.

by anticoagulation and compression alone is up to 50%. Mounting evidence indicates that catheter-directed thrombolysis and pharmacomechanical thrombolysis aimed at achieving early thrombus removal and symptom relief help maintain valvular competence and reduce the risk of PTS, the surgeon noted.

PTS is diagnosed using the validated Villalta scale, which incorporates clinical signs including pain on calf compression, skin edema and redness, and ulcers, as well as symptoms such as leg cramping, heaviness, itching, and paresthesia.

The Pittsburgh series included 102 consecutive patients treated with various combinations of catheter-directed or pharmacomechanical thrombolysis in 127 limbs with acute iliofemoral thrombosis. In 46 patients, the thrombus extended into the IVC, all the way up to the renal veins in most cases.

The groups with and without caval extension were similar in terms of age and prevalence of malignancy, hypercoagulable state, and clot age. However, a history of previous DVT was significantly more common in the group with IVC thrombus. Also, more than 60% of patients with caval extension got an IVC filter, a rate more than 10-fold greater than that in patients without caval extension.

In this series, caval thrombosis had no effect on the technical success of thrombolysis. The technical success rate – defined as at least 50% clot lysis – was 89% in both groups. Rates of recurrent DVT within 30 days were similar in the two groups as well: 11% in the caval thrombosis group and 14% in the noncaval group. At 2 years post intervention, 77%-78% of patients in both groups remained free of DVT recurrence. The rate of PTS – defined by a Villalta score of 5 or more – at 2 years was 34% in the noncaval group, which was significantly higher than the 11% rate in patients with IVC thrombus extension.

On multivariate analysis, incomplete clot lysis was associated with nearly a 23-fold increased risk of recurrent DVT and a 5.6-fold increased risk of PTS. Caval involvement was independently associated with a 78% reduction in PTS risk.

The Society for Vascular Surgery's guidelines recommend pharmacomechanical thrombolysis over

catheter-directed thrombolysis if the expertise is available.

"Pharmacomechanical techniques can be advantageous. They can expedite the lysis process by clearing most of the clot. In our series, 20 patients were treated with pharmacomechanical techniques in a single session," Dr. Chaer noted.

The use of IVC filters in the setting of caval extension of iliofemoral DVT is controversial: A thrombus that gets trapped in the filter is tough to remove, precluding successful recanalization.

"One-third of the patients in our series got a filter, but we've become more conservative nowadays. We don't use filters anymore. But I think those patients who might benefit from an IVC filter are those who present with a PE [pulmonary embolism], because that's telling you they might develop another PE, as well as those patients in whom pharmacomechanical thrombolysis is anticipated because we've seen that those patients are also more likely to develop a PE," he said.

The University of Pittsburgh study on the effect of IVC thrombus extension has been published (J Vasc Surg Venous Lymphat Disord. 2016 Oct;4[4]:385-91).

Dr. Chaer reported serving as a paid speaker for Boston Scientific.

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SOURCE: Chaer RA. Northwestern Vascular Symposium 2017.

Benefit of dabigatran over warfarin persists

BY M. ALEXANDER OTTO
Frontline Medical News

ANAHEIM, CALIF. – The benefit of dabigatran dual therapy versus warfarin triple therapy after percutaneous coronary intervention in patients with atrial fibrillation was consistent whether patients had drug-eluting or bare-metal stents, concomitant treatment with ticagrelor or clopidogrel, or acute coronary syndrome or stable disease as the indication for PCI, according to a subgroup analysis of the RE-DUAL PCI trial.

The trial, presented at the American Heart Association scientific sessions, randomized 2,725 patients to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin – the triple-therapy group – or dabigatran 110 mg or 150 mg twice daily plus clopido-

The incidence of the composite efficacy endpoint was 13.7% in the two dual-therapy groups, compared with 13.4% in the group that received triple therapy.

DR. OLDGREN

grel or ticagrelor – the dual-therapy groups (N Engl J Med. 2017 Oct 19;377[16]:1513-24).

After a mean follow-up 14 months, the incidence of the major or clinically relevant nonmajor bleeding was 15.4% in the 110-mg dual-therapy group (hazard ratio, 0.52; 95% confidence interval, 0.42-0.63; *P* less than .001) and 20.2% in the 150-mg dual-therapy group (HR, 0.72; 95% CI, 0.58-0.88; *P* less than .001), versus about 26% with triple therapy.

The incidence of the composite efficacy endpoint – death, unplanned revascularization, myocardial infarction, stroke, or systemic embolism – was 13.7% in the two dual-therapy groups versus 13.4% with triple therapy (HR, 1.04; 95% CI, 0.84-1.29; *P* = .005).

The investigators found consistent results when they analyzed their prespecified subgroups.

Acute coronary syndrome (ACS) was the indication for PCI in about half the patients; the rest had stable coronary artery disease. The two groups were well balanced except ACS patients were more likely to be new to oral anticoagulation. Results were consistent with the main trial in terms of bleeding. There was a trend for more embolic events in ACS patients on dabigatran 110 mg, but it was not significant, said investigator Jonas Oldgren, MD, of Uppsala (Sweden) University.

Drug-eluting stents were placed in 83% of patients; the rest had bare metal stents (BMS). The groups were well-balanced, except BMS patients were again more likely to be new to oral anticoagulation. Bleeding, thromboembolic events, and mortality were consistent with the main results regardless of the stent type, Most of the subjects were on clopidogrel, with just 12% on ticagrelor in both the dabigatran and warfarin groups. Ticagrelor patients were more likely to have ACS as their PCI indication and be new to oral anticoagulation. Ticagrelor patients were also more clinically complex, with a higher bleeding risk. Even so, they had relative bleeding risk reduction and efficacy results with dabigatran that were consistent with the overall finding, Dr. Oldgren said.

Patients were eligible for RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients with AF That Undergo a PCI With Stenting) if they had nonvalvular atrial fibrillation and a successful PCI within 120 hours. Those with bioprosthetic or mechanical heart valves, severe renal insufficiency, or other major comorbidities were excluded.

The trial was funded by Boehringer Ingelheim, the maker of dabigatran.

Several investigators were employees. Dr. Oldgren is an adviser to Boehringer Ingelheim. Other authors reported financial ties to the company as well.

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Guidelines call for drugs for diabetes with CVD

BY MICHELE G. SULLIVAN
Frontline Medical News

Recent studies that confirm the cardiovascular benefit of some anti-hyperglycemic agents are shaping the newest therapeutic recommendations for patients with type 2 diabetes and comorbid atherosclerotic cardiovascular disease (ASCVD).

Treatment for these patients – as all with diabetes – should start with lifestyle modifications and metformin. But in its new position statement, the American Diabetes Association now recommends that clinicians consider adding agents proved to reduce major cardiovascular events and cardiovascular death – such as the sodium glucose cotransporter-2 (SGLT2) inhibitor empagliflozin or the glucagon-like peptide 1 (GLP-1) agonist liraglutide – to the regimens of patients with diabetes and ASCVD (Diabetes Care. 2018;41[Suppl. 1]:S86-104. doi: 10.2337/dc18-S009).

Clinicians may also consider adding these agents for cardiovascular benefit alone.

DR. KALYANI

The medications are indicated if, after being treated with lifestyle and metformin therapy, the patient isn't meeting hemoglobin A1c goals, said Rita R. Kalyani, MD, who led the ADA's 12-member writing committee. But clinicians may also consider adding these agents for cardiovascular benefit alone, even when glucose control is adequate on a regimen of lifestyle modification and metformin, with dose adjustments as appropriate, she said in an interview.

"A1c remains the main target of sequencing antihyperglycemic therapies, if it's not reached after 3 months," said Dr. Kalyani of Johns Hopkins University, Baltimore. "But, it could also be that the provider, after consulting with the patient, feels it's appropriate to add one of these agents solely for cardioprotective benefit in patients with ASCVD."

The recommendation to incorporate agents with cardiovascular benefit is related directly to data from two trials, LEADER and EMPA-REG, which support this recommendation. All of these cardiovascular outcome trials included a majority of patients who were already on metformin. "We developed these evidence-based recommendations based on these trials and to appropriately reflect the populations studied," said Dr. Kalyani.

The ADA's "Standards of Medical Care in Diabetes 2018" is the first position statement from any professional society to provide specific recommendations for the incorporation of these newer antihyperglycemic agents for their cardioprotective benefit in the treatment algorithm for type 2 diabetes. But the document provides much more than an algorithm for treating patients with concomitant ASCVD, Dr. Kalyani said. It is a comprehensive clinical guide covering recommendations for diagnosis, medical evaluation, comorbidities, lifestyle change, cardiovascular risk management, and treating diabetes in children and teens, pregnant women, and patients with hypertension.

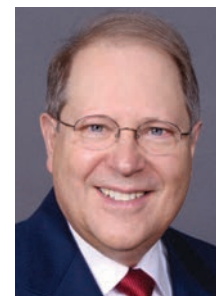
"This is a nice enhancement of previously published guidelines for diabetes therapy."

DR. JELLINGER

The 2018 update contains a number of new recommendations; more will be added as new data emerge, since the ADA intends it to be a continuously refreshed "living document." This makes it especially clinically useful, Paul S. Jellinger, MD, said in an interview. A member of the writing committee of the American Association of Clinical Endocrinologists' diabetes management guidelines, Dr. Jellinger feels ADA's previous versions have not been as targeted as this new one and, he hopes, its subsequent iterations.

"This is a nice enhancement of previously published guidelines for diabetes therapy," said Dr. Jellinger, professor of clinical medicine at the University of Miami. "For the first time, ADA is providing some guidance in terms of which agents to use. It's definitely more prescriptive than it was in the past, when, unlike the AACE Diabetes Guidelines, it was a palette of choice for clinicians, but with very little guidance about which agent to pick. The guidance for patients with cardiovascular disease in particular is big news because these antihyperglycemic agents showed such a significant cardiovascular benefit in the trials."

While the document gives a detailed algorithm of advancing therapy in patients with ASCVD, it doesn't specify a preference for a specific drug class after metformin therapy in patients without ASCVD. Instead, it provides a detailed table listing the drug-specific effects and patient factors to consider when selecting from different classes of antihyperglycemic agents (SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, thiazolidinones, sulfonylureas, and insulins). The table notes the drugs' general efficacy in diabetes, and their impact on hypoglycemia, weight gain, and cardiovascular and renal health. The table also includes the Food and Drug Administration black box warnings that are on some of these medications.



"[Providers] have a responsibility to ask if a patient is not taking certain medications because of the cost."

DR. HELLMAN

Another helpful feature is a cost comparison of antidiabetic agents, Dr. Kalyani noted. "Last year we added comprehensive cost tables for all the different insulins and noninsulins, and this year we added a second data set of cost information, to assist the provider when prescribing these agents."

The pricing information is a very important addition to this guideline, and one that clinicians will appreciate, said Richard Hellman, MD, clinical professor of medicine at the University of Missouri–Kansas City.

"In this document, ADA is urging providers of care to ask about whether the cost of their diabetes care is more than they can deal with. They present tables which compare the costs of the current blood glucose lowering agents used in the U.S., and it is plain to see that many patients, without insurance coverage, will find some of the medications unaffordable," said Dr. Hellman, a past president of AACE. "They also provide data that show half of all patients with diabetes have financial problems," and he suspects that medication costs are an important component of their financial insecurity.

The document also notes data from the 2017 National Health and Nutrition Examination Survey, which found that 10% of people with diabetes have severe food insecurity and 20% have mild food insecurity (Diabetes Educ. 2017;43:260-71. doi: 10.1177/0145721717699890).

"Another thing the document points out is that two-thirds of the patients who don't take all their medications due to cost don't tell their doctor," Dr. Hellman said. "The ADA is making the point that providers have a responsibility to ask if a patient is not taking certain medications because of the cost. We have so many better tools to manage this disease, but so many of these tools are unaffordable."

While the treatment algorithm for patients with ASCVD will likely be embraced, another new recommendation may stir the pot a bit, Dr. Hellman noted. The section on cardiovascular disease and risk management sticks to a definition of hypertension as 140/90 mm Hg or higher – a striking diversion from the new 130/80 mm Hg limit set this fall by both the American Heart Association and the American College of Cardiology.

"This difference in recommendations is very important and will be controversial," Dr. Hellman said, adding that he agrees with this clinical point.

Again, this recommendation is grounded in clinical trials, which suggest that people with diabetes don't benefit from overly strict blood pressure control. The new AHA/ACC recommendations largely drew on data from SPRINT, which was conducted in an entirely nondiabetic population. "These gave a clear signal that a lower BP target is beneficial to that group," Dr. Hellman said.

But large well-designed randomized controlled trials of intensive blood pressure lowering in people with diabetes, such as ACCORD-BP, did not demonstrate that intensive blood pressure lowering targeting a systolic less than120 mm Hg had a significant benefit on the composite primary cardiovascular endpoint.

Dr. Kalyani and Dr. Hellman had no financial disclosures. Dr. Jellinger has been a speaker for several pharmaceutical companies.

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SOURCE: Kalyani R et al. Diabetes Care. 2018;41(Suppl. 1):S86-104. doi: 10.2337/dc18-S009.

The power of flexibility is yours with **REVATIO Oral Suspension**

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Indication

REVATIO is a phosphodiesterase-5 (PDE-5) 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 PDE-5 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.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. 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.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

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Revatio® sildenafil

PP-REV-USA-0090-01

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INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (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 study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. 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-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.

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.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

MedPAC: Medicare hospital readmissions program is working

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – The Medicare Hospital Readmissions Reduction Program is working, according to an original analysis of Medicare claims data presented at a meeting of the Medicare Payment Advisory Commission.

"First, readmissions declined," MedPAC staff member Jeff Stensland, PhD, said during a congressionally mandated staff report to the commissioners. "Second, while observation stays increased, they did not fully offset the decrease in readmissions. Third, while [emergency department] visits also increased, those increases appear to largely be due to factors other than the readmission program. And fourth, in addition, all the evidence we examined suggests that the readmissions program did not result in increased mortality."

While the program is "not perfect, it has appeared to generate some benefits for patients and taxpayers," including a reduction in readmissions and patients spending less time in the hospital with "at least equal outcomes," Dr. Stensland said at the meeting.

Taxpayers benefited from a $2 billion reduction in spending on readmissions, which will "help extend the viability of the Medicare Trust Fund." He noted that improvements to the program will be discussed at future MedPAC meetings.

Not all MedPAC commissioners agreed with the staff analysis.

"It just leaves me with a slightly different conclusion, though,

"There were good things that happened with the readmission penalty [but] clearly there were other things going on."

DR. REDBERG

because I think it's really hard to know what's going on here," said Rita Redberg, MD, of the University of California, San Francisco. "It's all observational data. There are questions about temporal trends, other programs going on. I mean, clearly there were good things that happened with the readmission penalty. Hospitals started outpatient programs, pharmacists, nurse to call the patient, but then clearly there were other things going on. And some things are just not preventable, and it may have created perverse incentives not to readmit patients. We don't know."

David Nerenz, PhD, of the Henry Ford Health System, Detroit, also was not convinced the program was having an impact, noting that hospital readmissions began to decline even before the program started.

In looking at a graph presented that showed this trend, "I was impressed by the fact that the trend line started coming down all the way to the left side of the graph, and what my eye was impressed with was more just the continuation rather than a change, so I guess I feel cautious saying the program had certain effects because they certainly don't jump off the graph visually," Dr. Nerenz said. "I'm not disputing the numbers, but to say just as a clear unqualified conclusion the program reduced readmissions, I'm not so sure."

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: It is likely premature to make any firm conclusions about how effectively this program decreases unnecessary utilization of hospitals. However, it is heartening to know that it did not increase mortality. The one variable that would best control readmissions is patient education. What constitutes an emergency requiring hospital evaluation and potential admission is often not explained to the patient by you and me.

Health care gets little attention in State of the Union

BY GREGORY TWACHTMAN
Frontline Medical News

President Trump reaffirmed his campaign promise to lower prescription drug prices during his first State of the Union address – but gave no details on how he plans to do so.

"One of my greatest priorities is to reduce the price of prescription drugs," President Trump said in his Jan. 30 address to a joint session of Congress. "In many other countries, these drugs cost far less than what we pay in the United States, and it is very, very unfair. That is why I have directed my administration to make fixing the injustice of high drug prices one of my top priorities for the year."

He then emphatically stated: "Prices will come down substantially. Watch."

His words followed the confirmation of Alex Azar as Health & Human Services secretary. Mr. Azar's nomination was criticized by some who questioned whether the former president of Eli Lilly's U.S. operations could be effective at tackling the surging prices of pharmaceuticals.

President Trump also expressed his support for allowing terminally ill patients to access experimental drugs prior to Food and Drug Administration approval, the so-called right to try.

"We also believe that patients with terminal conditions, terminal illness, should have access to experimental treatment immediately that could potentially save their lives," he said. "People who are terminally ill should not have to go from country to country to seek a cure. I want to give them a chance right here at home. It's time for the Congress to give these wonderful incredible Americans the right to try."

The Senate passed a right to try bill (S. 204) in 2017 by unanimous consent, but the House has yet to act upon it.

President Trump reaffirmed his commitment to fighting the opioid epidemic and made a loose connection between it and his overall platform for immigration reform, saying that "these reforms will also support our response to the terrible crisis of opioid and drug addiction."

As far as addressing the epidemic itself, Mr. Trump said that his administration "is committed to fighting the drug epidemic and helping get treatment for those in need, for those who have been so terribly hurt. The struggle will be long and it will be difficult, but, as Americans always do, in the end we will succeed. We will prevail."

The president also commended Congress for effectively eliminating the Affordable Care Act's individual mandate that required people to have health insurance or suffer a financial penalty.

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WHITEHOUSE.GOV

President Donald J. Trump

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: As Congress nickles and dimes its way to more appropriate and affordable health care, the Presidential promises and platitudes ring somewhat hollow. There is an inherent problem with a system that spends an average of more than $10,000 per person for health care (the most for any country) but only made it to 37th place in the latest WHO Healthcare System rankings. One would think our elected officials should be able to improve on that, and yet I'm reminded of the words of George Will: "Politicians fascinate because they are such a paradox; they are an elite that accomplishes mediocrity for the public good."

Curbs on short-term health plans could be relaxed

BY JULIE APPLEBY
Kaiser Health News

Insurers will again be able to sell short-term health insurance good for up to 12 months under a proposed rule released Feb. 20 by the Trump administration that could further roil the marketplace.

"We want to open up affordable alternatives to unaffordable Affordable Care Act policies," said Health & Human Services Secretary Alex Azar. "This is one step in the direction of providing Americans health insurance options that are more affordable and more suitable to individual and family circumstances."

The proposed rule said short-term plans could add more choices to the market at lower cost and may offer broader provider networks than Affordable Care Act plans in rural areas.

But most short-term coverage requires answering a string of medical questions, and insurers can reject applicants with preexisting medical problems, which ACA plans cannot do. As a result, the proposed rule also noted that some people who switch to them from ACA coverage may see "reduced access to some services," and "increased out of pocket costs, possibly leading to financial hardship."

The directive follows an executive order issued in October to roll back restrictions put in place during the Obama administration that limited these plans to 3 months. The rule comes on the heels of Congress' approval of tax legislation that in 2019 will end the penalty for people who opt not to carry insurance coverage.

The administration also issued separate regulations Jan. 4 that would make it easier to form "association health plans," which are offered to small businesses through membership organizations.

Together, the proposed regulations and the elimination of the so-called individual mandate by Congress could further undermine the Affordable Care Act marketplace, critics say.

Seema Verma, who now heads the Centers for Medicare & Medicaid Services, which oversees the marketplaces, told reporters Feb. 20 that federal officials believe that between 100,000 and 200,000 "healthy people" now buying insurance through those federal exchanges would switch to the short-term plans, as well as others who are now uninsured.

The new rule is expected to entice younger and healthier people from the general insurance pool by allowing a range of lower-cost options that don't include all the

MS. VERMA

benefits required by the federal law – including plans that can reject people with preexisting medical conditions. Most short-term coverage excludes benefits for maternity care, preventive care, mental health services, or substance abuse treatment.

"It's deeply concerning to me, considering the tragedy in Florida and national opioid crisis, that the administration would be encouraging the sale of policies that don't have to cover mental health and substance abuse," said Kevin Lucia, a research professor and project director at Georgetown University's Health Policy Institute.

Over time, those remaining in ACA plans will increasingly be those who qualify for premium tax credit subsidies and the sick, who can't get an alternative like a short-term plan, predict Mr. Lucia and other experts. That, in turn, would drive up ACA premiums further.

"If consumers think Obamacare premiums are high today, wait until people flood into these short-term and association health plans," said industry consultant Robert Laszewski. "The Trump administration will bring rates down substantially for healthy people, but woe unto those who get a condition and have to go back into Obamacare."

If 100,000-200,000 people shift from ACA-compliant plans in 2019, this would cause "average monthly individual market premiums … to increase," the proposed rule states. That, in turn, would cause subsidies for eligible policyholders in the ACA market to rise, costing the government $96 million–$168 million.

Supporters said the rules are needed because the ACA plans have already become too costly for people who don't receive a government subsidy to help them purchase the coverage. "The current system is failing too many," said Ms. Verma.

And, many supporters don't think the change is as significant as skeptics fear.

"It simply reverts back to where the short-term plan rules were prior to Obama limiting those plans," said Christopher Condeluci, a benefits attorney who also served as tax counsel to the U.S. Senate Finance Committee. "While these plans might not be the best answer, people do need a choice, and this new proposal provides needed choice to a certain subsection of the population."

But, in their call with reporters, CMS officials said the proposed rule seeks comment on whether there are ways to guarantee renewability of the plans, which currently cannot be renewed. Instead, policyholders must reapply and answer medical questions again. The proposal also seeks comments on whether the plans should be allowed for longer than 12-month periods.

The comment period for the proposed rule runs for 60 days. Ms. Verma said CMS hopes to get final rules out "as quickly as possible," so insurers could start offering the longer duration plans.

Short-term plans had been designed as temporary coverage, lasting for a few months while, for instance, a worker is between jobs and employer-sponsored insurances. They provide some protection to those who enroll, generally paying a percentage of hospital and doctor bills after the policyholder meets a deductible.

They are generally less expensive than ACA plans, because they cover less. For example, they set annual and lifetime caps on benefits, and few cover prescription drugs.

Most require applicants to pass a medical questionnaire – and they can also exclude coverage for preexisting medical conditions.

The plans are appealing to con-

Continued on following page

Congress extends CHIP, funds opioid crisis response

BY GREGORY TWACHTMAN
Frontline Medical News

Congress, despite a second shutdown in less than a month, was able to pass a number of financial extenders to fund key health care programs.

The bipartisan spending bill (H.R. 1892), passed in the early morning hours on Feb. 9 by a 71-28 vote in the Senate (16 Republicans and 12 Democrats voted against it, and Sen. John McCain [R-Ariz.] was not present) and a 240-186 vote in the House (67 Republicans and 119 Democrats voted against and 5 representatives did not vote). President Trump signed the later that morning.

The spending bill and continuing resolution to fund the government through March 23 includes $6 billion to fund treatment for opioid addiction and other mental health issues, $2 billion in additional funding for the National Institutes of Health, and 4 additional years of funding for the Children's Health Insurance Program. The additional CHIP funding extends the program for a total of 10 years.

The funding bill also made a technical correction to the Merit-Based Incentive Payment System (MIPS) track of the Medicare Quality Payment Program. It removes Part B drug reimbursement from the MIPS payment adjustment, so any positive or negative change to physician payments based on the MIPS score will be applied only to

Continued from previous page

sumers because they are cheaper than Obamacare plans. They are also attractive to brokers, because they often pay higher commissions than ACA plans. Insurers like them because their profit margins are relatively high – and are not held to the ACA requirement that they spend at least 80 percent of premium revenue on plan members' medical care.

Extending short-term plans to a full year could be a benefit to consumers because they must pass the health questionnaire only once. Still, if a consumer develops a health condition during the contract's term, that person would likely be rejected if he or she tried to renew.

Both supporters and critics of short-term plans say consumers who do develop health problems could then sign up for an ACA plan during the next open enrollment because the ACA bars insurers from rejecting people with preexisting conditions.

"We're going to have two different markets, a Wild West frontier called short-term medical … and a high-risk pool called Obamacare," said Mr. Laszewski.

KHN senior correspondent Phil Galewitz contributed to this article. Kaiser Health News is a nonprofit news service covering health issues. It is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

physician fee schedule payments.

The bill also repeals the Independent Payment Advisory Board, a panel created by the Affordable Care Act that would have the power to slash Medicare spending under certain budget circumstances. That board was never convened.

The funding legislation also accelerates closure of the Medicare Part D "donut hole," the coverage gap in which beneficiaries must pay 100% of medication costs prior to entering catastrophic coverage.

Just over $7 billion was provided for community health centers and Medicare's therapy caps were repealed.

While the funding bill was written in the Senate with bipartisan input and received bipartisan support, Sen. Rand Paul (R-Ky.) held up votes over objections to the more than $1 trillion it will add to the nation's debt, as well as for the fact that there was no opportunity to introduce and vote on amendments, leading to an hours-long government shutdown.

There also were concerns about two issues that could have derailed the vote in the House. Democrats wanted to add language to address immigrants brought to this nation illegally as children, while some Republicans did not want to increase the federal debt.

However, there were enough votes to pass the funding legislation.

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Lung scan often not requested for new SSc patients

BY HEIDI SPLETE
Frontline Medical News

Only half of American general rheumatologists and two-thirds of global systemic sclerosis experts routinely request high-resolution CT chest scans for all their newly diagnosed systemic sclerosis (SSc) patients despite their increased risk of interstitial lung disease, according to survey data from approximately 200 clinicians.

The researchers, led by Elana J. Bernstein, MD, of Columbia University, New York, conducted the survey because of a lack of data on how often rheumatologists order high-resolution CT for their newly diagnosed patients and the absence of clinical practice guidelines that recommend screening for interstitial lung disease (ILD) in SSc.

In a study published in Arthritis & Rheumatology, the researchers surveyed 676 American College of Rheumatology members and 356 global experts on systemic sclerosis; of these, 76 ACR general rheumatologists and 135 SSc experts responded. The use of high-resolution CT varied widely by country or region: 0 of 5 respondents from Australia, 2 of 6 from Canada, 28 of 47 from the United States, 45 of 57 from Europe, 4 of 5 from Asia, and 7 of 7 from Latin America.

A lack of data on how often rheumatologists order high-resolution CT for their newly diagnosed patients and absence of clinical practice guidelines prompted the survey.

The researchers also found little consensus on indications for high-resolution CT in SSc patients. Among the SSc experts who do not routinely obtain screening high-resolution CTs in their SSc patients, 81% said they would request one for dyspnea on exertion, 74% would request one for an abnormal forced vital capacity less than 80% of predicted, and 52% would request one for an abnormal diffusion capacity for carbon monoxide less than 80% predicted.

A significant limitation of the study was the low response rate, and more research is needed on the clinical impact of high-resolution CT screening for ILD in SSc patients, the researchers noted. However, the results highlight the need for a clinical practice guideline to create a more consistent approach to identifying ILD in these patients, they said.

The researchers had no financial conflicts to disclose. Dr. Bernstein was supported by a Rheumatology Research Foundation Scientist Development Award, and two of her colleagues were funded in part by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Heart, Lung, and Blood Institute.

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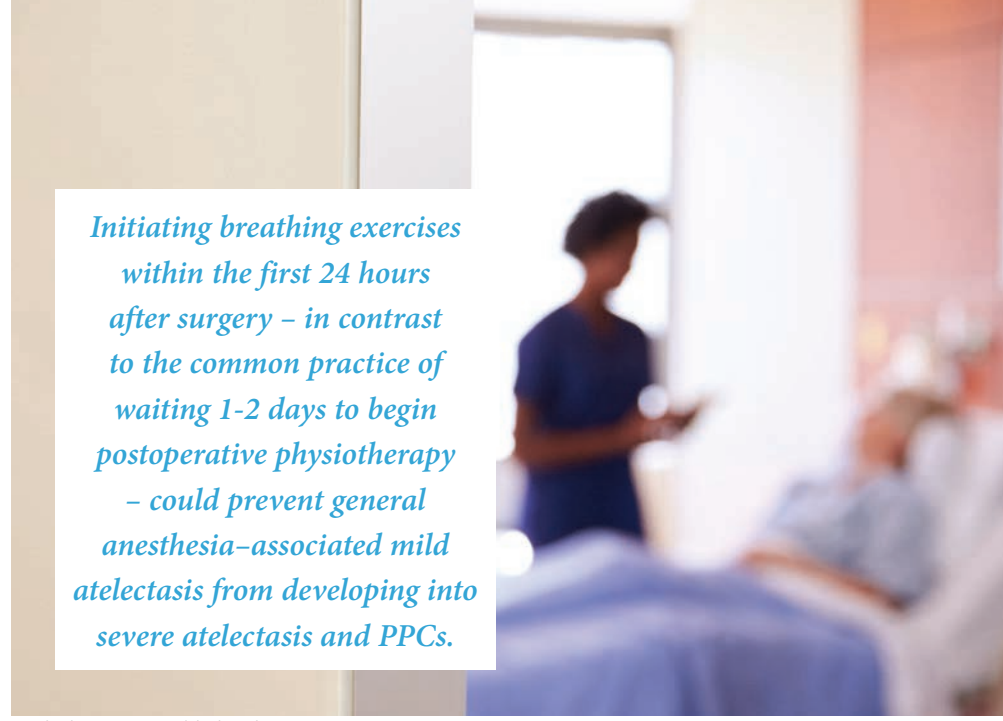
SOURCE: Bernstein E et al. Arthritis Rheumatol. 2018 Feb 9. doi: 10.1002/art.40441.

Preop physiotherapy training cuts risk of postop pulmonary complications



Initiating breathing exercises within the first 24 hours after surgery – in contrast to the common practice of waiting 1-2 days to begin postoperative physiotherapy – could prevent general anesthesia–associated mild atelectasis from developing into severe atelectasis and PPCs.

monkeybusinessimages/Thinkstock

BY TERRY L. KAMPS
Frontline Medical News

A single 30-minute coaching session with a physiotherapist within 6 weeks of major upper abdominal surgery significantly reduced postoperative pulmonary complications (PPC), according to the results of a prospective trial.

Ianthe Boden and her colleagues recruited 441 eligible adults scheduled for elective major upper abdominal surgery to participate in the prospective, multicenter, double-blinded, controlled superiority study to assess whether PPC outcomes were affected by preoperative physiotherapy. Consecutive participants were obtained from outpatient preadmission assessment clinics during June 2013 to August 2015; they were assigned randomly in a 1:1 ratio to the control (219) or intervention (222) groups. The median patient age was 68 years for the control and 63 for the intervention group, and each group was composed of 31% women.

As a component of accepted standard care, all participants in the trial were provided a booklet with written and pictorial information on occurrence of PPCs, along with prevention strategies that consisted of exercises involving early ambulation and prescribed breathing, according to Ms. Boden of Launceston (Tasmania) General Hospital, Australia, and her colleagues.

Immediately after receiving the booklets, however, participants in the intervention group were also given an added 30-minute education and training session by preoperative physiotherapists. This instruction covered factors contributing to PPC occurrence, strategies to help prevention it, and three coached repetitions of breathing exercises. Emphasis was placed on initiating prescribed breathing exercises upon regaining postoperative consciousness and continuing them every hour until the patients were fully ambulatory.

The primary outcome was evaluated by masked assessors using the Melbourne group score criteria to determine PPC incidence within 14 postoperative days or by the time of hospital discharge, whichever was sooner. Nine participants, four from the intervention and five from the control group, withdrew from the study. Of the total remaining 432 participants, 85 (20%) had a documented PPC incident, including hospital-acquired pneumonia, within the specified postoperative time frame, as reported in the BMJ.

Results showed that the physiotherapy group had significantly fewer PPC occurrences (27/218, 12%) than did the control group (58/214, 27%). The calculated absolute risk reduction was 15% (P less than .001). Adjustment for three of the prespecified covariates (age, respiratory comorbidity, and surgical procedure) showed PPC incidence remained halved (hazard ratio, 0.48; $P = .001$) for the intervention group with a number needed to treat of 7 (95% confidence interval, 5-14).

Ms. Boden and her colleagues proposed that the timing for patients to begin breathing exercises after major open upper abdominal surgery could be critical in reducing PPC incidence. Initiating breathing exercises within the first 24 hours after surgery – in contrast to the common practice of waiting 1-2 days to begin postoperative physiotherapy – could prevent general anesthesia–associated mild atelectasis from developing into severe atelectasis and PPCs.

The authors reported that they received grants from the Clifford Craig Foundation; the University of Tasmania, Hobart, Australia; and the Waitemata District Health Board in Auckland, New Zealand.

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SOURCE: Boden I et al. BMJ. 2018. doi: 10.1136/bmj.j5916.

DMARDs may hamper pneumococcal vaccine response

BY MICHELE G. SULLIVAN
Frontline Medical News

Patients taking disease-modifying antirheumatic medications for systemic sclerosis appear to have a decreased response to pneumococcal vaccines, a Swedish study has determined.

Those not taking disease-modifying antirheumatic medications (DMARDs), however, had a normal immune response, suggesting that it's the immunomodulating medications, not the disease itself, that is affecting antibody levels, Roger Hesselstrand, MD, of Lund (Sweden) University and his colleagues reported online in Rheumatology.

"The currently recommended prime-boost vaccination strategy using a dose of PCV13 [13-valent pneumococcal conjugate vaccine] followed by a dose of PPV23 [23-valent pneumococcal polysaccharide vaccine] might be a possible way of enhancing the vaccine immunogenicity in immunosuppressed patients," the authors wrote.

The study comprised 44 subjects with systemic sclerosis, 12 of whom were taking a DMARD (mycophenolate mofetil, azathioprine, or hydroxychloroquine), and 49 healthy controls; all underwent pneumococcal vaccination. The first 13 got a single dose of PPV23 intramuscularly. PCV13 was then licensed for adults in Sweden, and the remaining 31 patients received this vaccine. The primary outcome was 6-week change from baseline in the level of pneumococcal IgG to *Streptococcus pneumoniae* serotypes 23F and 6B.

Both vaccines were safe and well-tolerated by all patients, including those taking a DMARD.

Before vaccination, antibody levels to both serotypes were similar between the groups. After vaccination, antibody levels for both serotypes increased significantly in systemic sclerosis patients not taking a DMARD and in controls. However, patients taking a DMARD mounted only an adequate response to serotype 6B.

"Compared with [patients] without DMARDs, patients [taking DMARDs] had lower postvaccination antibody levels, [lower] mean fold increase in antibody concentration, and [a lower] percentage of patients reaching putative protective antibody levels for both serotypes," the authors wrote.

There were fewer responders among those taking DMARDs, whether they received the PCV13 or the PPV23 vaccine. An increase from prevaccination antibody levels of at least twofold occurred in fewer patients taking DMARDs than did in patients not taking DMARDs and in controls, regardless of vaccine type (PPV23, 50% vs. about 55% and 50%, respectively; PCV13, about 17% vs. 57% and 100%, respectively).

"We demonstrated that the antibody response ... as well as functionality of antibodies in [systemic sclerosis] patients not receiving DMARDs was as good as in controls regardless of vaccine type," the investigators concluded. "Systemic sclerosis patients treated with DMARDs, however, had lower proportion of patients with positive antibody response, although the functionality of the antibodies was preserved."

None of the authors had conflicts of interest to disclose.

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SOURCE: Hesselstrand R et al. Rheumatology [Oxford]. 2018 Jan 8. doi: 10.1093/rheumatology/kex471.

Status asthmaticus risk increased with IV labetalol

BY KARI OAKES
Frontline Medical News

DALLAS – A maternal death occurred at Columbia University Medical Center after a patient with asthma was given intravenous labetalol, prompting a study that found an elevated risk of status asthmaticus associated with intravenous labetalol administration but not with the uterotonic carboprost.

"Overall, 71.4% of status asthmaticus cases occurred among women receiving IV labetalol," said Whitney A. Booker, MD, speaking about the findings at the meeting sponsored by the Society for Maternal-Fetal Medicine.

Dr. Booker and her colleagues used a national database to determine that the incidence of status asthmaticus in patients with asthma was almost four times higher when patients with preeclampsia were given IV labetalol: The rate was 6.5 per 1,000 patients given IV labetalol, compared with 1.7 per 1,000 for patients who received other antihypertensives.

The risk of status asthmaticus didn't reach statistical significance when women with asthma who experienced postpartum hemorrhage were given carboprost, compared with other uterotonics (3.1 vs. 1.0 per 1,000 patients; $P = .56$).

Kari Oakes/Frontline Medical News

Dr. Whitney A. Booker: "Overall, 71.4% of status asthmaticus cases occurred among women receiving IV labetalol."

"Some regularly used medications in obstetrics can trigger bronchospasm," said Dr. Booker; the American College of Obstetricians and Gynecologists lists both carboprost and labetalol as contraindicated for use in patients with asthma because of the potential for bronchospasm with each medication.

However, she said, data on the actual risk of bronchospasm when these medications are used in obstetric patients are limited.

The retrospective cohort study constructed by Dr. Booker and her colleagues at Columbia University Medical Center's department of obstetrics and gynecology tapped 10 years' worth of data from a large inpatient drug utilization database.

Dr. Booker, a maternal-fetal medicine fellow, said that patients were included if they were admitted for delivery and had a diagnosis of preeclampsia or postpartum hemorrhage. Of the 5.7 million hospitalizations from 2006 to 2015, 2.5% were for postpartum hemorrhage, and 4.2% for preeclampsia.

Of the patients with hemorrhage, 5,633 had a prior history of asthma, as did 12,486 of the patients with preeclampsia. In both groups, a little more than a third of patients were younger than 25 years, and about a quarter were black. Half were on Medicaid, and most were in urban areas and cared for in a teaching hospital.

The first outcome that Dr. Booker and her colleagues looked at was how practice patterns for postpartum hemorrhage varied according to whether patients had asthma; to do so, they looked at receipt of carboprost, misoprostol, and methylergonovine. A similar analysis was performed for the second outcome addressing patients with preeclampsia, in which investigators examined the use of both IV and oral labetalol, hydralazine, and nifedipine. For this and the hemorrhage outcome, the investigators performed multivariable analysis, with receipt of carboprost and IV labetalol as the outcomes of interest.

Finally, the investigators assessed the risk of status asthmaticus by comparing receipt of either carboprost (for postpartum hemorrhage) or IV labetalol (for preeclampsia) with receipt of the other medications to treat these conditions.

They found that overall 11.4% of patients with asthma and 18% of patients without asthma received carboprost to treat postpartum hemorrhage, which makes for an adjusted risk model of 0.68 (95% confidence interval, 0.62-0.74) for receipt of carboprost for patients with asthma versus those without.

However, the pattern was different for IV labetalol: 18.5% of patients with asthma and preeclampsia received labetalol, compared with 16.7% of those without asthma. After statistical adjustment, patients with asthma had a risk ratio of 0.93 (95% CI, 0.90-0.97) for receiving IV labetalol for preeclampsia.

The analysis showed that pregnant patients with asthma were less likely to be given carboprost than labetalol, although the actual risk of status asthmaticus was higher when patients with asthma received labetalol than when they received carboprost.

"Given similar theoretical risks, obstetric providers currently administer carboprost differently than labetalol. ... Obstetricians should proceed with caution prior to giving labetalol to patients with underlying asthma," said Dr. Booker.

Dr. Booker and her colleagues reported that they had no conflicts of interest.

The study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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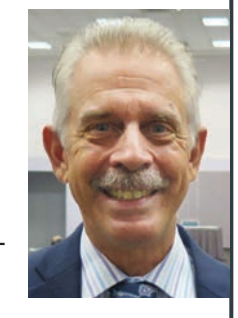
SOURCE: Booker WA et al. Am J Obstet Gynecol. 2018 Jan;218:S51.

VIEW ON THE NEWS



Daniel Ouellette, MD, FCCP, comments: I teach my residents and fellows the "rule of thirds": One-third of asthma patients get worse during pregnancy; one-third get better; one-third stay the same." Asthma during pregnancy remains a challenging problem, with physicians striving to treat two complicated patients (mother and child) safely and effectively. We learn now that the use of labetalol, a beta-blocker, to treat preeclampsia in pregnant asthma patients may be associated with an increased incidence of status asthmaticus. Until we learn more about these occurrences, we should use great caution in treating pregnant asthma patients with labetalol and other beta-blockers.

Ceftazidime-avibactam equals meropenem for nosocomial pneumonia

BY SHANNON AYMES
Frontline Medical News

Ceftazidime-avibactam was noninferior to meropenem for nosocomial pneumonia including ventilator-associated pneumonia from gram-negative organisms, results from the REPROVE trial demonstrated.

Nosocomial or hospital-acquired pneumonia is a common hospital-acquired infection associated with increased cost and mortality. Further, nosocomial pneumonia is associated with gram-negative pathogens such as *Pseudomonas aeruginosa* and Enterobacteriaceae that may carry extended-spectrum beta-lactamases and carbapenemase, thereby limiting the treatment options. However, ceftazidime-avibactam has both antipseudomonal and extended beta-lactamase coverage for multidrug-resistant gram-negative infections, and may provide an alternative to meropenem.

Antoni Torres, MD, of the University of Barcelona and his colleagues sought to compare the safety and efficacy of ceftazidime-avibactam to meropenem in patients with nosocomial and ventilator-associated pneumonia. The REPROVE study was a phase 3, double-blind, noninferiority trial performed at 136 centers in 23 countries. Patients were randomly assigned 1:1 to receive either ceftazidime-avibactam (500-2,000 mg every 8 hours) or meropenem (1,000 mg every 8 hours) with adjustment as needed for renal function.

Participants included in the study were 18-90 years of age with nosocomial pneumonia as evidenced by pneumonia 48 hours or more after admission or within 7 days after discharge from an inpatient facility. Patients with ventilator-associated pneumonia had lung infection within 48 hours of intubation and mechanical ventilation. Sputum culture and gram stains were obtained within 48 hours before randomization, and patients were excluded for evidence of gram positive–only pathogens or those not expected to respond to meropenem or ceftazidime-avibactam.

The study involved a safety population (808 patients), a clinically modified intention-to-treat population (726), and a clinically evaluable population (527). The intention-to-treat population demonstrated a predominance of *Klebsiella pneumoniae* (37%), and *Pseudomonas aeruginosa* (30%); 28% of the intention-to-treat population were identified as not susceptible to ceftazidime.

Overall, the clinically modified intention-to-treat group demonstrated a clinical cure rate of 68.8% (245/356) in the ceftazidime-avibactam and 73.0% (270/370) for the meropenem group (difference, –4.2%; 95% confidence interval, –10.8 to 2.5). The evaluable population demonstrated a clinical cure rate of 77.4% (199/257) in the ceftazidime-avibactam group and 78.1% (211/270) in the meropenem group (–0.7%; 95% CI, –7.9 to 6.4).

The all-cause mortality rate was similar between groups at the test-of-cure date and at day 28. The clinically modified intention-to-treat population demonstrated a mortality of 8.1% vs. 6.8% at the test-of-cure date and 8.4% vs. 7.3% at day 28 for ceftazidime-avibactam and meropenem, respectively.

Adverse events were noted in 75% vs. 74% of patients in the ceftazidime-avibactam groups and meropenem groups, respectively. Most adverse events were rated as mild to moderate and deemed likely unrelated to the treatment.

However, serious adverse events occurred in 19% (n = 75) in the ceftazidime-avibactam group and 13% (n = 54) in the meropenem group. Four serious adverse events were thought to be possibly related to the study drug ceftazidime-avibactam and included diarrhea, acute coronary syndrome, subacute hepatic failure, and abnormal liver function test results. The authors noted the adverse events in the trial were consistent and detected no new safety concerns for ceftazidime-avibactam.

The study was initially funded by AstraZeneca until the rights to ceftazidime-avibactam were acquired by Pfizer. Multiple authors reported financial relationships with AstraZeneca including grant funding, employment, and shareholding.

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SOURCE: Torres A et al. Lancet Infect Dis. 2017. doi: 10.1016/S1473-3099(17)30747-8.

California tops state tobacco prevention spending

BY RICHARD FRANKI
Frontline Medical News

California will spend almost as much money on tobacco prevention and smoking cessation as the other states combined in 2018, putting it closest to the spending level recommended for each state by the Centers for Disease Control and Prevention, according to a report on the effects of the 1998 tobacco settlement.

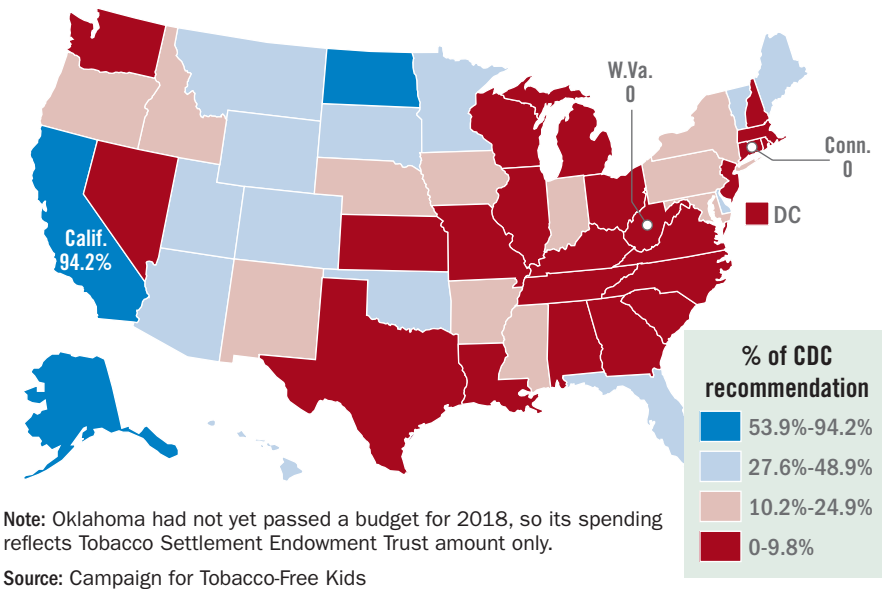
The Golden State has budgeted almost $328 million for tobacco prevention and cessation this year, which amounts to just over 45% of all states' total spending of $722 million and 94% of the CDC's recommendation of $348 million. Alaska is the only state close to that in terms of the CDC-recommended level, reaching 93% of its spending target of $10.2 million. In third place for recommended spending is North Dakota, which has budgeted $5.3 million for 2018, or 54% of its CDC target, the report said.

"Broken Promises to Our Children: A State-by-State Look at the 1998 Tobacco Settlement 19 Years Later" was released by the Campaign for Tobacco-Free Kids, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Robert Wood Johnson Foundation, Americans for Nonsmokers' Rights, and Truth Initiative.

The report also pointed out that the $722 million the states will spend this year amounts to just 2.6% of the $27.5 billion they will collect from the 1998 tobacco settlement and tobacco taxes.

As for actual spending, Florida is second behind California with almost $69 million – 35% of its CDC-recommended level – budgeted for tobacco prevention and smoking cessation in 2018, and New York is third at just over $39 million, which is 19.4% of the CDC recommendation.

State spending on tobacco prevention for fiscal year 2018



Note: Oklahoma had not yet passed a budget for 2018, so its spending reflects Tobacco Settlement Endowment Trust amount only.

Source: Campaign for Tobacco-Free Kids

Two states – Connecticut and West Virginia – will spend no money on such programs this year, the report noted.

The CDC has said that all states combined should be spending $3.3 billion for the year on prevention and cessation efforts, which is about 4.5 times higher than actual budgeted spending.

The report also pointed out that the $722 million the states will spend this year amounts to just 2.6% of the $27.5 billion they will collect from the 1998 tobacco settlement and tobacco taxes. By comparison, the report cited data from the Federal Trade Commission showing that the tobacco companies spent $8.9 billion on marketing in 2015.

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States judged on smoking cessation services

BY RICHARD FRANKI
Frontline Medical News

Minnesota and South Carolina are at the top of the class for access to smoking cessation services, but a new report card from the American Lung Association shows that the treatment coverage in most states earned barely passable or failing grades. In fact, 31 states received either a D (11 states) or an F (20 states) on the grading system. There were also 11 C's and 7 B's to go along with the two A's, the ALA said in "State of Tobacco Control 2018."

The cessation coverage grades are based on a 70-point total, with a maximum of 40 points awarded for a state's Medicaid coverage (smoking rates are much higher and incomes lower among Medicaid enrollees than the general population), 20 points for the investment per smoker in the state's phone quitline, and 10 points for state employee health plan coverage.

Minnesota received 66 points and South Carolina earned 63 after a 5-point deduction for not expanding Medicaid up to Affordable Care Act standards. The highest-finishing states with B's were Vermont with 62 points and Maine with 61, and the lowest total score was the 23 points earned by Virginia and Washington, although Washington's grade did not include the state employee category since the state did not provide data on its plan, the ALA noted.

The Department of Health & Human Services recommends that tobacco cessation coverage include the use of five nicotine-replacement therapies, bupropion and vanenicline, and three types of counseling, the report said.

The Department of Health & Human Services recommends that tobacco cessation coverage include the use of five nicotine-replacement therapies (gum, patch, lozenge, nasal spray, inhaler), bupropion and varenicline (nonnicotine medications), and three types of counseling (individual, group, and phone), the report said.

"It's imperative that all state Medicaid programs cover a comprehensive tobacco cessation benefit, with no barriers, to help smokers quit, including all seven [Food and Drug Administration]–approved medications and three forms of counseling for Medicaid enrollees. In 2017, only Kentucky, Missouri, and South Carolina provided this coverage," wrote Harold P. Wimmer, national president and CEO of the ALA.

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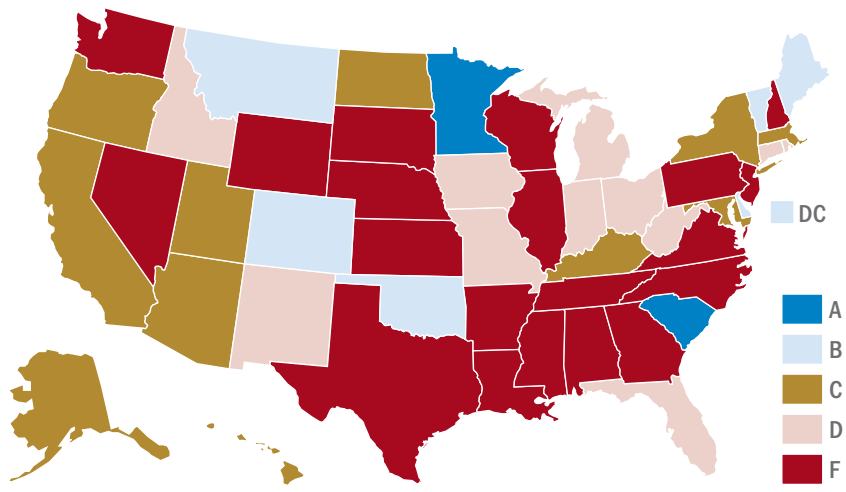
States' access to smoking cessation services graded



Note: The grading system covers three areas: Medicaid coverage, state employee health plan coverage, and investment per smoker each state makes in its phone quitline.

Source: American Lung Association

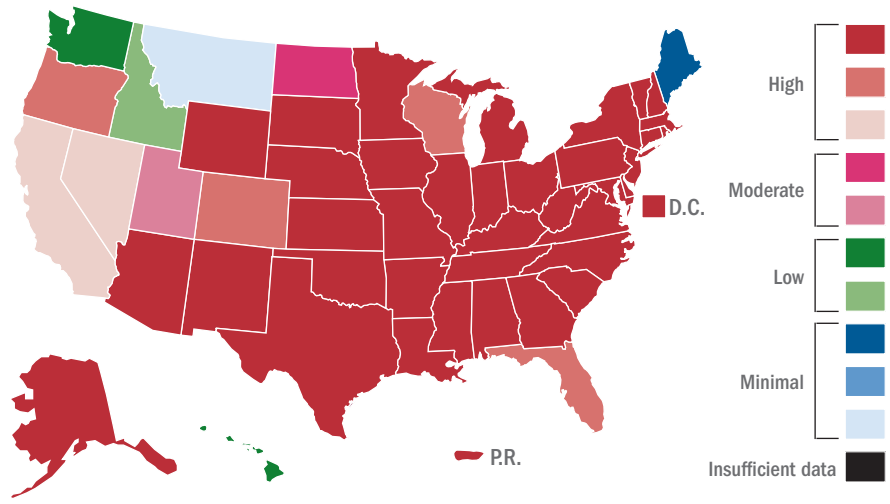
Flu increase may be slowing

BY RICHARD FRANKI
Frontline Medical News

A bit of revisionist history has outpatient influenza activity at a lower level than was reported last week, even though it hasn't dropped.

The proportion of outpatient visits for influenza-like illness (ILI) for the week ending Feb. 10 was 7.5%, according to the Centers for Disease Control. That is lower than the 7.7% previously reported for the week ending Feb. 3, which would seem to be a drop, but the CDC also has revised that earlier number to 7.5%, so there is no change. (This is not the first time an earlier ILI level has been retroactively lowered: The figure reported for the week ending Jan. 13 was revised in the following report from 6.3% down to 6.0%.)

Influenza-like illness activity level, week ending Feb. 10, 2018



Note: Based on data from the U.S. Outpatient Influenza-like Illness Surveillance Network.
Source: Centers for Disease Control and Prevention

These two consecutive 7.5%'s mean that ILI activity for the 2017-2018 season has not quite matched that of the pandemic in 2009, which hit 7.7% and also suggests that outpatient visits may have finally peaked. That is supported by a slight reduction in the number of states at the highest level of ILI activity, which went from 41 down to 39, although the number in the "high" range (8-10) on the CDC's 1-10 scale went up from 44 to 45, according to data from the CDC's Outpatient Influenza-like Illness Surveillance Network.

Hospital visits, however, continue to rise at record levels. The cumulative rate for the week ending Feb. 10 was 67.9 visits per 100,000 population, which is higher than the same week for the 2014-2015 (52.9 per 100,000) when flu hospitalizations for the season hit a high of 710,000. Flu-related pediatric deaths also went up, with 22 new reports; this brings the total to 84 for the 2017-2018 season.

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New device cuts postoperative pulmonary complications

BY ANDREW D. BOWSER
Frontline Medical News


OLLEGA/THINKSTOCK

SAN ANTONIO – A device that combines lung expansion, mucus clearance, and aerosol delivery appears to reduce postoperative pulmonary complications, according to results of a nonrandomized study including high-risk patients undergoing elective surgical procedures.

"For certain types of surgical procedures, this therapy (MetaNeb, Hill-Rom) may provide a benefit for high-risk patients in terms of reducing their pulmonary complications and their hospital stay," said Toan Huynh, MD, lead investigator and director of trauma research at Carolinas HealthCare System, Charlotte, N.C., at the Critical Care Congress sponsored by the Society for Critical Care Medicine.

Currently, aggressive management of high-risk patients with strategies such as optimal analgesia, early ambulation, secretion mobilization, and lung expansion are used to try to reduce the incidence of postoperative pulmonary complications, noted Dr. Huynh, in an interview.

In this study, Dr. Huynh and his colleagues from the University of Pennsylvania, Philadelphia, and the Lahey Hospital & Medical Center, Burlington, Mass., sought to evaluate the efficacy of the MetaNeb system, which delivers continuous high-frequency oscillation, continuous positive expiratory pressure, and in-line aerosol flow in one combined unit. To estimate usual postoperative pulmonary complication rates, they first queried CPT and ICD-9-CM codes to identify a total of 210 patients who had undergone thoracic, upper-abdominal, or aortic open surgical procedures. Then, in the second stage of the study, the investigators prospectively enrolled 209 subjects who underwent those types of surgery with the MetaNeb system in addition to a standard postoperative respiratory regimen. All patients were high risk as defined by having either an American Society of Anesthesiologists classification of at least 3 or an ASA classification of 2 along with one or more comorbidities, such as COPD or recent smoking history.

Among the patients managed with MetaNeb, 33 (15.8%) experienced one or more pulmonary complications, compared with 48 (22.9%) in the retrospective cohort ($P = 0.06$). For intubated patients, at least one complication was seen in 22 patients (36.7%) in the MetaNeb group, compared with 37 (69.8%) in the comparison group (P less than .05). Time on mechanical ventilation was 8.5 hours in the MetaNeb group versus 23.7 hours in the comparison group (P less than .05).

Use of the device was also associated with decreased length of hospital stay, but the difference between lengths of stay was not statistically significant. Hospital length of stay was 6.8 days in the MetaNeb versus 8.4 days in the comparison groups.

"In the current day and age of value-based health care, I think any kind of reduction in expenditure related to health care costs would be compelling for clinicians," Dr. Huynh said in the interview.

Further study may be needed to better define the role of the combined modality system in clinical practice, according to Dr. Huynh.

"This is sort of a 'before and after' nonrandomized trial," Dr. Huynh explained. "I think, ideally, if we can do a truly controlled, randomized trial, that will be much more powerful."

The study was sponsored by Hill-Rom, which manufactures the device under study. Dr. Huynh said he and coinvestigators had no financial conflicts related to the research.

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SOURCE: Huynh T et al. Critical Care Congress, Abstract 17.

Birth cohort affected 2015-2016 flu vaccine

BY BIANCA NOGRADY
Frontline Medical News

The influenza vaccine introduced in 2009 showed reduced effectiveness during the 2015-2016 influenza season, but only in adults born between 1958 and 1979, according to an analysis published online in the Journal of Infectious Diseases.

Using the Influenza Vaccine Effectiveness Network, researchers analyzed data from 2,115 patients with medically attended acute respiratory illness who tested positive for A(H1N1)pdm09 influenza virus, and 14,696 patients who tested negative for the influenza virus, from 2010-2011 to 2015-2016 (excluding the 2014-2015 influenza season).

Overall, 48% of the influenza virus–negative patients and 28% of the virus-positive patients had received at least one dose of the seasonal inactivated influenza vaccine more than 2 weeks before they fell ill.

However, the vaccine, which was based on the A/California/07/2009 strain of the A(H1N1) pdm09 virus, was only 47% effective during the 2015-2016 season, compared with 61% effectiveness during the 2010-2011 season through to the 2013-2014 season.

When researchers looked at vaccine effectiveness by birth cohort, they found that one particular cohort – individuals born between 1958 and 1979 – showed a significantly reduced vaccine effectiveness (22%) during the 2015-2016 season. By comparison, vaccine effectiveness in this cohort was 61% during the 2010-2013 seasons, and 56% during the 2013-2014 season.

When this birth cohort was excluded from analysis of the 2015-2016 season, the overall vaccine effectiveness for that season was 61%.

While the vaccine was based on an early reference strain of A(H1N1)pdm09, the virus itself later acquired mutations in the hemagglutinin gene, leading to the emergence of new genetic clades, including 6B, which dominated in the 2013-2014 influenza season, and 6B.1, which dominated in 2015-2016.

"Limited serologic data suggest that some adults born during 1958-1979 (age range in 2015-2016, 36-57 years) have decreased antibody titers against A(H1N1)pdm09 group 6B and 6B.1 viruses," wrote Brendan Flannery, PhD, from the Centers for Disease Control and Prevention, and his coauthors.

They suggested that individuals in this cohort may have been immunologically primed with A/USSR/90/1977-like viruses, which were the first group of A(H1N1) viruses that this cohort would have been exposed to. A(H1N1) strains didn't circulate between 1958 and 1977. Vaccination with A(H1N1)pdm09 viruses may have induced antibodies against shared antigenic components found on early versions of A(H1N1)pdm09.

"Limited serologic data suggest that some adults born during 1958-1979 (age range in 2015-2016, 36-57 years) have decreased antibody titers against A(H1N1) pdm09 group 6B and 6B.1 viruses."

If these shared antigenic epitopes were then altered in the later 6B and 6B.1 viruses, that might account for decreased antibody titers in this age group.

"Replacement of the A/California/07/2009 (H1N1)pdm09 vaccine reference strain with A/Michigan/45/2015 (group 6B.1) should lead to improved [vaccine effectiveness] against circulating A(H1N1)pdm09 viruses," the researchers noted.

The study was supported by the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Center for Advancing Translational Sciences. Eight authors declared funding, grants, and consultancies with the pharmaceutical industry, with five also declaring funding from the CDC.

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SOURCE: Flannery B et al. J Infect Dis. 2018 Jan 18. doi: 10.1093/infdis/jix634.

VIEW ON THE NEWS

Early influenza encounters could influence vaccine response

This study proposes that influenza virus strains encountered early in life focus the immune response to later infection or vaccination on shared epitopes between the early and later strains. Supporting this hypothesis is evidence from other studies showing that 60% of the serological response to inactivated influenza vaccines is the result of boosting pre-existing antibodies, rather than the creation of new, vaccine-induced antibodies.

However there are also some flaws to this argument, and we should be careful to avoid confirmation bias. For example, the reduction in effectiveness of vaccines against A(H1N1) has been observed in North America, where this study is located, but to a lesser extent in studies conducted in other regions. Reductions in vaccine effectiveness have also been observed in other birth cohorts and during other influenza seasons.

That aside, accumulating evidence suggests that the vaccine strain be updated from A/California/7/2009 to A/Michigan/45/2015 (a clade 6B.1 strain) for the 2016-2017 influenza seasons.

Allen C. Cheng, PhD, is from the School of Public Health and Preventive Medicine at Monash University, Melbourne, and Kanta Subbarao, MBBS, is from the World Health Organization Collaborating Centre for Reference and Research on Influenza and the Peter Doherty Institute for Infection and Immunity, Australia. These comments are taken from an accompanying editorial (J Infect Dis. 2018, Jan 18. doi: 10.1093/infdis/jix635). *The authors declared support from the Australian Department of Health and the Australian National Health and Medical Research Council. No conflicts of interest were declared.*

Drug combo indicated for bacterial pneumonia

BY CHRISTOPHER PALMER
Frontline Medical News

The Food and Drug Administration has approved expanding the indication for the drug combination of ceftazidime and avibactam (Avycaz) to include hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults.

Specifically, the approved indication is for infections caused by certain gram-negative bacteria – some of which are increasingly resistant to available antibiotics – including, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*.

There have not been new treatment options for HABP/VABP caused by Gram-negative bacteria in more than 15 years, according to Allergan, the drug's manufacturer.

The approval of the expanded indication was based on data from the phase 3, multinational, double-blind REPROVE trial. The study showed that ceftazidime/avibactam was noninferior to meropenem with respect to 28-day all-cause mortality.

This is the third approved indication for ceftazidime/avibactam; the other two indications are for complicated intra-abdominal infections (in combination with metronidazole) and for complicated urinary tract infections.

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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]

The majority of FEV_1 improvement occurred at:

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

SYMBICORT 160/4.5 for reducing COPD exacerbations

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REDUCTION IN COPD EXACERBATIONS

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

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

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

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

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

Study Designs

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

Comparator Arms in the SUN Study

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

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

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

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

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

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

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

Exacerbation Definitions

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

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

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

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

A reassuring sense of control

IMPORTANT SAFETY INFORMATION (CONT'D)

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

INDICATIONS

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

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

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

AstraZeneca

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

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

INDICATIONS AND USAGE

Treatment of Asthma

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

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

Important Limitations of Use:

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

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

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

Important Limitations of Use:

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

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

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

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

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

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

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

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

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

Salmeterol Multicenter Asthma Research Trial (SMART)

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

Formoterol Monotherapy Studies

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

Deterioration of Disease and Acute Episodes

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

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

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

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

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

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

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

Pneumonia and Other Lower Respiratory Tract Infections

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

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

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

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

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

Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

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

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

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

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

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

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

Effect on Growth

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

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

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

LABA use may result in the following:

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

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

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

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

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

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

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

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

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

Pediatric Patients 6 to Less than 12 Years of Age

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

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

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

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

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

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

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

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

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.
Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

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

Inhibitors of Cytochrome P4503A4

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

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

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

OVERDOSAGE

SYMBICORT

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

Budesonide

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

Formoterol

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

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

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Turning Up the Heat on ICU Burnout

BY CURTIS N. SESSLER, MD, FCCP

The work of critical care clinicians can create a perfect storm for emotional exhaustion, depersonalization, and reduced self-efficacy – widely known as burnout. Burnout is occurring in record numbers among physicians in general – more than twice as frequently as for non-health-care workers – and intensivists top the chart. Clinicians from all specialties in medicine today experience the frustrations of workplace chaos and loss of control, displacement of meaningful work with menial work, and ever increasing documentation requirements and electronic health record challenges – all contributing to burnout. Intensivists and other ICU professionals, such as advanced practice providers and nurses, however, experience the added challenge of working in a highly stressful environment characterized by fast-paced high-stakes decision making, long and irregular hours, and end-of-life scenarios often clouded by moral distress. These and other drivers contribute to high rates of burnout.

DR. CURTIS N. SESSLER

Being burned out takes its toll on health-care workers, contributing to psychological and physical manifestations, alcohol or substance abuse, posttraumatic stress disorder, and even suicidal ideation. Additionally, burnout carries important negative consequences for the organization and directly to the patient, including higher rates of employee turnover, lower quality of work, more medical errors, and reduced patient satisfaction. Unfortunately, burnout rates continue to rise with alarming speed.

Fortunately, there is increasing attention paid to the magnitude and potential impact of burnout, compelling important organizations to highlight the problem and assist clinicians in combating burnout and its consequences. For example, the National Academy of Medicine (NAM) has convened an Action Collaborative on Clinician Well-Being and Resilience and invited more than 100 organizations to publish their statement of commitment to improve clinician well-being and reduce clinician burnout (https://nam.edu/initiatives/clinician-resilience-and-well-being/). The American Medical Association (AMA) has developed modules and tools to assist clinicians and administrators in taking important steps to prevent burnout (https://www.stepsforward.org/modules/physician-burnout).

CHEST has been an active participant in addressing burnout in ICU professionals, including in an important partnership with the American Association of Critical-Care Nurses (AACN), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM) - the Critical Care Societies Collaborative (CCSC). The CCSC, whose members include greater than 150,000 critical care professionals in the United States, has established a principle goal of mitigating ICU burnout (#StopICUBurnout). One of the first CCSC efforts was to publish a white paper simultaneously in all four journals of the CCSC professional societies that provides the rationale and direction for a "call for action" to tackle ICU burnout (Moss M, Good VS, Gozal D, Kleinpell R, Sessler CN. Burnout syndrome in critical care health care professionals: A call for action. *Chest.* 2016;150[1]:17). Recently, the CCSC sponsored a National Summit on the Prevention and Management of Burnout in the ICU (http://ccsconline.org/optimizing-the-workforce/burnout). Fifty-five invited participants brought wide ranging expertise and substantial enthusiasm to the task of deconstructing ICU burnout and identifying knowledge gaps and future directions. Areas of focused discussion included factors influencing burnout, identifying individuals with burnout, the value of organizational and individual interventions to prevent and manage burnout, and translation of these discussions into a research agenda. *CHEST* and the CCSC are committed to the goals of enhancing clinician well-being and eliminating burnout in the ICU.

Get Ready for CHEST 2018 in San Antonio

Have you been thinking about how great of a time you had at CHEST 2017? Or, perhaps you weren't able to make it to CHEST 2017 and are looking forward to attending CHEST 2018? Well, we'd be happy to have you attend the annual meeting in sunny San Antonio, Texas, this fall. CHEST 2018 will occur earlier this year, from October 6-10, and we've got a few ways you can get involved leading up to the meeting.

CHEST 2018 Moderators

If you do not have original research to share, but believe you are qualified to moderate sessions, we have an opportunity for you! Moderating will take place on-site in San Antonio, and moderators will be recognized in the CHEST 2018 program and will receive a reduced registration rate to the meeting. See chestmeeting.chestnet.org.

CHEST Challenge 2018

Are you a US-based CHEST fellow-in-training? Compete with other programs across the country in CHEST Challenge 2018 for honor and prizes! The first round of the competition this year will consist of two parts; in addition to the traditional online quiz, there will be a number of social media challenges. The aggregate score for both of these components will be used to identify the top three-scoring teams. These top three teams will then be invited to send three fellows each to the CHEST Challenge Championship, a Jeopardy-style game show that takes place live during the CHEST Annual Meeting. http://www.chestnet.org/Hidden-Pages/CHEST-Challenge-US

CHEST Foundation Grants

We have had many talented and passionate people win our CHEST Foundation grants in research and community service. Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars in a field of expertise. Nearly 800 recipients worldwide have received more than $10 million in support and recognition of outstanding contributions to chest medicine.

How are you helping to champion lung health? The CHEST Foundation is accepting grant applications **February 1 through April 9, 2018,** in the following areas:

- CHEST Foundation Research Grant in **Lung Cancer** – $50,000 - $100,000 2-year grant*
- CHEST Foundation Research Grant in **Asthma** – $15,000 - $30,000 1-year grant*
- CHEST Foundation Research Grant in **Pulmonary Arterial Hypertension** – $25,000 - $50,000 1-year grant*
- CHEST Foundation and the **Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Pulmonary Fibrosis** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Chronic Obstructive Pulmonary Disease** – $30,000 1-year grant (multiple recipients selected)
- CHEST Foundation Research Grant in **Venous Thromboembolism** – $15,000 - $30,000 1-year grant*
- CHEST Foundation Research Grant in **Nontuberculous Mycobacteria Disease** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Women's Lung Health** – $10,000 1-year grant
- CHEST Foundation Research Grant in **Cystic Fibrosis** – $30,000 1-year grant
- The Eli Lilly and Company **Distinguished Scholar** in Critical Care Medicine – $150,000 over 3 years
- CHEST Foundation **Community Service** Grant Honoring D. Robert McCaffree, MD, Master FCCP – $2,500- $15,000 1-year grant*

**Amount contingent on funding.*

Learn more on how to apply now at chestfoundation.org/apply.

Things Happening in April

Don't forget to look out for CHEST 2018 registration, **opening April 5**. And, if you missed the first round of abstract submissions, submissions for late-breaking abstracts will open April 30. Stay updated on all things CHEST 2018 at chestmeeting.chestnet.org.

NAMDRC UPDATE

Collaboration: Now More Than Ever

BY RUSSEL ACEVEDO, MD, FCCP, AND GARRY KAUFFMAN, RRT

Ongoing hospital mergers, acquisitions, and closings demonstrate that reimbursement maximization and cost reduction are the twin sisters of health-care system reform. This focus is not going to change in the foreseeable future, as most experts now view "health system reform" as "health financing reform."

Reports document that more than 50% of acute care hospitals in the United States experienced negative operating margins for the federal fiscal year ending September 30, 2017. Equally alarming is the increasing number of organizations either reducing or eliminating the roles of medical directors for clinical departments. Hospital and health system executives are increasingly engaging external consultants to find ways to decrease operating costs, with the caveat of maintaining or improving quality, safety, and patient satisfaction and engagement.

Given these cost reduction pressures, what can respiratory therapy medical directors and administrative directors do to ensure that quality and safety are ensured?

We believe that quality and safety can be maintained and improved in this bottom-line-focused environment if we collaborate with stakeholders and communicate the value of respiratory care services. Following are some examples of how to reinvigorate this collaboration. The list is far from complete, but we believe it is a good starting point for making a significant difference.

Science

We recognize that much of our practice is based on levels of evidence, and we must use this evidence as a basis for our services.

In talking and working with RT administrative directors across the country, we continue to see non-value-added "treatments" being provided, such as incentive spirometry and aerosolized acetylcysteine. Not only is this a waste of resources, but, because of it, our clinical RTs are not providing therapy.

One of the best opportunities to decrease cost is to eliminate waste. These services must be eliminated. For those patients who require secretion clearance/lung expansion, we can provide evidence-based services such as oscillating positive expiratory pressure.

Protocols

Respiratory care protocols have been around for decades, but surveys indicate that only half of all RT departments utilize them. Under the guidance of NAMDRC, the AARC has been educating RTs to transition from "treatments" to evidence-based protocols. Various barriers remain, and our challenge remains to implement proven care plans in every department.

Quality Assurance

The health-care industry made the transition from "Quality Control" to "Quality Assurance" several decades ago. However, many RT administrative directors lack the knowledge and/or resources necessary to create a comprehensive QA program, much less participate in clinical research. We suggest creating a standardized model to be adopted by RT departments across the country that would measure and communicate the value of respiratory care services.

Productivity/Staffing

An area where consultants and executives often focus their cost-saving efforts is staffing. Given that 50% to 60% of operating costs are personnel, this is to be expected.

Many organizations, however, are using the wrong metrics—such as procedures, CPT codes , and billables—to project staffing FTEs. Physicians and RTs understand that these metrics are not useful and must convince consultants and executives of this. The AARC Uniform Reporting Manual, which is currently being updated, is the best guide for determining appropriate staffing.

Education

Another common step in cost control has been the significant reduction or total elimination of education budgets.

During the past 5 years, RT leaders attending the AARC Summer Forum have been polled regarding whether they received financial assistance to attend the Management Section program. Sadly, the number attending on their own dime far surpasses those receiving financial assistance.

Additionally, the RT profession is witnessing more department-based education, which, in some cases, is not education at all, but marketing, cleverly packaged in the form of CEUs.

We fully understand these changes and recognize why they have occurred. However, we suggest the need to work together to differentiate marketing from education and ensure that clinical staff receive what is needed to ensure quality care.

It is vital for us to educate our physician leaders and pulmonary and critical care fellows on the science of respiratory care. There is a significant knowledge gap, and we have a great opportunity to improve the training of fellows. It is difficult to attract active medical directors if they don't understand the science. We believe NAMDRC can play an important role by addressing these knowledge deficits.

Catching Up With Our Past CHEST Presidents

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

W. MICHAEL ALBERTS, MD, MBA, MASTER FCCP
President 2005 - 2006

My year at the helm began in Montreal in 2005 and ended in Salt Lake City in 2006. The year was a blur and seemed to fly by. The inauguration was very special as my entire immediate family made the effort to attend. It was the final time that my father was able to travel. Travel was definitely one of the highlights of my Presidential year. My wife, Debra, and I made many lasting friendships and very special memories while on the road for the College.

Looking back, it is hard to believe that I have been with the University of South Florida since 1983. I came to Tampa directly from my Pulmonary and Critical Care Fellowship in San Diego. After 16 years attending at the Tampa General Hospital and the James A. Haley VA, I was named the Chief Medical Officer at the Moffitt Cancer Center in 1999. In 2015, I stepped down from that position and have been serving as the Medical Director of Moffitt's satellite clinical location since that time. I no longer do in-patient rounding, which is a major boon to work-life balance. In addition to administrative duties , however, I continue to see outpatients two half-days a week.

At the risk of sounding like a "Christmas letter," let me update you on my family. Now that my wife's father is no longer able, Debra serves as the comptroller for several family businesses. I am not sure how, but she finds time to play tennis for several teams. My son Michael recently moved to Boston from Dallas. In Texas, he was working for an investment firm focused on health care. In Boston, he manages the business development group for Shields Health Solutions. My daughter Katie is a mergers, acquisitions, and securities attorney here in Tampa, and her husband Andy is a real estate transactions attorney. We are all looking forward to the arrival of Clara Grace Peluso in June. She will be Katie and Andy's first child and Debra and my first grandchild.

Dr. Alberts and son Michael at the 2017 Masters Tournament in Augusta, Georgia.

In our "abundant free time," Debra and I enjoy spending time at our place on Sand Key near Clearwater Beach. When possible, we enjoy traveling and have developed our "bucket list."

I look back at 2005-2006 with nothing but fondness. Serving as President of the College was both intellectually and personally fulfilling. It was certainly the highlight of my career.

CHEST NetWorks

Hurricane Maria, Bloodstream Infections, Lung Cancer in Women

Disaster Response

A Natural Disaster Creates Nationwide Threat

Hurricane Maria devastated Puerto Rico in late September 2017, and the lessons learned endure as the storm exposed the vulnerability of an increasingly interconnected and fragile medical community across the continental United States. According to the US Food and Drug Administration (FDA), Puerto Rico manufactures more drug products than any US state and just under 10% of all drugs consumed by Americans, some of which do not have therapeutic alternatives. In addition, certain medical devices are only produced in Puerto Rico. The humanitarian crisis caused by Hurricane Maria consequently created critical medication and medical device shortages across the United States (FDA. https://www.fda.gov/NewsEvents/. Accessed Feb 01, 2018).

The disruption and disorganization caused by Hurricane Maria was perhaps best exemplified by the resultant shortage of small-volume 0.9% saline injection bags, which coincided with a particularly bad flu season. The FDA temporarily allowed import of saline bags from outside the United States while concurrently expediting the approval of IV solutions from new manufacturers. The American Society for Health-System Pharmacists (ASHP), meanwhile, contributed guidance on managing fluid shortages (ASHP. https://www.ashp.org/Drug-Shortages/. Accessed Feb 01, 2018).

DR. MADAR

Hurricane Maria was a wake-up call for medical professionals across the United States to modernize institutional procedures and to develop contingency plans to deal with medication shortages, particularly IV fluids, since this is a recurring problem across the United States since 2014. Ultimately, the goal of health-care providers across the United States is to manage natural catastrophes, however distant, by effectively planning for and adapting to medical product shortages to ensure patient care is not interrupted and that critical shortages remain invisible to patients themselves.

Cristian Madar, MD
Steering Committee Member

Practice Operations

Are All Regulations Well Thought Out? Point of View!

Current medicine is complex, with patients presenting in the ICU with multiorgan dysfunction. The art and science of medicine is being replaced by protocolized medicine. To help streamline the care, societies and colleges are coming up with guidelines. The guideline, though, changes from year to year what has been practiced in the past has been obsolete, and what is current may not hold true in the future. With in-

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Continued from previous page

creasing health-care costs affecting physician and hospital practices, innovations are being undertaken on a daily basis. The payers, on the other hand, are trying to come up with regulations, whether one likes it or not, that have become the beacon for penalty and reward. Sometimes those regulations conflict with what is sound judgment and prudent care, cornering the providers in the box with unnecessary penalties.

Approximately 250,000 bloodstream infections occur in the United States yearly, mostly attributed to the presence of intravascular devices. The rate of central line-associated blood stream infection (CLABSI) in the United States is 0.8 per 1,000 central line days. The desirable rate is zero rate of CLABSI. The hospitals are being pushed to be prudent with the use of central lines and removal if not needed. The technique and sterile field along with appropriate innovation in dressing technique have been effective in reducing the CLABSI by 46% from 2008 to 2013. The hospitals and ICUs are being very vigilant in trying to avoid CLABSI and are striving to achieve the goal of a zero percentage CLABSI rate, leading to almost a state of paranoia. The efforts are being undertaken in many institutions to get all the cultures on admission to identify the organism on admission so as to be designated as a bloodstream infection (BSI) due to other causes and to avoid the CLABSI attribution. The CLABSI attribution follows a complex algorithm with no waiver for the exception outside the strict definition that is changing (The 2015 definition change resulted in an 83% increase in CLABSI rate.).

DR. BASSILY-MARCUS

We hereby present a simple scenario for point of view, where there is very clear-cut evidence of the bloodstream infection due to abdominal sources but that BSI would be designated as CLABSI as defined by National Healthcare Safety Network (NHSN). The patient postoperatively presents with fever, nausea, and abdominal discomfort. The CT scan showed fluid collection suggestive of infection. Culture from the abscess grew Escherichia coli and the blood culture grew Bacteroides fargilis. This patient was labeled as BSI due to intra-abdominal cause. On the other hand, patient has pus pockets in the abdominal wall with swelling and tenderness. Cultures from the pustule grew Streptococcus Group B and the blood culture grew Staphylococcus aureus. This would be classified as soft tissue infection and primary BSI and if the patient has the central line for 2 days, it would be classified as CLABSI, even though there was a clear cut source from where the infection originated. On the other hand, if a patient has a CT scan of the abdomen or any imaging study done, which showed the pus pocket, and even if there is no abscess culture done, and if there is BSI, it would be labelled as BSI due to intra-abdominal cause rather than CLABSI.

This is one of the many examples where there is unnecessary imaging needed to avoid the designation of CLABSI, or, in other instances, unnecessary cultures on admission to avoid the CLABSI or catheter-related urinary tract infection (CAUTI) when patient is coming in from other institutions or nursing facilities to avoid the attribution of CLABSI and CAUTI, rather than what is good for the patient. We are in the time of protocol-driven medicine, which has helped in improving the patient care in certain aspects, but where are the days when the physical examination meant something rather than having to prove it by imaging and laboratory studies? Are the guidelines and regulations a solution to health-care cost and waste, or are they part of problem? You be the judge.

Adel Bassily-Marcus, MD, FCCP
Chair
Salim Surani, MD, FCCP
Vice-Chair

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Transplant

Radius of Change: Will Expanding Organ Sharing Beyond Donor Service Area Enhance Access in Lung Transplantation?

In November 2017, the US Department of Health and Human Services (HHS) prompted the United Network for Organ Sharing Organ Procurement and Transplant Network (UNOS/OPTN) to reconsider geographical boundaries of donor allocation. The impetus for change was driven by a recent litigation and data that challenged the current organ allocation algorithm on the premise that it overlooked potential high acuity candidates listed at centers outside the primary DSA (donor service area) of the donor hospital, in favor of less sick local recipients. In response, the UNOS/OPTN Executive Committee recommended the adoption of a 250-nautical mile radius from the donor hospital in lieu of the DSA as the first circle or zone A of distribution for lungs. The putative merits of this change, due to last an experimental year, is intended to provide sicker candidates with access to a broader geographic range of donors. Its impact will then be evaluated by the Thoracic Organ Transplantation Committee to make further recommendations, including possibly extending zone A to 500 miles.

DR. KUMAR

The extended geographical limits have organ-specific implications. In contrast to other organs, constraints of cold ischemia limit the duration within which lungs and hearts must be transplanted. Indeed, this latter point is the basis for using a radius from the donor hospital, rather than the region, as the first circle of distribution. Furthermore, DSAs vary substantially in both size and population and performance, leading to considerable variation in access to organs for candidates based on their region of residence. Currently, more than 50% of the lung allocation in the United States occurs locally to recipients with lung allocation scores (LAS) less than 50 (Iribarne et al. *Chest*. 2009;135[4]:923). In addition, waiting time mortality remains high and actuarial survival remains low for those with higher LAS (Russo et al. *Chest*. 2010;137[3]:651). The new recommendations broaden the concentric circle approach and potentially provide enhanced access for the sickest candidates on the waiting list. However, this may increase duration of waitlist time for those with lower LAS, certain disease groups such as COPD and those listed in more conservative centers. It may conversely, however, drive transplantation in the sickest patients and increase the use of bridging strategies in high volume centers and those with ECMO capabilities, as there will now be a greater reassurance of donor offers with the wider catchment area. The implications are unclear at this time, and over the next year, the efficacy and the potential unintended consequences of this newly implemented directive should become more apparent.

Anupam Kumar, MD
Fellow-in-Training Member
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Steering Committee Member

Women's Health

Lung Cancer and Steroid Hormones: An Evolving Paradigm

Lung cancer remains to be the second most common cancer and the leading cause of cancer-related mortality in women. The risk for developing lung cancer in women is 1/17 and increases with age and smoking history. Women with stage I NSLC have better prognosis after surgical treatment compared with men (Graham et al. *South Med J.* 2013;106[10]:582); however. they are less likely to have undergone a low dose screening CT scan, even after meeting high risk criteria (Lamb et al. *Chest*. 2017;152[suppl] A623). The prognosis in advanced stage lung cancer at diagnosis does not differ among the genders or age groups (Santoro et al. *J Bras Pneumol.* 2017;43[6]:431).

DR. SHAIB

There is increasing interest in the role of steroid hormones in lung biology in health and disease with estrogen and progesterone receptors identified in both healthy and malignant tissue. The role of hormone receptors as a prognostication tool and a therapeutic target is being actively investigated.

Estrogen receptor Beta (ER-Beta) is the predominantly expressed estrogen receptor in lung cancer cells (Raso et al. *Clin Cancer Res.* 2009;15[17]:5359). Increased cytoplasmic ER-alpha and ER-beta is associated with tobacco smoking and likely indicates a hormonal-smoking interaction (Siegfried. *Mol Cancer Res.* 2014;12[1]:24). A higher nuclear expression ER-beta in women may be protective against hormone-related lung cancer (Schwartz et al. *J Clin Oncol.* 2007; 25[36]:5785), whereas higher cytoplasmic expression of ER-alpha and ER-beta was associated with worse lung cancer survival (Cheng. *J Natl Cancer Inst.* 2018; Jan 13). Therapies targeting ER-beta1 and its down-

regulation resulted in sensitizing the cells to epidermal growth factor receptor-tyrosine kinase inhibitors and may result in reversing EGFR-TK resistance (Fu et al. *Oncol Rep.* 2018;39[3]:1313).

The presence of progesterone receptors is associated with longer survival in NSCLC, and treatment with progesterone has been shown to induce apoptosis and inhibit migration and invasion of lung cancer cell lines (Ishibashi et al. *Cancer Res.* 2005;65[14]:6450). Women over the age of 60 were found to have significant survival benefit when compared with both men and younger women (Wakelee et al. *J Thoracic Oncol.* 2007b; 2:S570), whereas a worse survival and earlier age of occurrence of lung cancer was associated with the exposure to HRT (Ganti et al. *J Clin Oncol.* 2006;24[1]:59).

The future of hormone receptor targets in lung cancer may provide new therapeutic options for patients with lung adenocarcinoma, especially those with acquired resistance to the EGFR antagonists (Hsu et al. *Int J Mol Sci.* 2017; 18[8] pii: E1713. doi: 10.3390/ijms18081713).

Fidaa Shaib, MD, FCCP
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2 Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

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