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LUNG SAFE: ARDS goes unrecognized

BY KARI OAKES
Frontline Medical News

ORLANDO – Many patients meeting the criteria for acute respiratory distress syndrome (ARDS) went unrecognized in a global sample of ICU patients, and those ARDS patients did not receive adjusted ventilator management or positioning and pharmacologic adjunctive treatments, based on the results of the LUNG SAFE study.

Enrolling nearly 30,000 patients in 50 countries on five continents, the LUNG SAFE study (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) looked for real-world answers to whether and how patients with ARDS are treated. The LUNG SAFE results were published concurrently with the presentation of results in a late-breaking session at the Critical Care Congress, sponsored by the Society of Critical Care Medicine (JAMA. 2016;315[8]:759-61). The first author is Dr. Giacomo Bellani, professor of medicine at the University of Milan-Bicocca, Monza, Italy, and Dr. John Laffey, professor of anesthesia, critical care, and physiology at the University of Toronto, presented the results at the meeting.

About 10% of the enrolled

See **ARDS** • *page 7*

Sepsis, septic shock redefined by critical care groups

'Severe sepsis' term is eliminated.

BY KARI OAKES
Frontline Medical News

ORLANDO – New consensus definitions for sepsis and septic shock focus on host dysregulation in the face of infection, propose a three-item quick-scoring option for bedside assessment, and introduce serum lactate as an important marker of cellular metabolic stress in identifying septic shock.

Sepsis is now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection," according to a 19-member task force convened jointly by the U.S. Society for Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) (JAMA. 2016;315[8]:801-10. doi: 10.1001/jama.2016.0287).

Since sepsis itself is inherently a life-threatening diagnosis, the term "severe sepsis" is redundant and should be eliminated, according to Dr. Mervyn Singer and his fellow task force members and coauthors. Together with his coauthors, Dr. Singer, professor of intensive care medicine at University College London, also recommended moving away from an "excessive focus on inflammation" and "the

See **Sepsis** • *page 6*

INSIDE

Chronic cough guidelines issued

BY SHARON WORCESTER
Frontline Medical News

FROM CHEST

Neuromodulatory therapies and speech pathology–based cough suppression are suggested treatment options for unexplained chronic cough in new guidelines from the CHEST Expert Cough Panel.

The panel noted, however, that evidence supporting the diagnosis and management of unexplained chronic cough is limited. As part of the guideline development, they considered approaches for improving related research.

"Persistent cough of unexplained origin is a significant health issue that occurs in up to 5% to 10% of patients seeking medical assistance for a chronic cough and from 0% to 46% of patients referred to specialty cough clinics. Patients with unexplained chronic cough experience significant impairments in quality of life ... there is a need to identify effective treatment

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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 Esbriet 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%) were 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.

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- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[3,4†]
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ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

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†The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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.

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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.

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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 disease requiring dialysis is not recommended.

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References: 1. Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19. **2.** Data on file. Genentech, Inc. **3.** Esbriet Prescribing Information. InterMune, Inc. October 2014. **4.** 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. **5.** 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.

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Speech therapy, steroids advised

Cough *from page 1*

approaches," Dr. Peter Gibson of Hunter Medical Research Institute, New South Wales, Australia, and his colleagues reported on behalf of the panel (Chest. 2016;149[1]:27-44).

The panel defined unexplained chronic cough as a cough that persists longer than 8 weeks, and that remains unexplained after evaluations and supervised therapeutic trials are conducted according to guidelines.

The panel also suggested the following therapeutic approaches:

- That adult patients have objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis, or be offered a trial of corticosteroid therapy.
- That adult patients have a trial of multi-modality speech pathology therapy.
- That inhaled corticosteroids not be prescribed in adult patients who test negative for bronchial hyperresponsiveness and eosinophilia.
- That a therapeutic trial of gabapentin be offered as long as the

risk-benefit profile is discussed with the patient, and as long as reassessment of the risk-benefit profile be conducted at 6 months – before continuing the drug. The recommended starting dose is 300 mg daily in those without contraindications, with dose escalation daily as tolerated up to a maximum tolerable dose of 1,800 mg daily in two divided doses.

Persistent cough of unexplained origin is a significant health issue that occurs in up to 5% to 10% of patients seeking medical assistance for a chronic cough.

- That adult patients with a negative workup for acid gastroesophageal reflux disease not be prescribed a proton pump inhibitor.

The panel's suggestions are the result of a systematic review of 11 randomized controlled trials and 5 systematic reviews to discern whether treatment is more efficacious than usual care with respect to cough severity, cough frequency, and cough-related quality of life.

Studies reviewed included data on 570 subjects over age 12 years with chronic cough who received a variety of interventions.

Positive effects on cough-related quality of life were noted for both gabapentin and morphine, but the panel determined that only gabapentin was supported as a treatment recommendation.

After controlling for intervention fidelity bias, inhaled corticosteroids were not found to be effective for unexplained chronic cough, and esomeprazole was not effective in patients without features of gastroesophageal acid reflux.

Most of the recommendations are based on consensus opinion and limited data.

As a result, the panel examined clinical trial design, chronic cough registries, and potential research questions in an effort to identify ways to improve research. Among other conclusions, the panel said future trials should include comparison groups as a significant placebo effect can occur in cough trials. Also, quality of life should be used as the primary study outcome.

"Registries for unexplained chronic cough could be used to document patient characteristics and outcomes, as well as clinical trials in progress. They could also serve as a source of research participants for trials and may allow for phenotyping according to age, sex, cough duration, cough severity, cough reflex sensitivity, and other biomarkers. Registries can be used for genetic studies in chronic cough."

"Unexplained chronic cough requires further study to determine consistent terminology and the optimal methods of investigation using established criteria for intervention fidelity," the panel concluded.

Dr. Gibson reported having no disclosures. One other author, Dr. Lorcan McGarvey, reported serving on advisory boards for Novartis and GlaxoSmithKline in relation to novel compounds with a potential role in treatment of cough, and serving as chairman for the Mortality Adjudication Committee for UPLIFT and TIOSPIR – two phase IV chronic obstructive pulmonary disease clinical trials for Boehringer Ingelheim.

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SIRS differs from sepsis

Sepsis *from page 1*

misleading model that sepsis follows a continuum through severe sepsis to shock."

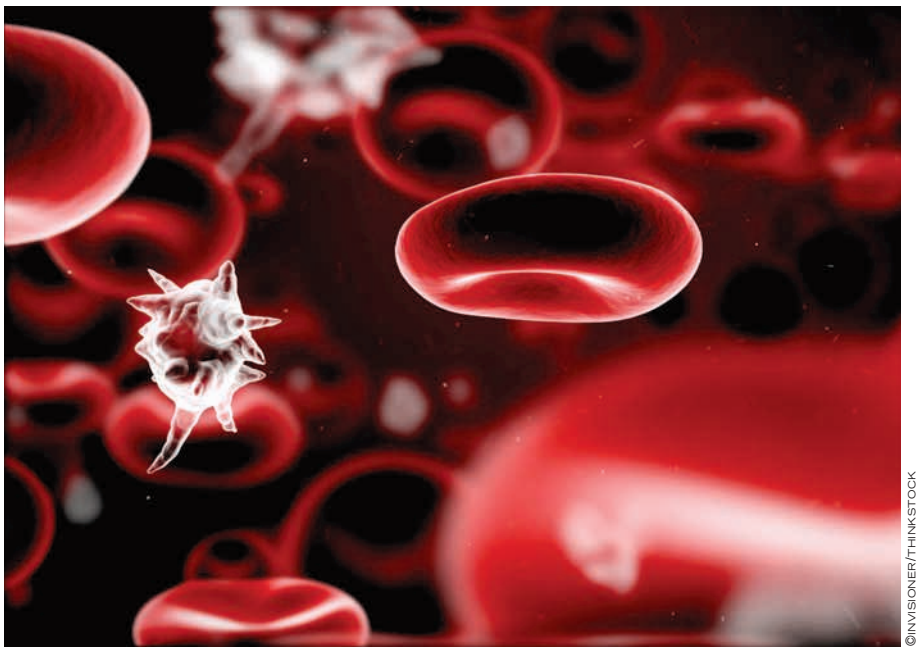
Systemic inflammatory response syndrome (SIRS) is a serious manifestation of an appropriate host response to infection, rather than the dysregulated host response that characterizes sepsis. So although it's no longer included in sepsis criteria, "we are not discounting SIRS," Dr. Singer said in a presentation at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

The consensus statement was released and the presentation was made simultaneously.

Organ dysfunction, for the purposes of the revised definition, is defined as a 2 or more point increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score. This increase is associated with a 10% or more rise in mortality while in hospital. Task force members, after review, recommended standardizing sepsis assessment with the SOFA score.

The criteria require an increase of 2 or more points on the SOFA score because many patients suspected of sepsis will have comorbidities that will "earn" them SOFA points at baseline, said Dr. Singer.

Operationalizing the sepsis definition through SOFA made sense, said Dr. Singer, because the set of five laboratory measures and one clinician-administered scale – the Glasgow Coma Scale (GCS) – are already likely to be part of daily assessments for a seriously ill hospitalized adult.



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Septic shock, as defined by the task force, is associated with in-hospital mortality of over 40%. Septic shock is now defined as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone."

Clinically, patients have septic shock if they require a vasopressor to maintain a mean arterial pressure of 65 mm Hg or greater, and have a serum lactate level greater than 18 mg/dL (2 mmol/L) without hypovolemia.

The definitions introduce an abbreviated bedside sepsis identification tool termed quickSOFA (qSOFA). For adults suspected of infection, qSOFA requires two of the three clinical criteria of respiratory rate of 22 breaths/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

"This model was robust to multiple sensitivity analyses," wrote Dr. Singer and his coauthors, and worked well in out-of-hospital, emergency department, and ward settings within and outside of the United States.

"We are encouraging prospective validation in different health care settings," for example, in resource-poor environments, said Dr. Singer.

The extensive review process included a large meta-analysis and systematic review of observational studies of adults with sepsis to evaluate diagnostic systems and criteria currently in use. The results of the review were used to inform the task force's Delphi study, which then led

Continued on following page

IN THIS ISSUE

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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Few clinicians using higher PEEP levels

ARDS *from page 1*

patients met ARDS criteria; of those, less than two-thirds received ventilator tidal volumes of 8 mL/kg or less of predicted body weight. Fewer than 18% of patients received positive end–expiratory pressure (PEEP) of more than 12 cm H_2O, and clinicians used prone positioning for about 16% of patients with severe ARDS.

Clinicians recognized 60.2% of ARDS cases overall; recognition ranged from 51.3% of the cases of mild ARDS to 78.5% of the severe ARDS cases. For all patients, ARDS was associated with an in-hospital mortality rate of 40%. Nearly half of those with severe ARDS died, as did over a third of those with mild ARDS.

To this end, the LUNG SAFE investigators chose 4 consecutive weeks in the winter to enroll patients from a convenience sample of ICUs that they attempted to make broadly representative. They enrolled during February and March 2014 in the Northern hemisphere and July and August 2014 in the Southern hemisphere, and included all patients 16 years and older who were admitted to a participating ICU and received invasive or noninvasive ventilation.

Enrolled patients received daily evaluation for acute hypoxemic respiratory failure. Patients who met these criteria were then tracked with expanded data collection up to day 28 after respiratory failure was identified, or until ICU discharge or death. Overall, 3,022 patients met the Berlin Definition for ARDS.

All but 436 patients (85.4%) received invasive ventilation, and those who did not were excluded from most data analysis.

One unexpected finding, said Dr. Laffey in an interview, was how common ARDS was in this ICU population.

"Based on prior studies, we had anticipated finding an incidence of ARDS of approximately half of what we actually found in the LUNG SAFE study. We think that the difference is explained by the fact that we did not rely on clinician recognition of ARDS, but rather collected data directly on each of the Berlin diagnostic criteria, enabling us to make the diagnosis directly." One possibility is that choosing the winter months for data collection may have resulted in overrepresentation of ARDS.

But Dr. Laffey said that LUNG SAFE's most surprising finding was the low percentage of clinicians using higher PEEP levels. "It appeared that clinicians used lower-than-expected levels of PEEP, and that the use of PEEP didn't increase in patients with the more severe forms of ARDS," he said. "We think we need to increase our efforts to find more reliable ways to diagnose ARDS," said Dr. Laffey. "While the reasons underlying clinician failure to recognize ARDS in critically ill patients are complex, the fact that there is no single test for diagnosing ARDS is a likely contributing factor."

"This finding likely reflects the lack of a clear evidence base for the effectiveness of higher levels of PEEP in patients with ARDS" said Dr. Laffey. "It emphasizes the need for additional research to answer this and other important questions relating to the optimal treatment of patients with ARDS."

However, if physicians did recognize ARDS, then they were more likely to use higher PEEPs (mean 8.9 cm H_2O vs. 7.5 cm H_2O for nonrecognized ARDS; *P* less than .001), prone positioning, and neuromuscular blockade (43.9% adjunctive treatment vs. 21.7% adjunctive treatment for nonrecognized ARDS; *P* less than .001), though they didn't adjust the breath size used in ventilation.

In multivariable analysis, factors that made it more likely that ARDS would be recognized were higher nurse-to-patient and physician-to-patient ratios, younger patient age, lower $Pa0_2/Fi0_2$ ratios, and a pneumonia or pancreatitis diagnosis. Patients without an identified risk factor, and those with heart failure, were less likely to be diagnosed with ARDS.

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The study was supported by the European Society of Intensive Care Medicine, by St. Michael's Hospital, Toronto, and by the University of Milan-Bicocca, Monza, Italy. The authors reported no conflicts of interest.

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to cohort studies to test the proposed variables, through the Surviving Sepsis Campaign.

A comprehensive description of the work of the task force was published concurrently with the new sepsis and septic shock definitions (JAMA. 2016;315[8]:775-87. doi: 10.1001/jama.2016.0289).

"We had what I call a soft launch" of the new definitions, said Dr. Singer. The definitions and criteria have been available for review and discussion for about a year, and discussions in the public forum are already shaping thoughts about the way forward. "We expect lots and lots of discussion," said Dr. Singer.

Limitations of the new definitions were enumerated by Dr. Singer and his coauthors, and also brought forward in an accompanying editorial by Dr. Edward Abraham, dean of the Wake Forest School of Medicine, Winston-Salem, N.C.

These include that sepsis is not defined for children, that the reliance on serum lactate levels may not be feasible in resource-poor environments, and that there are limitations to the datasets used to generate the new guidelines.

The guidelines also offer suggested International Classification of Diseases-9 (ICD-9) and ICD-10 codes for sepsis and septic shock, in the hope that "greater clarity and consistency will also facilitate research and more accurate coding," wrote Dr. Singer and his coauthors.

Multiple task force members reported relationships with pharmaceutical companies.

The work of the task force was supported in part by grants from SCCM and ESICM.

The guidelines and accompanying information are available at www.sccm.org/sepsisredefined.

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Pulmonary vascular distensibility loss precedes PH

BY MARY ANN MOON
Frontline Medical News

FROM CHEST

Loss of distensibility in the pulmonary vasculature may be a marker that allows earlier detection of impending pulmonary hypertension, based on hemodynamic data from the medical records of 90 patients across the spectrum of pulmonary vascular disease.

Normal pulmonary circulation allows distension and recruitment of the pulmonary vasculature during exertion that in turn reduces pulmonary vascular resistance. Loss of this distensibility increases resistance and thus pulmonary arterial pressure, and is a characteristic of mild pulmonary vascular disease. Such disease is a precursor of full-blown pulmonary hypertension (PH), which "is a relatively late hemodynamic event in the evolution of pulmonary vascular disease," wrote Dr. Edmund M. T. Lau of Université Paris-Sud, and his associates.

The percentage change in vascular diameter per mm Hg increase in distending pressure has been proposed for estimating the distensibility of resistive pulmonary vessels. This "distensibility value" has been assessed in animal studies and in healthy human subjects, but has not yet been assessed as a possible marker of mild pulmonary vascular disease or PH.

The researchers assessed this distensibility value in 31 patients with PH, 33 with mild pulmonary vascular disease but no PH as yet, and 26 control subjects with no pulmonary vascular disease. The data were obtained from the medical records of these patients, who had undergone right-sided heart catheterization, both at rest and during exercise, over a 6-year period.

The percentage change in vascular diameter per mm Hg increase in distending pressure was "strikingly reduced" (0.45%/mm Hg) in the mild pulmonary vascular disease group compared with the control group (1.4%/mm Hg). As expected, the group with PH had the lowest distensibility value, at 0.25%/mm Hg.

Using a cutoff value of 0.76%/mm Hg allowed the researchers to distinguish control subjects from patients with mild disease with a sensitivity of 88% and a specificity of 100%.

"To our knowledge, this is the first study to validate the fit of [this] model in subjects with pulmonary vascular disease and to demonstrate that [percentage change in vascular diameter per mm Hg increase in distending pressure] is dramatically reduced in patients who have mild pulmonary vascular disease without manifest PH.

"Taken together, our findings suggest that vascular distensibility is markedly attenuated prior to the development of PH and that [this value] may serve as a useful vascular index in the setting of early disease detection," Dr. Lau and his associates wrote (CHEST 2016;149:353-61).

The distensibility value calculated (1.4%/mm Hg) for this study's control group was slightly lower than that reported in the literature for normal, healthy subjects and in vitro animal vessels (2%/mm Hg). That is likely because the control participants were older than the subjects in previous studies, and vascular distensibility is known to decrease with increasing age, the researchers said.

They added that it might be useful to calculate the distensibility value when patients suspected of having pulmonary vascular disease undergo invasive pulmonary hemodynamic evaluations. "It would be of particular interest to assess [it] in populations at a high risk of developing PH, such as carriers of the BMPR2 mutation and patients with systemic sclerosis."

Obviously, estimating the distensibility value using noninvasive evaluation would be preferable, the researchers noted. Preliminary studies of healthy control subjects and carriers of the BMPR2 mutation undergoing stress ECG testing have shown that calculating the distensibility value is feasible using Doppler echocardiography data, the researchers added.

This study was supported by Fonds de Dotation Recherche en Santé Respiratoire, Fondation du Souffle, and the INSERM–University of Sydney Exchange Grant. Dr. Lau reported having no relevant financial disclosures; his associates reported ties to Actelion, Aires, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics Corporation.

VIEW ON THE NEWS

Findings may revamp screening process

These findings have the potential to completely revamp screening for pulmonary vascular disease, but first they must be validated in further research.

It will also be important to determine whether, as the authors suggest, a noninvasive method to determine vascular distensibility can be developed, perhaps using stress echocardiography or stress cardiac magnetic resonance testing. Only then can this measure – the percentage change in vascular diameter per mm Hg increase in distending pressure – translate from the realm of novel research into real-world clinical practice.

Dr. Richa Agarwal is in the department of medicine at Temple University, Philadelphia, and at the Cardiovascular Institute at Allegheny General Hospital, Pittsburgh. Dr. Mardi Gomberg-Maitland is in the department of medicine at the University of Chicago. Dr. Agarwal reported having no relevant financial disclosures; Dr. Gomberg-Maitland reported ties to Actelion, Bayer, GeNo, Gilead, Medtronic, Novartis, Lung Biotechnology, Reata, Bellerophon, United Therapeutics, Medscape, and ABComm. Dr. Agarwal and Dr. Gomberg-Maitland made these remarks in an editorial accompanying Dr. Lau's report (Chest 2016;149:295-7).

Late risks of breast cancer RT are higher for smokers

BY SUSAN LONDON
Frontline Medical News

SAN ANTONIO – The late side effects of modern radiation therapy for breast cancer depend in part on a woman's smoking status, based on the results of a meta-analysis of data from more than 40,000 women presented at the San Antonio Breast Cancer Symposium.

For nonsmokers, radiation therapy had little impact on the absolute risks of lung cancer or cardiac death, the main risks identified, which in combination totaled less than 1%, Dr. Carolyn Taylor reported on behalf of the Early Breast Cancer Trialists' Collaborative Group. But for women who had smoked throughout their adult life and continued to do so during and after treatment, it increased that absolute risk to roughly 2%.

"Smoking status can determine the net long-term effects of breast cancer radiotherapy on mortality. Stopping smoking at the time of radiotherapy may avoid much of the risk, and that's because most of the risk of lung cancer starts more than 10 years after radiotherapy," said Dr. Taylor, a radiation oncologist at the University of Oxford (England).

Radiation therapy remains an important tool in treating breast cancer, ultimately reducing the likelihood of death from the disease, she said. "The absolute benefit in women treated according to current guidelines is a few percent. Let's remember the magnitude of that benefit as we think about the risks of radiotherapy."

Stopping smoking at the time of radiotherapy may avoid much of the risk, as risk starts over 10 years after RT.

DR. GOODWIN

Attendee Dr. Steven Vogl of Montefiore Medical Center, New York, asked whether information was available on the location of the lung cancers that occurred in the trials.

"We didn't have the location of the lung cancers. We didn't even know if it was ipsilateral or contralateral to the previous breast cancer in this study," Dr. Taylor replied. "But we've done other studies where we have known the location of the lung cancer, and there were similar findings in those studies."

"In the last 4 years, we've had very good information that annual CT screening substantially and very quickly reduces the mortality from lung can-

Continued on following page

Continued from previous page

cer," Dr. Vogl added as a comment. "Any of us who care for patients who have been radiated where, really, any lung has been treated, who continue to smoke, should be screened – and screened and screened and screened again," he remarked.

The researchers analyzed data from 40,781 women with breast cancer from 75 randomized trials conducted worldwide that compared outcomes with and without radiation therapy.

The median year of trial entry was 1983. On average, women in the trials received 10 Gy to both lungs combined and 6 Gy to the heart.

Comparing women who did and did not receive radiation therapy, the rate ratio for lung cancer was 2.1 at 10 or more years out, and the rate ratio for cardiac mortality was 1.3 overall.

Given the mean radiation doses in the trials, the excess risk translated to 12% per Gray for lung cancer and 4% per Gray for cardiac mortality. "These rate ratios are likely to apply today," Dr. Taylor maintained.

However, she noted, contemporary breast cancer radiation therapy techniques are much better at sparing normal tissues.

To derive absolute risk estimates that are relevant today, she and her colleagues reviewed the literature for 2010-2015 and determined that women now receive an average of 5 Gy to both lungs combined and 4 Gy to the heart, with some centers achieving even lower values.

Among nonsmokers, the estimated cumulative 30-year risk of lung cancer was 0.5% for women who did not receive radiation therapy and 0.8% for those who received radiation therapy with a mean dose of 5 Gy to both lungs combined, Dr. Taylor reported. However, among long-term smokers, it was 9.4% without radiation and a substantially higher 13.8% with it.

Similarly, among nonsmokers, the estimated cumulative 30-year risk of ischemic heart disease death was 1.8% for women who did not receive radiation therapy and 2.0% for women who received radiation therapy with a mean dose of 2 Gy to the heart. Among long-term smokers, it was 8.0% without radiation and a slightly higher 8.6% with it.

Additional analyses looking at other late side effects showed no radiation therapy–related excess risk of sarcomas, according to Dr. Taylor. The risk of leukemia was increased with radiation, but actual numbers of cases were very small, she cautioned.

Attendee Dr. Pamela Goodwin, University of Toronto, said, "I'm just wondering whether you considered if it was valid to assume that there was a linear relationship between radiation dose and the risk of lung cancer in the range of radiation doses that you looked at, so, from the higher range in the earlier studies to the much lower dose now."

Numbers of heart disease events were sufficient to establish a linear relationship, according to Dr. Taylor. Numbers of lung cancers were not, but case-control studies in the literature with adequate numbers have identified a linear relationship there, too.

"We use what we can, and we have got now several hundred events, if you combine all of the literature together. And they do suggest the dose-response relationship is linear, but we can't know that for certain," she said.

Chronic pulmonary aspergillosis guidelines issued

BY NEIL OSTERWEIL
Frontline Medical News

European respiratory disease and infectious disease specialists have banded together to issue new clinical guidelines on the diagnosis and management of an uncommon but serious problem: chronic pulmonary aspergillosis (CPA).

Pulmonary infections with Aspergillus species can be a complicating factor in several lung diseases, especially tuberculosis, and aspergillosis is a serious, often fatal opportunistic infection in transplant recipients who are on chronic immunosuppression or patients who are immunocompromised from disease or cytotoxic chemotherapy.

Approximately 240,000 people in Europe and 3 million people worldwide have chronic pulmonary aspergillosis (CPA). The Centers for Disease Con-

trol and Prevention notes that because aspergillosis is not classified as a reportable disease, data on the actual incidence of infections in the United States are hard to come by.

"You don't see this every day, whether you're an infectious disease specialist or pulmonologist, so you really can't rely on your experience to guide you in managing these cases, which is why guidelines such as this can be very helpful," commented Dr. Norman Edelman, a pulmonologist and senior consultant for scientific affairs for the American Lung Association.

The guidelines were issued by the European Society for Clinical Microbiology and Infectious Diseases in cooperation with the European Confederation of Medical Mycology and the European Respiratory Society (Eur Respir J. 2015. doi: 10.1183/13993003.00583-2015).

The most recent U.S. guidelines, issued under the aegis of the Infectious Diseases Society of America (IDSA) in 2000 and revised in 2008 (CID 2008;46:327-360), differ from the European recommendations in their level of detail, explained Prof. David W. Denning, professor of infectious diseases in global health at the University of Manchester (England) and lead author of the European guide-

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lines. "The IDSA guidelines assume that you know how to make the diagnosis, but actually for chronic pulmonary aspergillosis that's not so easy," he said in an interview. "The European ones go into in great detail about the diagnosis, the radiology, whether this test is better than that test, how they all add up. "The guidelines recommend duration of therapy and comment on the use of steroids and interferon-gamma immunotherapy.

Diagnostic criteria

The European guidelines categorize Aspergillus infections according to differences in clinical management:

• **Simple aspergilloma.** A single pulmonary cavity containing a fungal ball, supported by serologic or microbiologic evidence of infections with Aspergillus species in patients who are not immunocompromised and are asymptomatic or have only minor symptoms and no radiographic evidence of progression for at least 3 months.

• **Chronic cavitary pulmonary aspergillosis (CCPA).** The presence of one or more pulmonary cavities that may contain one or more aspergillomas or irregular intraluminal material, evidence of Aspergillus species, significant pulmonary/systemic

symptoms, and overt progression on radiography over 3 or more months.

• **Chronic fibrosing pulmonary aspergillosis (CFPA).** Severe, fibrotic destruction of at least two lung lobes as a complication of CCPA, causing a major loss of lung function. Destruction of a single lobe is designated as CCPA of that lobe.

• **Aspergillus nodules.** This unusual presentation is marked by the presence of one or more nodules that may or may not cavitate.

The nodules may resemble tuberculoma, carcinoma of the lung, or coccidioidomycosis; histology is required to make an accurate diagnosis.

• **Subacute invasive aspergillosis (SAIA).** This can occur over the course of 1-3 months in patients who are mildly immunocompromised. Radiologic features can vary, and may include cavitation, the presence of nodules, and progressive consolidation with the appearance of abscess formation. Fungal hyphae (filaments) can be seen in biopsied lung tissues, and there may be evidence of Aspergillus galactomannan antigen in respiratory fluids or blood.

Treatment

The guidelines note that most of the evidence for managing CPA is based

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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** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

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**]. 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, post menopausal 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, 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 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, bone mineral density 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** and **USE IN SPECIFIC POPULATIONS**].

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, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month 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** in full Prescribing Information (12.2)]. 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

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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

Patients 12 years 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 mcg taken two 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 1 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 two 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 two 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 1 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 1 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*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg 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**

* All treatments were administered as two 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.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled 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 two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (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 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 2 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*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	160/4.5 mcg 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**

* All treatments were administered as two 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, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported 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.

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on cohort studies and case reports, and that there have been no head-to-head trials comparing oral triazoles.

For treatment of CPA, the European guidelines recommend:

• Itraconazole 200 mg twice daily, with therapeutic drug monitoring and dose adjustment as necessary (Grade A [strong] recommendation).

• Voriconazole 150-200 mg twice daily, with monitoring and dose adjustment. The guidelines recommend lower doses for patients older than 70 years, those with low body weight, significant liver disease, and/or those of Northeast Asian descent, who may be genetically inclined to slow drug metabolism (Grade A).

• Posaconazole liquid 400 mg twice daily, or tablets 300 mg once daily (Grade B [moderate] recommendation].

In general, the recommended duration of therapy for control of infection in patients with CPA or curative intent for patients with SAIA or chronic necrotizing pulmonary aspergillosis is 6 months or more, depending on patient status and drug tolerance.

For patients with CPA with progressive disease, those whom therapy has failed, or those who are intolerant of or have disease resistant to triazoles, intravenous therapy with micafungin, 150 mg day (Grade B); amphotericin B deoxycholate, 0.7-1.0 mg/kg per day (Grade C [marginal] recommendation); liposomal amphotericin B, 3 mg/kg per day (Grade B); or caspofungin, 50-70 mg/day (Grade C) are recommended.

The guidelines also recommend surgical excision of simple aspergilloma, preferably by a video-assisted thoracic surgery technique, if technically feasible. "In my own experience, we resort to surgery infrequently," Dr. Edelman said.

He noted that it would be helpful if the guidelines had also allergic bronchopulmonary aspergillosis as a separate entity.

Ideal not always achievable

Prof. Denning points out that the optimum therapies and practices described in the guidelines can't always be implemented.

Worldwide, he said, antifungal therapy is not widely available, with the exception of fluconazole, which has no activity against *Aspergillus*, and is inferior to itraconazole and other extended azoles for other fungal diseases such as histoplasmosis, blastomycosis, and paracoccidioidomycosis.

The price of antifungal therapies can also be a barrier to effective treatment in many parts of the world.

"If you're having to pay for your medicines and you're living on $5 or $10 a day in Kenya, say, you can't afford to buy them. So even if the drugs are physically there, it may not be really affordable for a course of therapy for these patients, and there's some advocacy to be done around that for the whole world," he said.

The guidelines were funded primarily by grants from ESCMID and ERS with additional support from ECMM. Authors' travel expenses were funded jointly by ESCMID and ERS. Dr. Denning has received grant support and founder shares in F2G, and has received grants from the Fungal Research Trust, Wellcome Trust, Moulton Trust, Medical Research Council, Chronic Granulomatous Disease Research Trust, National Institute of Allergy and Infectious Diseases, National Institute of Health Research and the European Union, and AstraZeneca. Dr. Edelman reported no relevant disclosures.

Using the new game-changing heart failure drugs

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – Ivabradine and sacubitril/valsartan are paradigm-changing drugs approved last year for the treatment of heart failure with reduced ejection fraction – and it's entirely reasonable to begin using them now in the appropriate patients, Dr. Akshay S. Desai said at the Annual Cardiovascular Conference at Snowmass.

The impressive positive results seen in the pivotal trials for these novel agents – the SHIFT trial for ivabradine (Corlanor) and PARADIGM-HF for sacubitril/valsartan (Entresto) – have rocked the heart failure world.

The studies showed that, in the right patients, these two medications improve heart failure morbidity and mortality significantly beyond what's achievable with the current gold standard, guideline-directed medical therapy.

That's exciting because even though great therapeutic strides have been made during the past 15 years, symptomatic patients with heart failure with reduced ejection fraction (HFrEF) treated with optimal guideline-directed pharmacotherapy still have substantial residual risk for heart failure hospitalization and death, noted Dr. Desai, director of heart failure disease management at Brigham and Women's Hospital in Boston.

The U.S. heart failure guidelines panel hasn't yet addressed the use of either of these recently approved drugs, but Dr. Desai provided his best sense of the data and how to start using them now.

Ivabradine and sacubitril/valsartan are first-in-class agents with novel mechanisms. Ivabradine's demonstrated safety and efficacy in the SHIFT trial confirmed the hypothesis that elevated heart rate is a legitimate therapeutic target in HFrEF.

Sacubitril/valsartan, an angiotensin II receptor/neprilysin inhibitor, provides what is to date a unique ability to enhance the activity of endogenous vasoactive peptides, including natriuretic peptides, bradykinin, substance P, adrenomedullin, and calcitonin gene–related peptide.

These peptides are antifibrotic, antihypertrophic, and they promote vasodilation and diuresis, thus counteracting the adverse effects of neurohormonal activation. But in HFrEF, these vasoactive peptides are less active and patients are less sensitive to them.

Ivabradine

This selective sinus node inhibitor decreases heart rate and has essentially no other effects. The drug has been available for years in Europe, and the European Society of Cardiology (ESC) has had sufficient time to integrate ivabradine into its guidelines for pharmacotherapy in HFrEF.

The ESC treatment algorithm for HFrEF (Eur Heart J. 2012 Jul;33[14]:1787-847) is built upon a foundation of thiazide diuretics to relieve signs and symptoms of congestion along with a beta-blocker and an ACE inhibitor or angiotensin receptor blocker (ARB). In a patient who still has New York Heart Association class II-IV symptoms after those drugs are titrated to guideline-recommended target levels or maximally tolerated doses, a mineralocorticoid receptor antagonist – either spironolactone or eplerenone – is added. And, in a patient who still remains symptomatic, has a left ventricular ejection fraction of 35% or less, is in sinus rhythm, and has a heart rate of 70 beats per minute or more, it's time to consider adding ivabradine.

"This is how our own guidelines may elect to incorporate ivabradine, but of course, we don't know yet," Dr. Desai observed.

In the randomized, double-blind SHIFT trial involving 6,558 HFrEF patients who fit the description of ivabradine candidates described in the ESC guidelines, those who received ivabradine titrated to a maximum of 7.5 mg twice daily experienced a 26% reduction in hospital admissions for worsening heart failure, compared with placebo, a 26% reduction in deaths from heart failure, and fewer adverse events than the control group (Lancet. 2010 Sep 11;376[9744]:875-85).

The important question is who should get ivabradine and who should just get a little more beta-blocker in order to slow the heart rate. The fact is, many heart failure patients simply can't tolerate the guideline-recommended target dose of beta-blocker therapy, which is 12.5 mg twice daily of carvedilol or its equivalent. Indeed, only 26% of SHIFT participants were able to do so.

"My interpretation of the SHIFT trial is that the goal is to reduce heart rate by any means necessary; preferentially, with a beta-blocker, and with ivabradine as an adjunct in patients who can't get to target doses," the cardiologist said.

Sacubitril/valsartan

In the landmark double-blind, 8,442-patient PARADIGM-HF trial, the group randomized to sacubitril/valsartan had a 20% reduction in the primary endpoint of cardiovascular death or heart failure hospitalization over 27 months of follow-up, compared with controls on enalapril at the guideline-recommended dose of 10 mg twice a day. The number needed to treat (NNT) was 21. Moreover, all-cause mortality was reduced by 16% (N Engl J Med. 2014 Sep 11;37[11]:993-1004).

In a recent follow-up cause of death analysis, Dr. Desai and his coinvestigators reported that 81% of all deaths in PARADIGM-HF were cardiovascular in nature. The NNT for sacubitril/valsartan in order to prevent one cardiovascular death was 32. The risk of sudden cardiac death was reduced by 80%, while the risk of death due to worsening heart failure was decreased by 21% (Eur Heart J 2015 Aug 7;36[30]:1990-7).

Lower heart rate; preferentially, with a beta-blocker, and with ivabradine as an adjunct if needed.

DR. DESAI

In another secondary analysis from the PARADIGM-HF investigators, the use of the angiotensin receptor/neprilysin inhibitor was shown to prevent clinical progression of surviving patients with heart failure much more effectively than enalapril. The sacubitril/valsartan group was 34% less likely to have an emergency department visit for worsening heart failure, 18% less likely to require intensive care, and 22% less likely to receive an implantable heart failure device or undergo cardiac transplantation. The reduction in the rate of heart failure hospitalization became significant within the first 30 days (Circulation. 2015 Jan 6;131[1]:54-61).

Moreover, the absolute benefit of sacubitril/valsartan in PARADIGM-HF was consistent across the full spectrum of patient risk (J Am Coll Cardiol. 2015 Nov 10;66[19]:2059-71).

To put this into perspective, Dr. Desai continued, for every 1,000 HFrEF patients switched from an ACE inhibitor or ARB to sacubitril/valsartan, the absolute benefit over the course of 27 months includes 31 fewer cardiovascular deaths, 28 fewer hospitalizations for heart failure, and 37 fewer hospitalizations for any reason.

"This is potent therapy for patients with HFrEF who have the right phenotype," he observed.

While substitution of sacubitril/valsartan for an ACE inhibitor or ARB may be appropriate in many patients with chronic HFrEF who continue to have NYHA Class II-IV symptoms on guideline-directed medical therapy, several caveats apply, according to Dr. Desai.

It's important to be aware of the PARADIGM-HF eligibility criteria, because it's only in patients who fit that profile that sacubitril/valsartan provides evidence-based therapy. There are as yet no data to support the drug's use in patients with new-onset HFrEF, acute decompensated HFrEF, in patients who are immediately post-MI, or in those with advanced chronic kidney disease, he emphasized.

"I think you have to be mindful of eligibility because the label that's applied to this drug is basically 'patients with HFrEF who are treated with guideline-directed medical therapy.' There's no specific requirement that you follow the detailed eligibility criteria of the PARADIGM-HF trial, but you should realize that the drug is known to be effective only in patients who fit the PARADIGM-HF eligibility profile," he said.

Dr. Desai gave a few clinical pearls for prescribing sacubitril/valsartan.

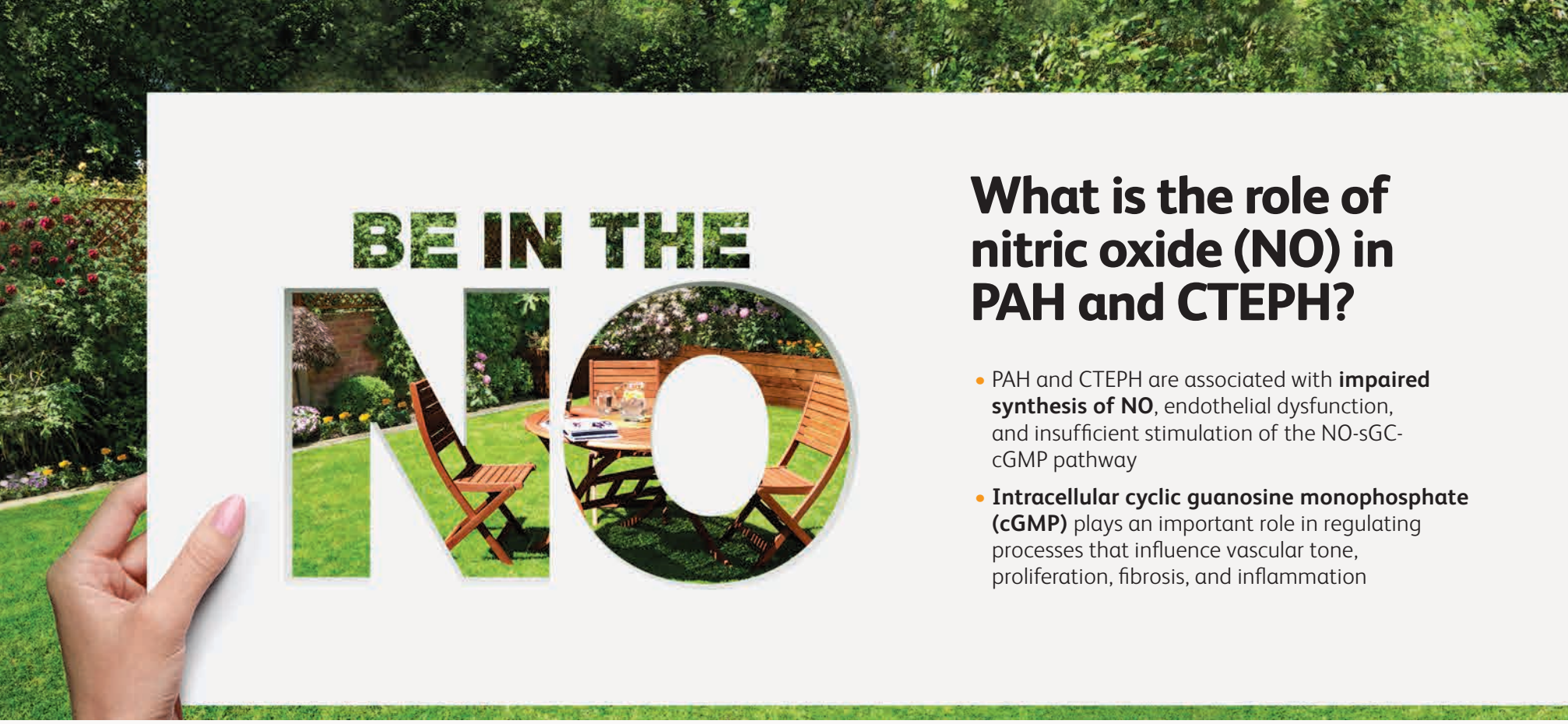
For most patients, the initial recommended dose is 49/51 mg twice daily. In those with low baseline blood pressure and tenuous hemodynamics, it's appropriate to initiate therapy at 24/26 mg BID.

It's important to halt ACE inhibitor therapy 36 hours prior to starting sacubitril/valsartan so as to avoid overlap and consequent increased risk of angioedema.

And while serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) remains a useful biomarker to monitor heart rate severity and response to treatment while a patient is on sacubitril/valsartan, BNP is not because serum levels of that biomarker rise with neprilysin inhibition.

Dr. Desai reported receiving research support from Novartis and St. Jude Medical and serving as a consultant to those companies as well as Merck and Relypsa.

bjancin@frontlinemedcom.com

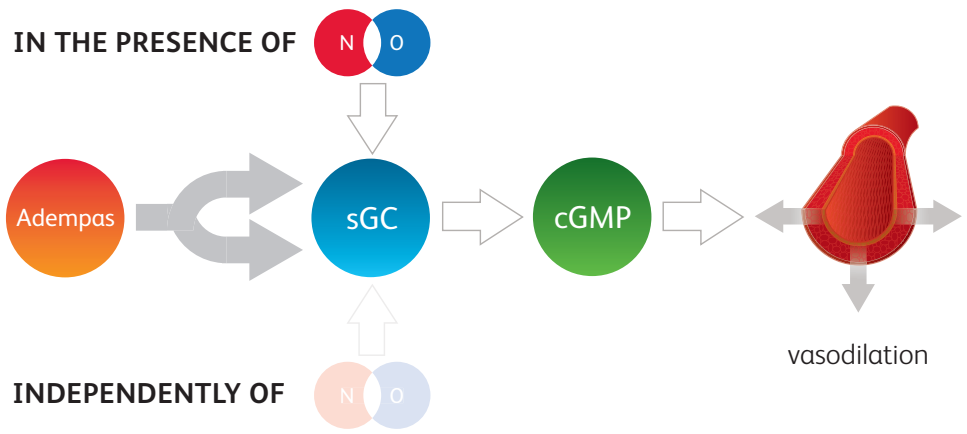


What is the role of nitric oxide (NO) in PAH and CTEPH?

- PAH and CTEPH are associated with **impaired synthesis of NO**, endothelial dysfunction, and insufficient stimulation of the NO-sGC-cGMP pathway
- **Intracellular cyclic guanosine monophosphate (cGMP)** plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation

Adempas stimulates sGC regardless of NO level to produce more cGMP

- Adempas **sensitizes** soluble guanylate cyclase (sGC) to endogenous NO by stabilizing sGC-NO binding
- Adempas directly **stimulates** sGC independently of NO via a different binding site
- Increased cGMP leads to **vasodilation**



INDICATIONS

- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.*

  Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Take your PAH and CTEPH patients farther with Adempas

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

In pulmonary arterial hypertension (PAH), (WHO Group 1)

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II-III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

In inoperable and persistent/recurrent chronic thromboembolic hypertension (CTEPH), (WHO Group 4)

46m improvement (mean) in 6MWD over placebo at Week 16 (95% CI: 25m-67m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 261 adult patients with persistent/recurrent CTEPH after surgery or who were inoperable. The primary endpoint was change from baseline in 6MWD at 16 weeks.

CONTRAINDICATIONS (continued)

- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

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100 Bayer Boulevard, Whippany, NJ 07981 USA

PP-400-US-1777 May 2015

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

Visit Adempas-US.com

BE IN THE NO

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[See Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered *[see Clinical Pharmacology (12.3)]*.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. 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 patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas *[see Clinical Pharmacology (12.3)]*.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)]*.

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling *[See Boxed Warning]*.

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program *[see Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines *[see Adverse Reactions (6.1)]*. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

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Bayer HealthCare

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Whippany, NJ 07981

Manufactured in Germany

Issued May 2014

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SLEEP STRATEGIES: The sleep apnea care delivery paradigm

BY DR. VAISHNAVI KUNDEL AND DR. NEOMI SHAH, MPH

Epidemiology and diagnostics of OSA

Sleep disorders are increasingly prevalent in the United States and are associated with reduced quality of life, increased health-care utilization, and numerous medical and psychiatric disorders (Edinger et al. *Sleep*. 2016;39[1]:237). The most common sleep disorder in the United States is obstructive sleep apnea (OSA). The major risk factor for OSA is obesity. As the obesity epidemic has grown, the prevalence of OSA has also increased (Romero-Corral et al. *Chest*. 2010;137[3]:711), and the need for sleep testing has, therefore, risen dramatically. OSA is traditionally diagnosed using attended in-laboratory polysomnography (PSG) conducted overnight. It requires special equipment, dedicated software for data processing, and trained technicians to conduct and later score the sleep study. A trained sleep medicine physician then interprets the data and provides a diagnosis.

DR. KUNDEL

DR. SHAH

A brief overview of the ACA

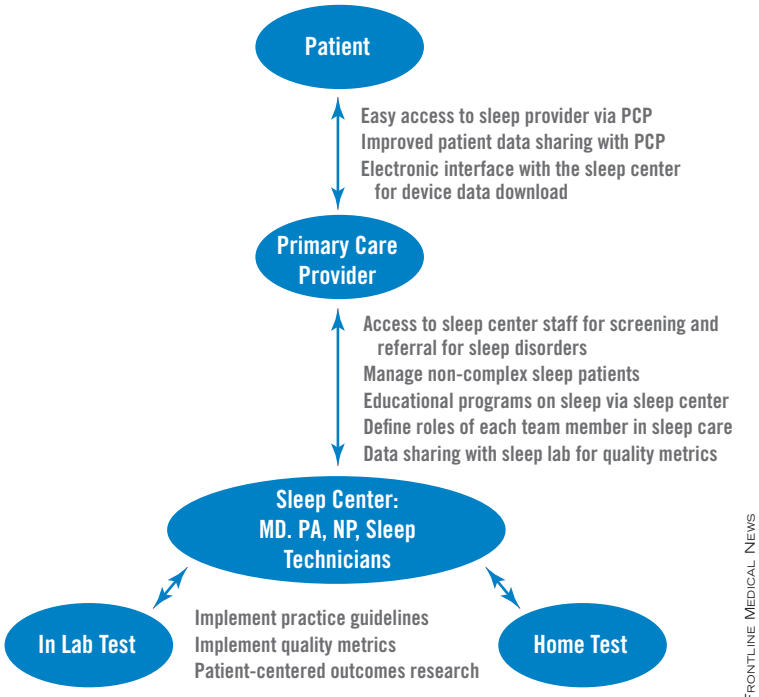
The Affordable Care Act (ACA) strives to provide high quality, affordable health care to all Americans. In our current health-care delivery model, primary care providers (PCPs) are often not involved with subspecialists in a coordinated process. This has resulted in fragmented patient care, leading to increased health-care delivery costs. In contrast, the ACA is gearing toward the patient-centered medical home (PCMH) model, where PCPs are at the heart of health-care delivery and provide comprehensive, patient-centered, coordinated care (Davis et al. *J Gen Intern Med*. 2011;26[10]:1201). The expression "medical neighborhood" is increasingly more popular where the PCMH is surrounded by specialty clinics and ancillary service providers with primary care at the core (Huang et al. *N Engl J Med*. 2014;370[15]:1376). Therefore, it is obvious that primary care will be an integral part of health-care delivery in the years to come, as opposed to current circumstances where primary care accounts for only 6% to 7% of total health-care spending (Phillips et al. *Health Affairs*. 2010;29[5]:806).

Impact of the ACA on sleep medicine delivery

With the provisions of the ACA now in place, its impact on sleep medicine delivery is substantial. Despite the increasing prevalence of sleep disorders, the sleep medicine field faces numerous challenges in sleep disorders diagnostics and management. It has confronted implementation of sizeable cuts in reimbursement rates for in-lab PSG. As a result, use of home sleep testing (HST) has increased rapidly. HST is a cost-effective alternative to in-lab testing and provides an expedited route of care for patients who usually have to wait months for in-lab PSG appointments in sleep centers (Masa et al. *Sleep*. 2013;36[12]:1799). The American Academy of Sleep Medicine (AASM) has endorsed HST as an alternative method to diagnosing OSA among appropriately screened individuals; however, it must be conducted in conjunction with a comprehensive clinical sleep assessment (Collop et al. *J Clin Sleep Med*. 2007;3[7]:737). Therefore, having a sleep program at the center of this process (vs independent referrals to home sleep testing companies) is crucial for enforcement of the HST parameters established by the AASM.

Yet, PCPs – in order to comply with insurance company requirements – often refer patients needing evaluation for OSA for HST via an independent HST company that does not have a comprehensive sleep program. These patients are then prescribed automated treatment devices without appropriate education or access to follow-up with experienced sleep providers. This leaves PCPs, who often have limited training and access to sleep medicine resources, to manage problems with sleep apnea treatment devices, subsequently resulting in poor compliance to treatment and fragmented care (Pack. *Chest*. 2015;148[2]:306). Therefore, it is imperative to identify segments in our current sleep practice model that require restructuring, and provide a model inspired by ACA provisions to improve sleep care delivery.

Patient-centered medical home model for integrated sleep care



FRONTLINE MEDICAL NEWS

MEGAFLOPP/THINKSTOCK

Why move toward the PCMH?

Several studies have shown that primary care-led care for moderate to severe sleep apnea is not inferior when compared with care provided by sleep specialists. In one study (Antic et al. *Am J Respir Crit Care Med*. 2009;179:501), patients with suspected moderate-to-severe OSA were assigned to receive care from an experienced nurse, specialized in sleep disorders management, vs sleep-physician-directed care and laboratory PSG to confirm the diagnosis of OSA. Results showed that the simplified model of care was not inferior to the specialist sleep physician–led model, with no significant difference in continuous positive airway pressure (CPAP) adherence or Epworth Sleepiness Scale (ESS) score between the two groups. Costs were significantly less in the simplified model. Another study showed that primary care management of OSA in patients with moderate to severe

Continued on page 22

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OSA was not inferior to specialist management with regards to the change in ESS and showed no difference in OSA symptoms, adherence to CPAP, patient satisfaction, and health-care costs between the two groups (Chai-Coetzer et al. *JAMA*. 2013;309[10]:997). It is crucial to note, however, that although PCPs and community nurses were encouraged to take primary responsibility for patient management, prior experience, training, and education in sleep disorders management, as well as access to sleep specialists, were imperative in producing good outcomes in these studies.

A more recent study tested a collaborative care model, integrating sleep specialists with PCPs to enhance patients' sleep disorders management. Patients with sleep complaints in the intervention group underwent a one-time consultation with a sleep specialist who provided diagnostic feedback and treatment recommendations to the patient and his/her PCP, in contrast to the control group consisting of usual primary care (UPC). Results showed that provider-initiated sleep-focused interventions were significantly higher in the intervention group for PSG and mental health clinic referrals. Intervention recipients also showed increases in sleep efficiency and improved ESS scores at the 10-month follow-up. This demonstrates that a one-time sleep consultation, with access to, and oversight from, a specialist sleep center can serve to increase health-care providers' attention to sleep problems. Subsequently, it increases sleep disorders screening and diagnosis and results in benefits to patients' sleep/wake symptoms (Edinger et al. *Sleep*. 2016;39[1]:237).

Integration of sleep centers and primary care

As noted above, the quality of sleep medicine-related care that patients are receiving under our current model is suboptimal. In order to better fit the requirements of the ACA and provide integrated and coordinated sleep medicine care for our patients, we must consider refining our model of sleep medicine delivery by taking the steps below:

- Encourage partnership of sleep centers with primary care services to develop an integrated care paradigm for sleep medicine by placing PCPs at the center of our sleep care delivery model.
- Educate PCPs on the importance of sleep health, and provide them with appropriate access to resources for sleep testing.
- Allow PCPs to refer patients to a comprehensive sleep program that will be integrated in a PCMH model, providing HST, which will discourage referrals to independent home testing companies that do not offer comprehensive care.
- Strengthen and expand our sleep medicine teams within sleep centers and primary care centers by integrating trained nurse practitioners and physician assistants, who can serve as a resource for PCPs, and reduce fragmentation of care, thereby reducing costs of unnecessary testing.

Conclusions

In summary, the ACA has and will continue to impact sleep care delivery in the United States. An integrated sleep care model will result in not only meaningful improvements in the quality of sleep disorders care, but it will also help diagnose a vastly underdiagnosed condition. It will do so via a PCP-based model, providing access to sleep providers and sleep testing, yet it will encourage and educate the PCP to screen and treat noncomplex sleep disorders in their own practices. Below, we provide an example of this model. Patients via this model will have appropriate access to comprehensive sleep care that will reduce fragmentation of care. This PCMH sleep model is necessary in this post-ACA era that demands primary care provider-based, coordinated, high quality care.

Dr. Kundel and Dr. Shah are with the Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; and Dr. Shah is with the Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY.

Prenatal vitamin D failed to prevent wheezing

BY MARY ANN MOON
Frontline Medical News

Among pregnant women at high risk for having a child with asthma, high doses of vitamin D administered during the third trimester failed to prevent persistent wheezing illness in their children at age 3, according to two separate reports published online Jan. 26 in JAMA.

Both studies were conducted because vitamin D insufficiency during pregnancy is commonplace and is thought to affect fetal immune programming and to contribute to asthma pathogenesis. In addition, observational studies have found an association between low levels of vitamin D in cord blood and later asthma in the child.

The two randomized, double-blind placebo-controlled clinical trials found that neither 2,800 IU/day nor 4,400 IU/day of vitamin D significantly reduced the risk of persistent wheeze in the offspring through 3 years of age. However, both research groups noted that their studies may have been underpowered to detect a clinically important protective effect, and both recommended longer-term observation of their study participants, as well as further studies using larger sample sizes, higher doses of vitamin D, administration earlier in pregnancy, and postnatal supplementation to establish a definitive result.

The percentage of women with sufficient levels of vitamin D after the intervention was 81% in the vitamin D group, compared with 44% in the control group.

In the first study – conducted as part of the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort – 623 Danish women already taking the standard 400 IU of vitamin D_3 during pregnancy were randomly assigned to receive an additional 2,400 IU (315 women) or a matching placebo (308 women) from 22 to 26 weeks' gestation until delivery. After exclusions, researchers analyzed data on 581 children.

Maternal serum vitamin D levels increased markedly in the active-treatment group. The percentage of women with sufficient levels of vitamin D (greater than 30 ng/mL) after the intervention was 81% in the vitamin D group, compared with 44% in the control group, wrote Dr. Bo L. Chawes of Copenhagen Prospective Studies on Asthma in Childhood, University of Copenhagen, and his associates.

Persistent wheeze developed in 104 (18%) of the 581 children: 47 (16%) in the vitamin D group and 57 (20%) in the control group, a nonsignificant difference.

Similarly, asthma was diagnosed in 79 children: 32 (12%) in the vitamin D group and 47 (14%) in the control group, another nonsignificant difference.

Vitamin D supplementation also made no difference in infants' levels of C-reactive protein, interleukin-6, tumor necrosis factor–alpha, or CXCL8, nor in the number of upper respiratory tract infections (5.2 per year vs 5.3 per year), the number of lower respiratory tract infections (32% vs 33%), the risk of allergic sensitization as measured by skin prick test or specific IgE level, or the development of eczema (23% vs 25%).

However, the risk of persistent wheeze was higher in children whose mothers' vitamin D levels were lowest, compared with those whose mothers' vitamin D levels were in the middle and upper tertiles. And high-dose vitamin D was protective with regard to some secondary endpoints, such as preventing more episodes of "troublesome lung symptoms" (5.9 vs. 7.2).

This finding, together with the study's somewhat reduced statistical power, mean that a clinically important protective effect cannot be ruled out.

In addition, the supplementation dose may have been too low or may have been given too late in the course of pregnancy to produce a significant effect, Dr. Chawes and his associates wrote (JAMA. 2016;315[4]:353-61. doi: 10.1001/jama.2015.18318).

In the second study – the Vitamin D Antenatal Asthma Reduction Trial – 876 pregnant women in Boston, St. Louis, and San Diego who were already taking the standard 400 IU of vitamin D were randomly assigned to receive either an additional 4,000 IU/day (440 participants) or a matching placebo (436 participants).

Maternal levels of vitamin D rose markedly in the active-treatment group (mean, 39.2 ng/mL), compared with the control group (mean, 26.8 ng/mL), and the proportion of women who achieved higher than "inadequate" levels was much greater (74.9% vs 34.0%), reported Dr. Augusto A. Litonjua of Brigham and Women's Hospital, Boston, and his associates.

A total of 24.3% of the vitamin D group and 30.4% of the control group developed asthma or recurrent wheeze by age 3 years, a nonsignificant difference. However, the incidence of asthma was so much lower than anticipated in both study groups that the study may have lost statistical power to detect a clinically meaningful difference, according to the investigators (JAMA. 2016;315[4]:362-70. doi: 10.1001/jama.2015.18589).

It remains unclear whether vitamin D supplementation during pregnancy will reduce asthma and persistent wheezing in the offspring. "Larger studies and longer follow-up of the children in this study will be needed to answer the question," the investigators wrote. "If additional studies identify a significant effect, given the high prevalence of low vitamin D levels in pregnant women, the effect of this inexpensive intervention on child health could be substantial."

The first study was supported by the Copenhagen Prospective Study on Asthma in Childhood, which is funded by private and public research groups. One of the coauthors reported receiving consulting fees from Chiesi. The Vitamin D Antenatal Asthma Reduction Trial was supported by the U.S. National Heart, Lung, and Blood Institute and the National Centers for Advancing Translational Sciences. The lead author, Dr. Litonjua, reported receiving personal fees from UpToDate and Springer Humana Press; his associates reported ties to numerous industry sources.

THINKSTOCK

VIEW ON THE NEWS

Sobering results

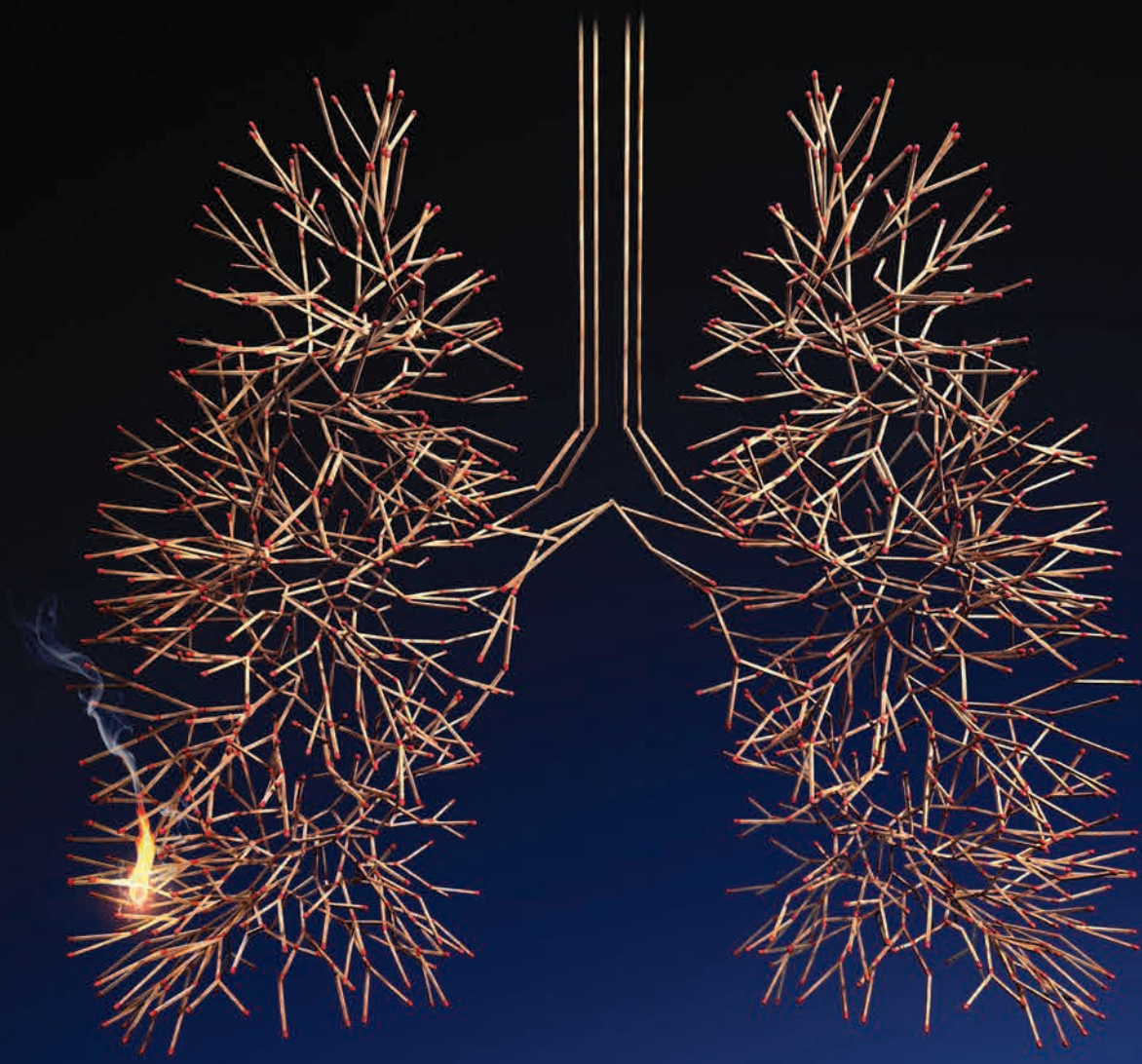
These are sobering findings. Even if we assume that prenatal vitamin D supplementation will prove more protective as the children in these studies grow older, vitamin D insufficiency still would explain only a small portion of the current asthma epidemic.

But neither study showed any unwanted effects from supplementation, so it seems reasonable for clinicians to prescribe vitamin D to mothers at high risk of having children with asthma by virtue of their own asthma, eczema, or allergic rhinitis – especially if those mothers are deficient in vitamin D. However, the data in these two clinical trials do not support the use of very high-dose vitamin D, since any beneficial effects achieved with 4,400 IU/day were identical to those achieved with approximately half as high a dose.

Dr. Erika von Mutius is at Ludwig Maximilians University, Munich. Dr. Fernando D. Martinez is at the asthma and airway disease research center and the department of pediatrics at the University of Arizona, Tucson. Both reported having no relevant financial disclosures. Their remarks are adapted from an editorial accompanying the two reports (JAMA 2016;315[4]:347-8.).

For reducing the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

BEFORE ONE EXACERBATION CAN LEAD TO ANOTHER,[1] ADD DALIRESP



INDICATION AND USAGE

DALIRESP® (roflumilast) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

Contraindications

DALIRESP® (roflumilast) is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate

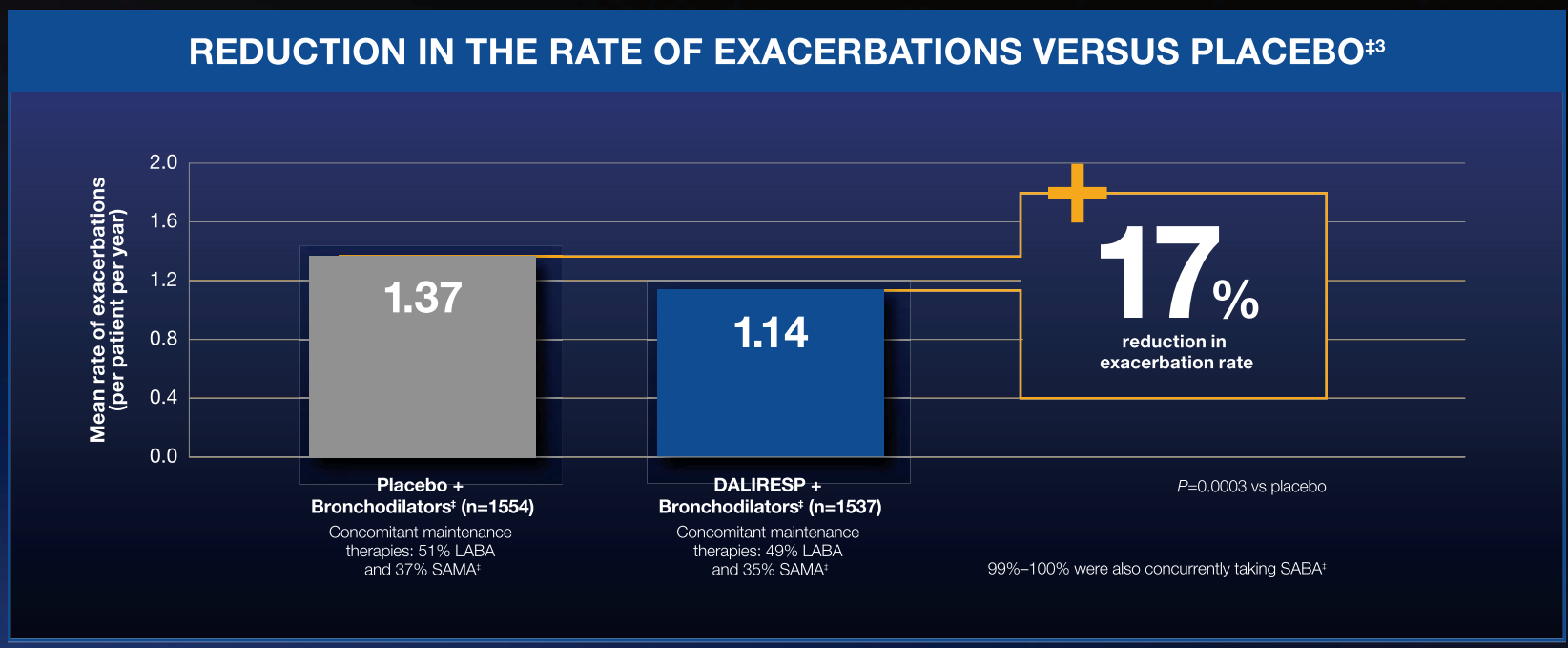
AstraZeneca

The first and only once-daily tablet to provide enhanced protection against COPD exacerbations*[2]

- **DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm**

In the two 1-year pivotal studies:

Significantly reduced the rate of moderate or severe exacerbations† on top of current bronchodilator therapy‡[3]



weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost

- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP

Adverse Reactions

In clinical trials, the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see Brief Summary on the following page.

*In the two 1-year pivotal studies, DALIRESP was added to bronchodilators, including long-acting β_2 agonists (LABA), or short-acting muscarinic antagonists (SAMA), and short-acting β_2 agonists (SABA).

†Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids, and severe exacerbations were defined as those resulting in hospitalization or death.

‡Patients were allowed to be on LABA or SAMA at stable doses. SABA was allowed for rescue use. In the pooled analysis, the use of concomitant bronchodilators in the placebo group vs DALIRESP group were: LABA (51% vs 49%), SAMA (37% vs 35%), and SABA (99% vs 100%).

Study design: A pooled analysis of two identical, 1-year, double-blind, placebo-controlled studies of 3091 patients with severe COPD associated with chronic bronchitis and a history of exacerbations compared DALIRESP (n=1537) and placebo (n=1554). Subjects were current or ex-smokers with a smoking history of >20 pack-years, aged >40 with a clinical diagnosis of COPD with chronic cough and sputum production. The study included a 4-week run-in period followed by a 1-year treatment period. Subjects could use SABAs as needed and could continue treatment with LABAs or SAMAs at stable doses. The studies were designed to assess the rate of moderate or severe COPD exacerbations and the change from baseline in pre-bronchodilator FEV_1.

References: 1. Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179:369-374. **2.** DALIRESP Prescribing Information. Wilmington, DE; AstraZeneca Pharmaceuticals LP; November 2015. **3.** Calverley PMA, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 Study Groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694.

Daliresp®
(roflumilast) tablets
500 mcg

DALIRESP® (roflumilast) tablets

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

INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

DOSAGE AND ADMINISTRATION

The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following condition:
Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6) in the full Prescribing Information*].

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo. Cases of suicidal ideation and behavior, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1) in the full Prescribing Information*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [*see Drugs that Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

ADVERSE REACTIONS

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

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Weight Decrease *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Adverse Reactions in Clinical Studies

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.

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP**	**Placebo**
	(**N=**4438)	**(N=**4192)
	n (%)	n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:
Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting
Infections and infestations - rhinitis, sinusitis, urinary tract infection
Musculoskeletal and connective tissue disorders - muscle spasms
Nervous system disorders - tremor
Psychiatric disorders - anxiety, depression

Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of DALIRESP received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to DALIRESP. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to DALIRESP exposure: hypersensitivity reactions (including angioedema, urticaria and rash), gynecomastia.

DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 *[see Clinical Pharmacology (12.3) in the full Prescribing Information].*

Drugs that Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3) in the full Prescribing Information].*

Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3) in the full Prescribing Information].*

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3) in the full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses >2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of >2 mg/kg/day).

Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were >65 years of age and 471 were >75 years of age. 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 patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3) in the full Prescribing Information].*

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3) in the full Prescribing Information].*

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information].*

OVERDOSAGE

Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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3217200 1/16 Iss.11/15

Technology could boost cystic fibrosis screening

BY BARBARA FEDER OSTROV, KAISER HEALTH NEWS

Stanford University scientists say they've devised a more accurate and comprehensive DNA test to screen newborns for cystic fibrosis.

Every state screens newborns for cystic fibrosis, but the current sequence of tests can miss cases. The new method, presented in a study published Feb. 1 in the Journal of Molecular Diagnostics, promises to be more efficient and cost effective, researchers said. It may also improve screening for nonwhite babies, for whom cystic fibrosis is rarer and harder to diagnose.

The test "offers the promise of potentially eliminating the false negative results that lead to miss ed cases," said Dr. Philip Farrell, a former dean of the University of Wisconsin School of Medicine and Public Health, Madison.

The new test uses "next generation" DNA sequencing that can quickly and more cheaply look at the entire CFTR gene, not just selected mutations. It does not require an extra blood sample. Rather, it uses blood drawn from the common newborn heel stick test that's already used to screen for a number of diseases, including cystic fibrosis. The advance can enable testing labs to review many newborn samples at a time and reduce costs, allowing a technology previously used to diagnose only individual cases to be applied to a large population.

"Next generation" DNA sequencing is only now becoming cheap and fast enough to even be considered for large-scale population screening. Scientists from Stanford, the California Department of Public Health, and the University of Texas at Austin conducted the research. Other U.S. scientists have been working on similar newborn screening approaches using next-generation DNA sequencing.

The test is not only quicker and cheaper, but also "very accurate," said Dr. Iris Schrijver, a Stanford University Medical School pathology professor who is one of the study's authors. "We can look at the entire gene and assess … all kinds of mutations in this single test," possibly in half the time of a current DNA test.

A spokesman for the California Department of Public Health, which oversees newborn screenings, said the current cost, including DNA testing, is approximately $113 per newborn, which is typically covered by insurers. In general, the spokesman noted, the agency's newborn screening program evaluates potential new testing methods for effectiveness and cost. "Historically, changes to existing testing methods have been rare, so the department cannot speculate on a timeline for this process," the spokesman wrote in an email.

A Stanford spokeswoman said its laboratory is running side-by-side comparisons of the new test and the current one, and its lab physicians expect to meet with public state health officials soon to discuss next steps.

This story was produced by Kaiser Health News, which publishes California Healthline, a service of the California Health Care Foundation.

ICU care bundle cut delirium, in-hospital deaths

BY KARI OAKES
Frontline Medical News

ORLANDO – Implementing an ICU care plan got patients moving and breathing on their own sooner. The interventions resulted in significantly less delirium and better in-hospital survival in 6,000 patients treated at seven community hospitals, according to data presented at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

The care bundle focused on minimizing sedation and maximizing patient mobilization. For each 10% increase in compliance with the care plan, community ICUs saw a 15% increase in delirium-free ICU days. In-hospital survival also increased by 15% for every 10% increase in implementation.

Each 10% increase in compliance with the care bundle was associated with a 15% increase in hospital survival.

The ICU Liberation project set forward the ABCDEF care bundle to operationalize the Society for Critical Care Medicine (SCCM) 2012 guidelines regarding pain, agitation, and delirium in the ICU.

"It's never quite clear whether guidelines, which are developed from randomized controlled trials in academic university hospitals, can be implemented in the community hospital setting. And as we know, the majority of critical care in our country is provided in the community hospital setting," said Mary Ann Barnes-Daly, an RN who is the regional clinical initiative lead for ICU Liberation at Sutter Health in Sacramento, Calif.

The care bundle calls for all ICU patients to have daily assessments for pain and delirium, spontaneous awakening and breathing trials, minimal sedation, early mobilization and exercise, and family involvement as part of the care team.

A dedicated RN, whose sole responsibility was to implement the ICU Liberation program, led the on-site teams. Other team members were an administrative RN, a pharmacist, a physical therapist, a respiratory care practitioner, and an ICU physician. In some hospitals, the physician was an intensivist, while in others, a hospitalist provided ICU care.

"We provided clinical education, and more importantly, interprofessional team education, where the teams learned to work together," said Ms. Barnes-Daly. Rounds were audited and audit results, along with ongoing data collection and reporting, were the basis for ongoing reporting and process improvement.

The mantra for care bundle implementation was "every patient, every day," said Ms. Barnes-Daly. Patient exclusions were based on safety and included such factors as hemodynamic, respiratory, or neurologic instability; open abdomen; active alcohol withdrawal; and new coronary ischemia.

Altogether, 6,064 patients were involved in the program; about one in four patients received mechanical ventilation during their stay. When patients were mechanically ventilated, all aspects of the care bundle were to be implemented. When patients were not receiving mechanical ventilation, only four aspects of the bundle applied and were measured. Overall, patients were mechanically ventilated for about 20% of the days observed.

Compliance with the care bundle was measured in two ways, said Ms. Barnes-Daly: One analysis was all-or-none, measuring the proportion of a patient's ICU stay for which all applicable bundle elements were implemented. The other measure allowed partial compliance; dose compliance was calculated by averaging the proportion of care bundle compliance for each day over the patient's ICU stay. This second analysis proved more sensitive in assessing the effects of the care bundle.

A dose-response ratio was noted between the number of delirium-free and coma-free days and the number of care bundle components delivered (*P* less than .001). Similarly, hospital survival also increased as bundle delivery increased, with each 10% increase in compliance associated with a 15% increase in hospital survival (*P* less than .001). When palliative care patients were removed from data analysis, hospital survival increased by 23% with each 10% increase in bundle compliance, said Ms. Barnes-Daly.

The study's strengths include "the large sample size, and the fact that we adjusted for age, Apache score, and mechanical ventilation," said Ms. Barnes-Daly. The limitations are that this was not a randomized controlled trial, and data were initially collected by the nurse team leader. Data collection was subsequently switched to the electronic ICU team.

The QI program was sponsored by the Society for Critical Care Medicine, and conducted at Sutter Health community Hospitals. Ms. Barnes-Daly reported receiving honoraria from the Society for Critical Care Medicine.

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AWS patients may not need pre-emptive intubation

BY NICOLA GARRETT
Frontline Medical News

FROM ANNALS OF THE AMERICAN THORACIC SOCIETY

People hospitalized with alcohol withdrawal syndrome (AWS) and treated with continuously infused high dose sedatives may not need to be intubated, as long as they are monitored for signs of worsening gas exchange and aspiration, suggests a single-center retrospective study.

Standard practice is to treat AWS patients with sedating drugs in order to mitigate the catecholamine storm and agitation. Even at low doses, these medications can cause cardiorespiratory instability and the issue of when to secure the airways of these patients has remained a clinical question.

In their study, (Ann Am Thorac Soc. 2016 Feb 1. 13[2],162-4) Dr. Robert Stewart of Texas A&M University, College Station, and his colleagues described the outcomes of 188 patients with AWS given lorazepam as a continuous infusion up to 1.2 mg per hour with intermittent boluses of 1-2 mg when their Clinical Institute Withdrawal Assessment Score was greater than 6.

Transfer to the ICU was initiated only as clinically indicated or when higher doses of continuous hypnotics were needed. For instance, 170 of the patients also received midazolam, all but 2 by continuous intravenous infusion (median total dose, 527 mg; all administered in ICU); 19 received propofol (median total dose, 6,000 mg); and 19 received dexmedetomidine (median total dose, 1,075 mg).

All patients were monitored by continuous pulse oximetry and nasal capnography and were only intubated when gas exchange worsened or

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macro-aspiration was observed.

No explicit criteria mandated intubation and clinicians, most of whom were ICU residents, were required to determine ad hoc the degree of gas exchange failure or apparent aspiration that warranted intubation.

Overall, 36 (19%) of the 188 patients required intubation. These patients tended to have a higher APACHE II score (greater than 10) and to receive substantially more benzodiazepine than non-intubated patients (761 mg of lorazepam equivalent vs 229 mg; *P* less than 0.0001).

Intubated patients also had longer hospital lengths of stays (median, 14.7 vs. 6.0 days; *P* less than 0.0001) and more pneumonias (58.3% vs. 5.9%; *P* less than 0.0001). One patient died, and had been intubated.

"Our study adds to those cited previously suggesting that high doses of sedatives can be given without mandatory intubation, provided patients are closely monitored," the researchers said. "Whether this practice is safer and more effective than pre-emptive intubation for such patients remains an open question."

The researchers declared no relevant conflicts of interest.

VIEW ON THE NEWS

Not every drip needs a plumber

Many clinicians feel comfortable administering benzodiazepines by intravenous bolus to patients without high levels of monitoring, yet will use continuous infusions only in more monitored settings such as an ICU in patients with "protected airways" via intubation and mechanical ventilation. The current study forces critical care clinicians to question the status quo.

Are we really helping patients by racing to intubate those we deem in need of continuous sedative infusions for AWS for fear of what might happen, when we know intubation and mechanical ventilation have their own risks?

Mechanical ventilation can be associated with pneumonia, weakness, and delirium. Further, patients with alcohol withdrawal syndrome who receive invasive mechanical ventilation are more likely to have poor outcomes.

The current study illustrated the use of low-dose continuous benzodiazepines (lorazepam) on the general hospital wards and deferred intubation. Nevertheless, there were limitations to the study stemming from its design as a retrospective analysis of a single center's experience. Also, it was not clear how safe or effective a similar protocol of continuous benzodiazepine infusions coupled with delayed intubation might be in a setting in which practitioners are less comfortable with the complications of AWS and its treatments and have less access to continuous end-tidal carbon dioxide measurements.

Dr. Hayley B. Gershengorn is with the Albert Einstein College of Medicine, New York. She made her remarks in an editorial (Ann Am Thorac Soc. 2016 Feb 1. 13[2], 162–4) that accompanied the study.

A better way to relieve rib fracture pain in the ICU

BY M. ALEXANDER OTTO
Frontline Medical News

AT THE EAST SCIENTIFIC ASSEMBLY

SAN ANTONIO – A new pain relief option for multiple rib fractures means that you might not have to wait around anymore for anesthesiology to place thoracic epidurals.

It's called posterior paramedian subrhomboidal (PoPS) analgesia. A skin incision is made below the lowest fractured rib just paramedian to the spinus processes; a tunneling device is then used to work a catheter upwards under the rhomboids just past the highest fractured rib. The catheter has multiple openings along its length – like a sprinkler hose – so analgesic bathes the intercostal nerves as it runs down from a reservoir into the patient. The reservoir can be set to a desired flow rate or for on-demand use (ON-Q Pain Re-

lief System – Halyard).

A pilot study at the University of Kansas, Kansas City, found that pain control from PoPS was at least equivalent to standard thoracic epidural analgesia (TEA), and that the system can be placed by a variety of hospital staff, not just anesthesiologists.

The 11 PoPS patients also used fewer rescue narcotics than the 19 TEA patients and had less hypotension. Because they weren't at risk for epidural hematomas, they started venous thromboembolism prophylaxis without delay and at full dose.

"Our results are very promising. PoPS provides pain control similar to that of TEA," with several "other benefits. You are not relying on one specialty for pain control," so patients probably get faster relief. "PoPS can also be placed in patients whose injuries prohibit TEA, such as those with spinal cord injuries or increased intracranial pressure," said investigator Dr. Casey Shelley, a University of

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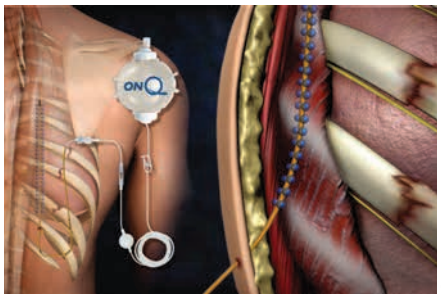

COURTESY OF DR. MICHAEL TRUITT, METHODIST DALLAS MEDICAL CENTER

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Kansas general surgery resident.

PoPS was placed in the study either by anesthesiologists or by a trauma surgeon who practiced placement beforehand in the cadaver lab. The do-it-yourself potential for surgeons "is key. Most of us trauma surgeons are sick of begging anesthesiologists to come place thoracic epidurals," said an audience member after Dr. Shelley's presentation at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Ropivacaine 0.2% was used in both PoPS and TEA patients, all of whom had at least three broken ribs.

Median pain scores dropped from 8.5 to 2.5 on a 10-point scale an hour after PoPS placement, versus a median drop from 8 to 5 points an hour after TEA ($P = .03$). Although not statistically significant, median pain scores were about 1.5 points better with PoPS over the next several days, hovering around 3.5 versus around 5 points with TEA. Anesthesiology "usually won't place high thoracic epidurals. With PoPS, you can tunnel up as far as you need to go to get to higher ribs," which might explain the better pain control, Dr. Shelley said.

PoPS patients used about 70 mg/day oral mor-

phine equivalents versus about 90 mg/day with TEA through day 6, but again the difference was not statistically significant. Even so, it might explain why six TEA patients (32%) were hypotensive over that time, compared with two PoPS patients (18%).

PoPS patients were a little older on average (mean 63 versus 55 years), with more fractured ribs (mean eight versus seven), and higher Injury Severity Scale scores (mean 20 versus 16). They were also more likely to have bilateral fractures, longer ICU stays (mean 4.9 versus 3.1 days), and longer overall lengths of stay (mean 14.8 versus 9.8 days), but none of those trends were statistically significant.

Both groups had mean chest Abbreviated Injury Scale scores of 3, and there were no statistical differences in daily spirometry readings. The majority of patients in both groups were men.

Favorable results were also reported in 2010 for ON-Q rib pain control, but the investigators did not compare the system to TEA (World J Surg. 2010 Oct;34:2359-62).

Dr. Shelley said Halyard was not involved in the study, and that she has no disclosures.

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NSQIP calculator fails to stratify stage I NSCLC risk

BY MARK S. LESNEY
Frontline Medical News

A study performed to validate the National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator for use in patients receiving surgery or stereotactic body radiation therapy (SBRT) for stage I non–small cell lung cancer showed the calculator to be inadequate for both classification and risk stratification.

The study was reported in the Journal of Thoracic and Cardiovascular Surgery (2016;151;697-705). Dr. Pamela Samson of Washington University in St. Louis and her colleagues performed a retrospective analysis of 485 patients with clinical stage I NSCLC who underwent either surgery (277) or SBRT (195) from 2009 to 2012. Surgery was either wedge resection (19.3%) or lobectomy (74.5%), with smaller percentages receiving segmentectomy (4.0%), pneumonectomy (1.5%), and bilobectomy (0.7%).

A large majority of surgical patients (84.1%) underwent a video-assisted thoracoscopic surgery (VATS) approach.

The researchers calculated NSQIP complication risk estimates for both surgical and SBRT patients using the NSQIP Surgical Risk Calculator. They compared predicted risk with actual adverse events.

Compared with patients undergoing VATS wedge resection, patients receiving SBRT were older, had larger tumors, lower forced expiratory volume (FEV_1) and diffusing capacity of the lungs for carbon monoxide (DLCO), higher American Society of Anesthesiologist scores, higher rates of dyspnea and higher NSQIP serious complication risk estimates, all significant at *P* less than .05. Similar disparities were seen in comparing patients receiving SBRT vs. VATS lobectomy.

The actual serious complication rate for surgical patients was significantly higher than the NSQIP risk calculator prediction (16.6% vs. 8.8%), as was the rate of pneumonia (6.0% vs. 3.2%), both at *P* less than .05.

Overall, the NSQIP Surgical Risk Calculator provided a fair level of discrimination between VATS lobectomy and SBRT on receiver operating characteristic (ROC) curve analysis, but it was a poor model for differentiating between VATS wedge resection and SBRT.

"Unfortunately, it is this latter population of the highest risk surgical patients (for whom a lobectomy is not a surgical option) where risk models and decision aids are needed most," Dr. Samson and her colleagues stated.

"Counseling the high-risk but operable patient with clinical stage I NSCLC in regard to lobectomy, sublobar resection, or SBRT is challenging for both the clinician and the patient," according to the researchers.

"We believe that a model tailored to patients with clinical stage I needs to serve as both an estimator of operative risks and a patient decision aid for surgery versus SBRT, espe-

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Poor adherence to quality indicators in NSCLC surgery

BY DOUG BRUNK
Frontline Medical News

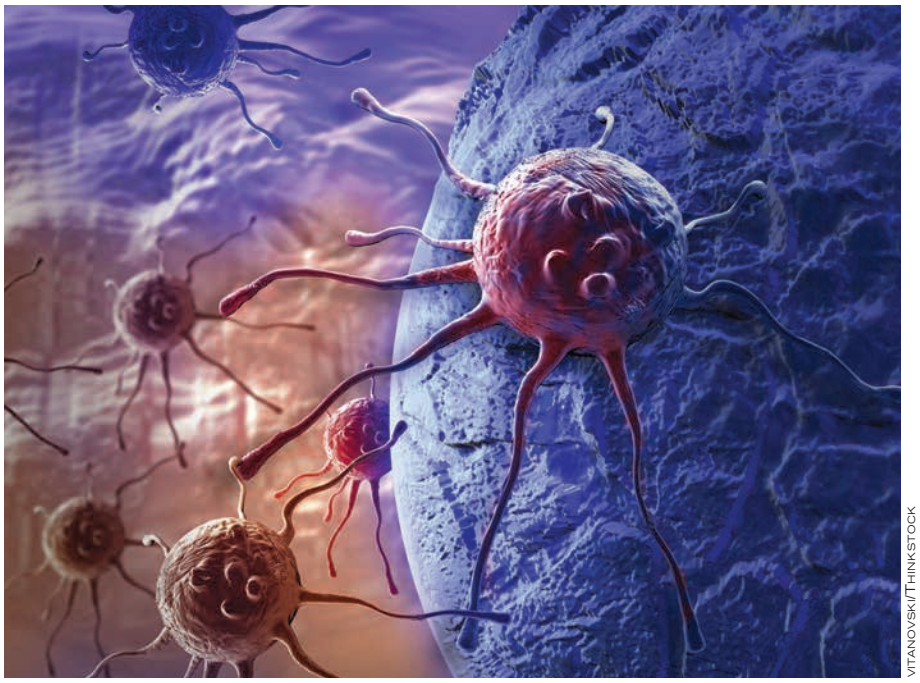
PHOENIX – National adherence to quality indicators for surgery in stage I non–small cell lung cancer is suboptimal, results from a large analysis of national data suggest.

"Compliance with such guidelines is a strong predictor of long-term survival, and vigorous efforts should be instituted at the level of national societies to improve such adherence," researchers led by Dr. Pamela P. Samson wrote in a study presented at the annual meeting of the Society of Thoracic Surgeons.

"National organizations, including the American College of Chest Physicians (CHEST), the National Comprehensive Cancer Network, and the American College of Surgeons Commission on Cancer, have recommended quality standards for surgery in early-stage non–small cell lung cancer (NSCLC). The determinants and outcomes of adherence to these guidelines for early-stage lung cancer patients are largely unknown."

Dr. Samson, a general surgery resident at Washington University in St. Louis, and her associates used the National Cancer Data Base to evaluate data from 146,908 patients undergoing surgery for clinical stage I NSCLC between 2004 and 2013.

They selected the following four quality measures for evaluation: performing an anatomical pulmonary resection, surgery within 8 weeks of diagnosis, R0 resection, and evaluation of 10 or more lymph nodes. Next, the researchers fitted multivariate models to identify variables independently associated with adherence to quality measures, and created a Cox multivariate model to evaluate long-term overall survival.



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The strongest determinant of long-term overall survival included pathologic upstaging (HR 1.84) and meeting all four quality indicators (HR 0.39). Every additional quality measure met was associated with a significant reduction in overall mortality.

Dr. Varun Puri, senior author of the study, presented the findings at the STS meeting on behalf of Dr. Samson.

The researchers found that between 2004 and 2013, nearly 100% of patients met at least one of the four recommended criteria, 95% met two, 69% met three, and 22% met all four. Sampling of 10 or more lymph nodes was the least frequently met measure, occurring in 31% of surgical patients.

Patient factors associated with a greater likelihood of receiving all four quality measures included average income in ZIP code of at least $38,000 (odds ratio, 1.20), private insurance (OR, 1.22), or having Medicare (OR, 1.16). Institutional factors associated with a greater likelihood of meeting all four quality measures included higher-volume centers, defined as treating at least 38 cases per year (OR, 1.18), or being an academic institution (OR, 1.31).

At the same time, factors associated with a lower likelihood of recommended surgical care included increasing age (per year increase, OR, 0.99) and a higher Charlson/Deyo comorbidity score (OR, 0.90 for a score of 1 and OR, 0.82 for a score of 2 or more). The strongest determinant of long-term overall survival included pathologic upstaging (HR 1.84) and meeting all four quality indicators (HR 0.39). Every additional quality measure met was associated with a significant reduction in overall mortality.

"We believe this study can be a starting point to draw attention to institution- and surgeon-specific practice patterns that may vary widely," Dr. Samson said in an interview prior to the meeting. "At our own institution, we are working to decrease time to surgery, as well as implementing quality improvement measures to increase nodal sampling rates. Improving these trends nationally must start at the local level, with a tailored approach."

Dr. Samson is currently supported by a T32 NIH training grant for research fellows in cardiothoracic surgery. Study coauthor Dr. Bryan Meyers, has received honoraria from Varian Medical Systems and is a consultant/advisory board member of Ethicon. Senior author Dr. Varun Puri is supported by NIH career awards.

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Continued from previous page

cially with projected increases in the number of early-stage lung cancers as a result of increased lung cancer screening efforts," they added.

"Our analysis suggests that the NSQIP Surgical Risk Calculator likely does not profile the risk of a patient with lung cancer closely enough to dichotomize surgical and inoperable SBRT cases (especially when patients are being considered for a wedge resection) or adequately estimate a surgical patient's risk of serious complications," Dr. Samson and her colleagues concluded.

The study was supported by grants from National Institutes of Health. The authors had no relevant financial disclosures.

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VIEW ON THE NEWS

Risk calculators can be useful, but...

In their reported study, Dr. Samson and her colleagues found that the NSQIP tool underestimated morbidity. They also found that risk predicted by the NSQIP tool was not necessarily aligned with their institution's actual treatment selection for stage I NSCLC, which they based upon a number of factors. "This study potentially has important clinical implications," according to Dr. Xiaofei Wang and Dr. Mark F. Berry in their invited commentary (J Thorac Cardiovasc Surg. 2016 Mar;151:706-7). "This present study shows that even a robust, well-managed tool from the NSQIP does not adequately stratify surgical risk... Their analysis implies that the treatment decision made by the institutional clinicians is optimal."

"The lackluster performance of the NSQIP score is understandable, because it was not designed to optimally differentiate patients who benefited most from surgery or SBRT. Randomized clinical trials or well-controlled prospective observations are needed to develop and validate specific predictive tools for optimal treatment selection. These models must consider not only treatment morbidity, but also the cost of possible recurrence with each therapy," Dr. Wang and Dr. Berry stated.

"Perhaps the most important conclusion that can be drawn from this present study is that current risk assessment tools can be helpful, but cannot replace evaluation by clinicians for whom all management options are available when therapy is chosen for a specific patient," they concluded.

Dr. Wang is from the department of biostatistics and bioinformatics at Duke University, Durham, N.C., and Dr. Berry is from the department of cardiothoracic surgery, Stanford University, Stanford, Calif. They had no relevant financial disclosures.

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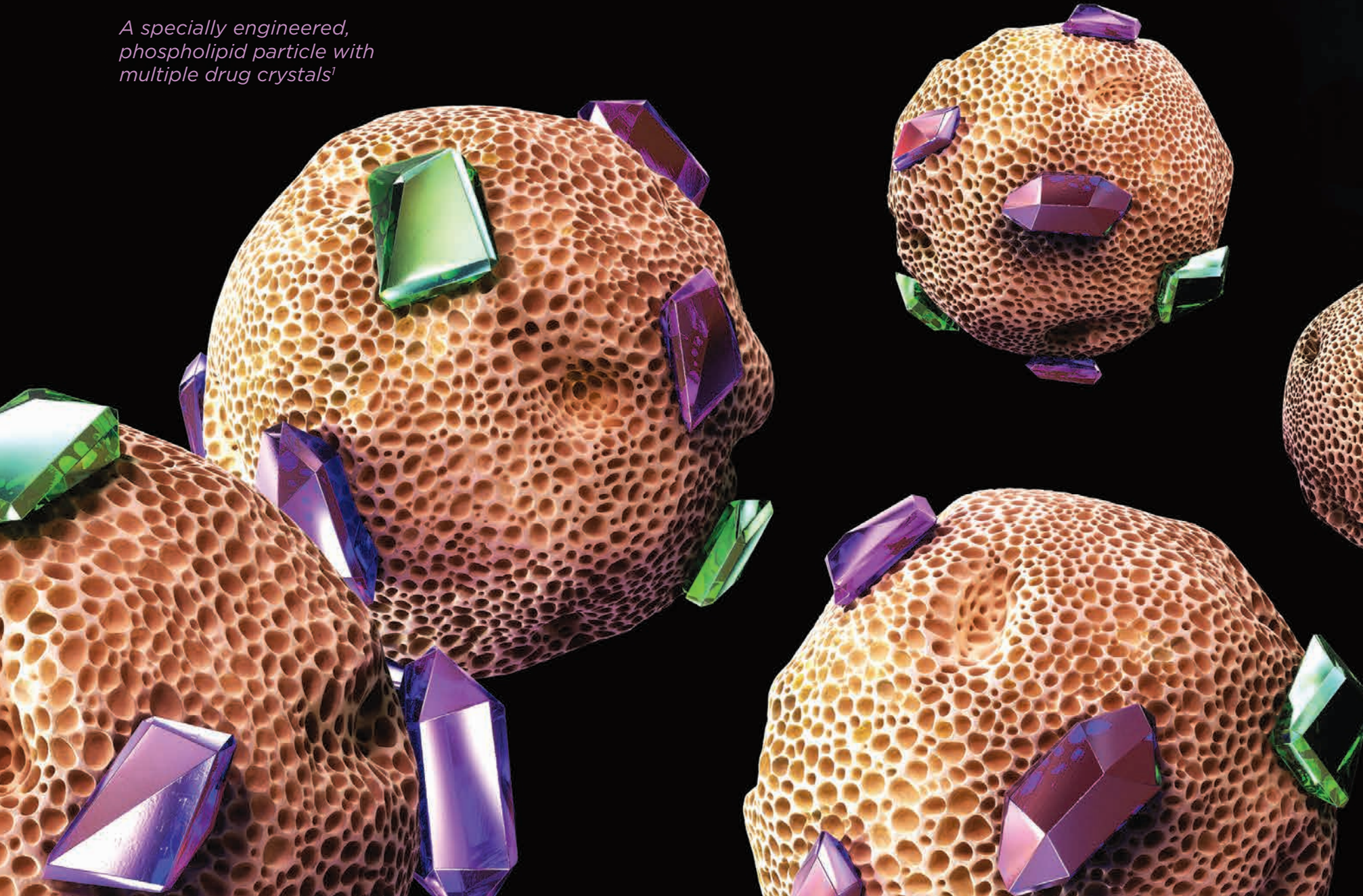

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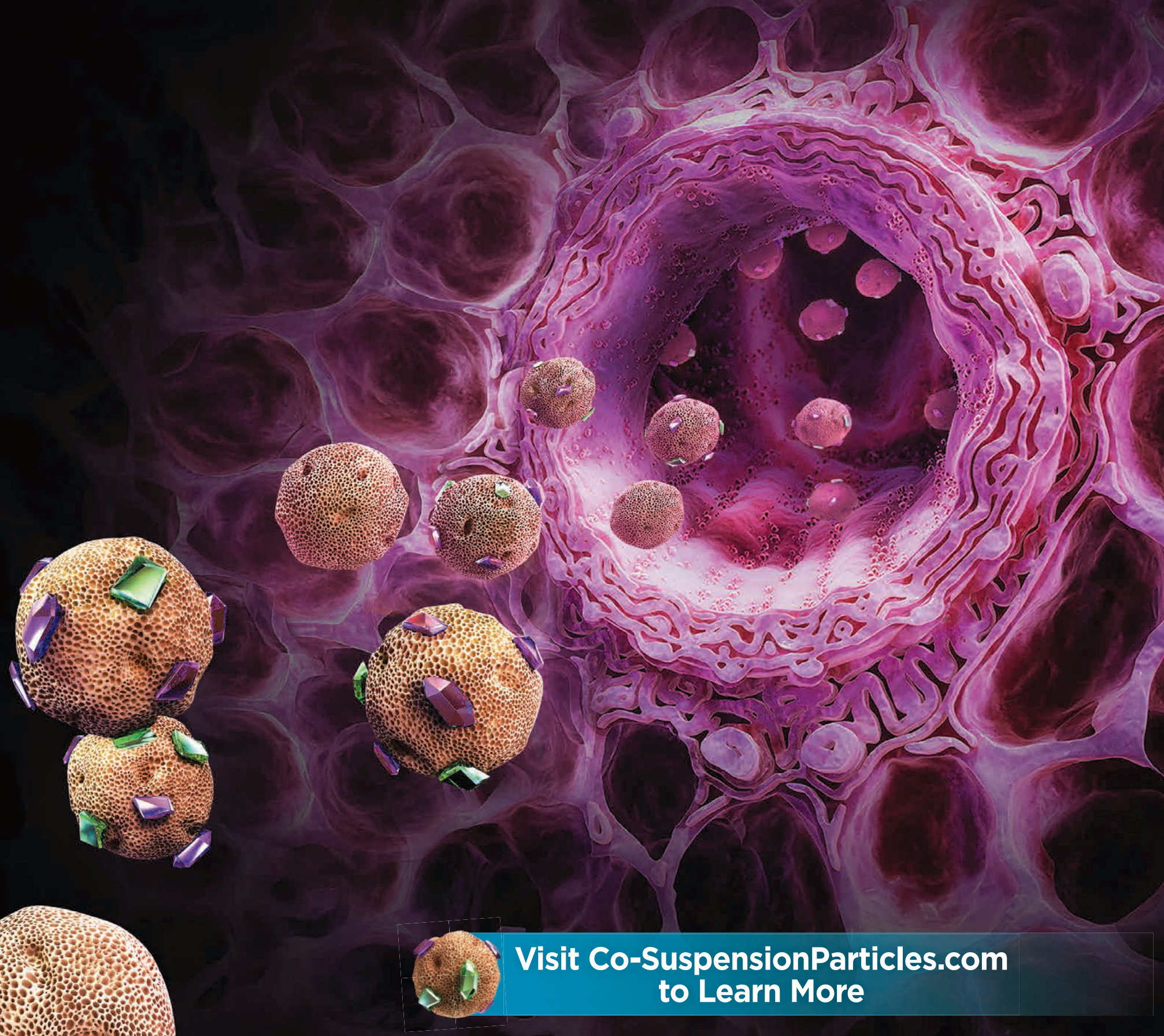

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AstraZeneca

Selecting lesions for endoluminal bronchoscopy

BY DOUG BRUNK
Frontline Medical News

PHOENIX – According to Dr. Moishe Liberman, promising lesions for bronchoscopic endoluminal treatment include endobronchial lesions and intraluminal exophytic tumors within the trachea or main bronchus, provided that the distal airway lumen is visible and you can get past the tumor with a flexible endoscope.

"We always teach the fellows that if you get pus back when you're trying to get around the tumor or play with the tumor, you're usually going to have a very good result," said Dr. Liberman, a thoracic surgeon who directs the endoscopic tracheo-bronchial and oesophageal center at the Centre hospitalier de l'Université de Montréal, Quebec, Canada. "If you play with the tumor and you get the tumor out and you get nothing back, usually the CT scan or the X-ray postoperatively is going to look just like it did preoperatively, even though endoscopically you might have a good result."

Central lesions are also excellent candidates for endoluminal therapy, he said at the meeting.

Distal lesions in the small bronchi "are candidates but are much more difficult and require more specialized tools. The shorter the lesion, the more likely you are to have good success."

Available options for delivering energy endoscopically include electrocautery, argon plasma coagulation, laser, and cryotherapy.

A disadvantage of all of the thermal modalities except for cryotherapy "include the potential for airway fire and you have to work with low FiO2s [fraction of inspired oxygen]," Dr. Liberman noted. "A lot of these patients need high FiO_2s to saturate, so I think that's always an issue. We never go on cardiopulmonary bypass to do these cases and we never cannulate patients to do these cases. You also have to worry about gas emboli, especially when you open up big vessels. These modalities can also cause inadvertent airway injury, delayed effects, and bronchoscope damage."

In general, he continued, laser-tissue interactions depend on the power and the wavelength of the laser as well as the color and the water content of the target tissue.

"The power density of the wavelength you choose determines its ability to cut, coagulate, or vaporize the tissue," he said. "As the power density increases, the laser fiber approaches the target tissue. Power density is more important than the energy delivered."

The Nd:YAG (neodymium-doped yttrium aluminium garnet) laser, which causes more destruction in the deep tissue than on the surface, is the most common laser used in interventional airway procedures, he said.

Two other commonly used lasers include the KTP (potassium titanyl phosphate) and the CO_2.

"I like CO_2s a lot for upper airway and subglottic problems as well as vocal cord problems," Dr. Liberman said. "It's very precise and has low penetration. The Nd:YAG is very good for deep penetration. You need familiarity with these. I don't think you can just take one of these off the shelf if you've never used it before. Sometimes your ENT [ear nose and throat] or urology colleagues can help you, because they're using a lot more of these lasers than we are."

Contraindications for laser bronchoscopy include operable lesions.

Dr. Liberman said that while he and his associates use lasers in a preoperative setting, "we're very careful not to damage proximal or distal airway when we know we're going to do a sleeve resection or pneumonectomy."

Other contraindications for laser bronchoscopy include patients with a poor short-term prognosis, severe coagulation disorder, extrinsic airway obstruction, tracheoesophageal fistula or T-Med fistula, those with extensive submucosal disease causing obstruction, and those with lesion adjacent to the esophagus or to a major vessel.

Dr. Liberman reported having received research grants from Ethicon, Boston Scientific, Olympus, Covidien, and Baxter.

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BMI impacts risk for complications after lung resection

BY DOUG BRUNK
Frontline Medical News

PHOENIX – Being underweight is associated with a substantially increased risk of complications following lung resection for cancer, results from a large database study found.

"This is not generally known among surgeons or their patients," Dr. Trevor Williams said in an interview before the annual meeting of the Society of Thoracic Surgeons. "Studies are conflicting about the relationship of BMI [body mass index] to surgical outcomes. Most of the previous studies simply categorize BMI as overweight or not. We've stratified based on World Health Organization categories to get a more precise look at BMI."

Dr. Williams, a surgeon at the University of Chicago Medical Center, and his associates evaluated 41,446 patients in the STS General Thoracic Surgery Database who underwent elective anatomic lung resection for cancer between 2009 and 2014. Their mean age was 68 years, and 53% were female. The researchers performed multivariable analysis after adjusting for validated STS risk model covariates, including gender and spirometry.

According to WHO criteria for BMI, 3% were underweight (less than 18.5 kg/m^2); 33.5% were normal weight (18.5-24.9 kg/m^2); 35.4% were overweight (25-29.9 kg/m^2); 18.1% were obese I (30-34.9 kg/m^2); 6.4% were obese II (35-39.9 kg/m^2), and 3.6% were obese III (40 kg/m^2 or greater).

Dr. Williams and his associates observed that women were more often underweight, compared with men (4.1% vs. 1.8%, respectively; *P* less than .001), and underweight patients more often had chronic obstructive pulmonary disease (51.7% vs. 35.2%; *P* less than .001). Pulmonary complication rates were higher among underweight and obese III patients (*P* less than .001), while being underweight was also associated with higher rates of infections and any surgical complications.

Surprisingly, obese patients have a lower risk of overall complications than 'normal'-BMI patients.

DR. WILLIAMS

Multivariable analysis revealed that pulmonary and any postoperative complications were more common among underweight patients (odds ratio, 1.44 and OR, 1.41, respectively), while any major complication was more common among obese III patients (OR, 1.18). Overweight and obese I-II patients were less likely to have any postoperative and pulmonary complications, compared with patients who had a normal BMI.

"The finding of underweight patients being such a high-risk patient population is suggested in the literature but not demonstrated as clearly as in this study," Dr. Williams said. "A truly surprising finding was that obese patients actually have a lower risk of pulmonary and overall complications than 'normal'-BMI patients."

He concluded that according to the current analysis, "careful risk assessment is appropriate when considering operating on underweight patients. Whether there are interventions that could be instituted to improve an individual's risk profile has not been determined. Any preconceived notions about not operating on obese patients due to elevated risk appear to be unfounded."

Dr. Williams reported having no financial disclosures.

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PRESIDENT'S REPORT: An open letter to President Obama

BY DR. BARBARA A. PHILLIPS, MSPH, FCCP

This month, we sent a letter to President Obama supporting ratification of the Framework Convention on Tobacco Control (FCTC) by the United States. Our goal was to let the President know it is our feeling that now is the right time for the United States to start playing a leading role in world tobacco control based on the scientific support of CHEST. Joining me in sending this letter was Dr. Panagiotis K. Behrakis, FCCP, who serves as a Regent-at-Large on the CHEST Board of Regents. As President of the Scientific Committee on the European Network of Smoking and Tobacco Prevention and a former Chair of CHEST's Council of Global Governors, Dr. Behrakis has been closely following the history of the FCTC since its beginning more than 10 years ago. He suggested that this open letter to President Obama might be a very effective first step toward the desired ratification of FCTC by the United States. I was happy to join Dr. Behrakis in sending the following letter, on behalf of CHEST.

DR. PHILLIPS

DR. BEHRAKIS

CHEST
AMERICAN COLLEGE of CHEST PHYSICIANS

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chestnet.org

To champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

March 1, 2016

The President
The White House
1600 Pennsylvania Avenue NW
Washington, DC 20500

Dear Mr. President,

Addiction to tobacco is the largest preventable cause of death and disability worldwide, expected to cause one billion deaths this century. In addition, passive smoking is estimated to cause over 600,000 deaths annually, 150,000 of which are among children.

These staggering numbers can only be prevented by a global consensus on the protection of public health from tobacco use. A supranational coordination for the solution to the problem is the Framework Convention on Tobacco Control of the World Health Organization (FCTC, WHO). The FCTC is an evidence-based treaty reaffirming the right of all people to the highest standard of health. As stated in its preamble, it seeks "to protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke" by enacting a set of universal standards stating the dangers of tobacco and limiting its use in all forms worldwide. To this end, the treaty's provisions include rules that govern the production, sale, distribution, advertisement, and taxation of tobacco.

The FCTC was adopted as the first global treaty negotiated under the auspices of the WHO by the World Health Assembly in May 2003, entered into force in February 2005, and very soon became one of the most rapidly and widely embraced treaties in the history of the United Nations. Currently, the FCTC has been ratified by 180 countries, corresponding to more than 80% of the world population. Only seven countries, the most prominent of which being the United States of America, have signed but not yet ratified the treaty. Interestingly, the USA played an active role in the long preparatory phase and the signing of the treaty in May 2004 but has not yet ratified the FCTC.

Within the past six Conferences of the Parties (COP) of FCTC, the absence of the USA as an active member results as following:

- The leading role of the USA is absent from the most important efforts of the United Nations toward the protection of public health.
- In the decision-making process of the FCTC, the most powerful nation in the world is silent.
- The excellent national actions to curb the tobacco epidemic in the USA fail to be transferred to the global level.

As an ambassador for the protection of human rights at a global level, the USA's leadership is needed to ensure implementation worldwide of FCTC articles for the protection of children, women, and other vulnerable populations.

(continued)

We are reaching out to you on behalf of the American College of Chest Physicians (CHEST). With more than 19,000 members representing 100+ countries around the world, CHEST is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. Our mission is to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research. Over our 80+ years in existence, CHEST has been active on a global level raising awareness about the dangers of tobacco use and the importance of lung health. We were one of the first medical organizations to recognize the dangers of cigarette smoking and were instrumental in helping pass legislation requiring printing the Surgeon General's warning on cigarette packages. We were also instrumental in the passage of legislation banning smoking on domestic flights.

In light of the above, as a board member and as a board chair and President of CHEST, we feel it is our duty to urge the First Citizen of the strongest nation in the world to take the historic decision of addressing the largest preventable threat to human health and to ratify the WHO Framework Convention on Tobacco Control.

Most Respectfully,

Panagiotis K. Behrakis, MD, PhD (McGill), FCCP, Pulmonologist-Intensivist
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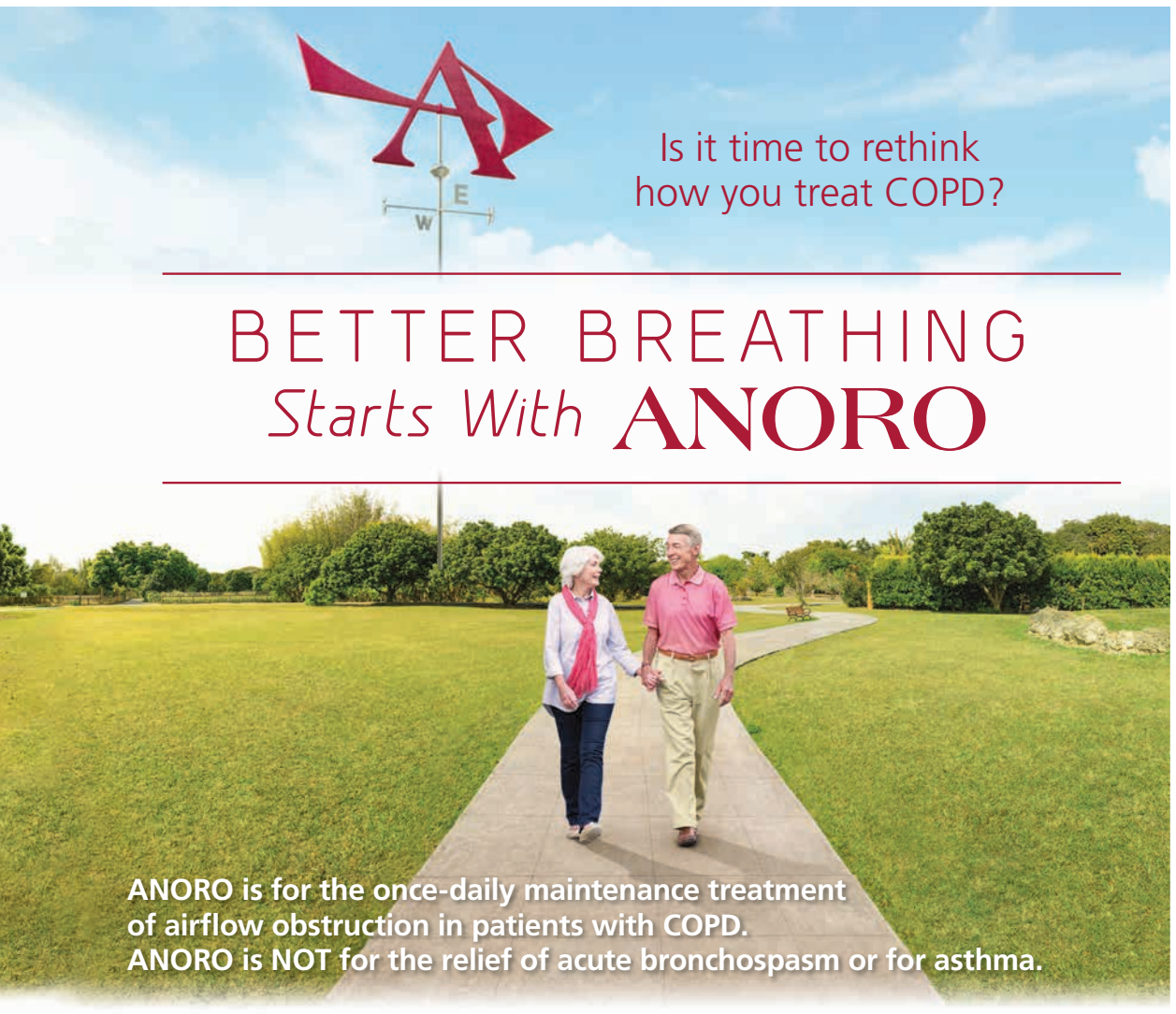
Continued on page 46

In a subset (n=366) of a managed care population with a diagnosis of COPD

81% of patients had moderate or worse COPD at spirometry-confirmed diagnosis[1]



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

In the study referenced above, COPD severity was based on GOLD classification at time of study: 50% moderate, 26% severe, 5% very severe.
COPD=chronic obstructive pulmonary disease; GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. 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 LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA 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.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this advertisement.

gsk | Theravance

ANORO for the maintenance treatment of COPD

Description of Lung Function Comparison Studies[2-4]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) were evaluated in 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted (ranges for each study were within GOLD classification 2, 3, or 4). The studies were not powered to compare the safety profile of ANORO ELLIPTA with that of SPIRIVA HandiHaler.

Primary endpoint: Trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).

FEV_1=forced expiratory volume in 1 second.

SPIRIVA and HandiHaler are registered trademarks owned by Boehringer Ingelheim.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

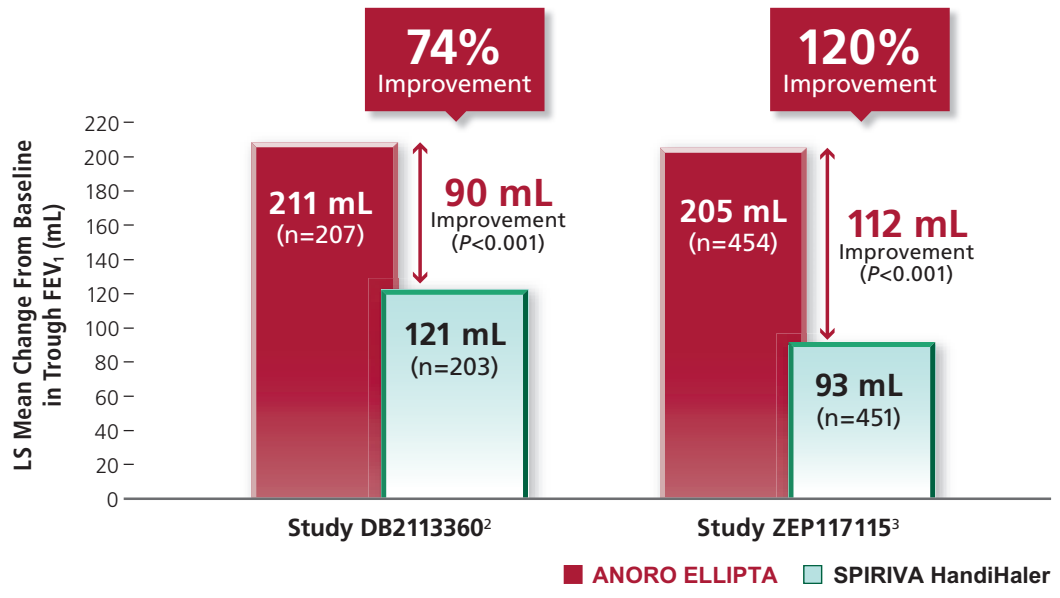
ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

For patients with moderate or worse COPD

Start with ANORO ELLIPTA instead of SPIRIVA HandiHaler for superior improvement in lung function

ANORO ELLIPTA DELIVERED SIGNIFICANT IMPROVEMENT IN TROUGH FEV_1 vs SPIRIVA HandiHaler AT DAY 169 IN 2 STUDIES[2,3]



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

SPIRIVA HandiHaler is an anticholinergic for the maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[5]

In a separate study, ANORO ELLIPTA showed a 60-mL difference* compared with SPIRIVA HandiHaler (208 mL and 149 mL, respectively), but due to testing hierarchy, statistical significance cannot be inferred.[2]

LS=least squares.
*Reflects rounding.

Important Safety Information (cont'd)

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA 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, such as vilanterol, on the cardiovascular system may be potentiated by these agents.

DRUG INTERACTIONS (cont'd)

- 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 electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Learn more at
StartWithANORO.com

Please see additional Important Safety Information for ANORO ELLIPTA on preceding pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

References: 1. Mapel DW, Dalal AA, Blanchette CM, et al. Severity of COPD at initial spirometry-confirmed diagnosis: data from medical charts and administrative claims. *Int J Chron Obstruct Pulmon Dis*. 2011;6:573-581. **2.** Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*. 2014;2(6):472-486. **3.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med*. 2014;108(12):1752-1760. **4.** Data on file, GSK. **5.** SPIRIVA HandiHaler [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE
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) 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 LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

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

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

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

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

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

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. Instruct patients to consult a physician immediately should any of these signs or symptoms develops.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a 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 (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 05/2014 ANR:2BRS

FROM THE EVP/CEO: Focused on our international initiatives

BY PAUL A. MARKOWSKI, CAE

CHEST leaders participated in a February meeting of the Forum of International Respiratory Societies (FIRS) in Kyoto, Japan, along with representatives from Asociación Latinoamericana del Thorax (ALAT), the American Thoracic Society (ATS), the Asian Pacific Society of Respirology (APSR), the European Respiratory Society (ERS), the International Union Against Tuberculosis and Lung Disease (The Union), and the Pan African Thoracic Society (PATS). Established in 2001, the forum aims to promote advocacy in matters of global respiratory health and the identification of new areas for global initiatives. CHEST leaders attending included Dr. Darcy Marciniuk, FCCP; Dr. Barbara Phillips, FCCP; and Mr. Paul Markowski (3rd, 4th, and 5th from right, respectively).

CHEST is committed to being the global leader in clinical chest medicine. Our vision affirms it: CHEST is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. Our organization is a diverse community of experts and peers, representing more than 100 countries, giving us ample opportunity to collaborate and advance chest medicine around the world. Recently, we reviewed our international work to ensure we're meeting education needs and fulfilling leadership responsibilities around the world. I'm happy to say we're in good standing on both counts.

To be effective and efficient in our international education offerings, we have identified premier programs and products that readily allow us to share the CHEST brand and reputation across the globe. We offer standardized delivery and execution to ensure everyone receives the same high-quality CHEST experience. These programs include:

- CHEST live learning events, held in international locations
- *CHEST* journal-branded meetings
- Grant partnerships for international fellows
- Captured content from live events

Our live learning events are scalable to accommodate larger or smaller meetings, enabling them to be delivered across multiple locations and countries. We invite CHEST leadership and faculty to collaborate with local partners to provide expertise and lead sessions.

Similarly, *CHEST* journal-branded meetings, developed and held in partnership with our journal publisher Elsevier, offer the same value and benefits as our live learning events. Content can focus on a specific disease state or have a broader topic reach. Journal editors or associate editors and top researchers are available to assist by serving as faculty. Both these options mean CHEST-branded education is accessible around the world.

In addition to bringing our programs to international audiences, we're also able to bring international audiences to our programs, specifically to CHEST Annual Meeting and CHEST World Congress. Grant partnership opportunities are extended to sponsoring organizations that wish to cover registration, travel, housing, and per-diem living expenses for international fellows. As part of the program, we assign a CHEST liaison to each sponsored physician to further enhance his or her meeting experience. Again, this program makes CHEST-branded education more accessible throughout the world.

Knowing health-care professionals aren't always able to travel to our events, we capture education content to make it available on demand. We have hundreds of sessions from our CHEST Annual Meeting and CHEST Board Review available for purchase in the CHEST store at chestnet.org/store. Or, international partners can license this content, and provide it to health-care professionals in their areas. Both options extend the reach of our education programs to those who may not be able to participate in a live event.

On the leadership front, we continue to lead the promotion of lung health awareness around the world. A founding member of the Forum of International Respiratory Societies (FIRS), we work with the world's leading respiratory societies to improve lung health globally. Our initiatives to date include declaring 2016 to 2025 as the Decade of the Lung and engaging organizations to improve lung health through prevention efforts. Under the Decade of the Lung umbrella, FIRS organizations brought awareness to the need for pneumonia prevention and stronger management strategies. More recently, CHEST participated with FIRS to raise global concerns of lung cancer on World Cancer Day, February 2.

As an established and recognized leader in chest medicine, CHEST is in an ideal position to advance lung health around the world. This is an opportunity we take seriously and will continue to focus on meeting our vision.

If you have thoughts or ideas about how we can enhance our work to be a global leader in chest medicine, feel free to connect with me. I invite you to follow me on Twitter (@PMarkowskiACCP), or look for me at upcoming CHEST events.

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Call for case reports

Submission Deadline: April 1

Submit case reports for presentation during special sessions. Accepted case reports (excluding clinical case puzzlers) will be published in an online supplement to *CHEST*. Four types of case reports will be considered:

- Affiliate Case Reports
- Medical Student/Resident Case Reports
- Global Case Reports
- Clinical Case Puzzlers

Learn more and submit at chestmeeting.chestnet.org.

Call for moderators

Moderators are needed on-site during the meeting. Responsibilities include reviewing the abstracts and case reports prior to the meeting, then facilitating discussion, questions, and answers within your assigned session(s). All slide sessions and most poster sessions will have two moderators. Moderators will be recognized in the CHEST 2016 program and will receive a reduced registration rate to the meeting. Travel reimbursement will not be offered. Learn more at chestmeeting.chestnet.org.

The CHEST Foundation 2016 Grants Program

Application Deadline: April 30

The CHEST Foundation tradition of recognizing and rewarding health-care professionals for scholarly projects and research continues. This year, a total of $500,000 is available, including:

- The CHEST Foundation Research Grant in Lung Cancer - *$90,000 2-year grant*
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension - *$50,000 1-year grant*
- CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency - *$25,000 1-year grant*
- CHEST Foundation Research Grant in Pulmonary Fibrosis - *$30,000 1-year grant*
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease - *$50,000 1-year grant*
- CHEST Foundation Research Grant in Venous Thromboembolism - *$30,000 1-year grant*
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria - *$25,000 1-year grant*
- CHEST Foundation Research Grant in Women's Lung Health - *$10,000 1-year grant*
- CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP - *up to $15,000 1-year grant (multiple awards available!)*
- GlaxoSmithKline Distinguished Scholar in Respiratory Health - *$150,000 3-year grant*

See which grants you are eligible for, and apply today at chestnet.org/grants.

ABIM continues to expand options to earn MOC, extends practice assessment decision through 2018

BY DR. SERPIL C. ERZURUM, FCCP, AND DR. MICHAEL E. NELSON, FCCP, FOR THE ABIM PULMONARY DISEASE BOARD

On behalf of the American Board of Internal Medicine's (ABIM) Pulmonary Disease Board, we are excited to share the following updates to the Maintenance of Certification (MOC) program that was developed based on feedback from the internal medicine community and illustrates ABIM's commitment to ensuring that MOC recognizes the activities physicians are already doing in practice.

The first is an update on the partnership between ABIM and the Accreditation Council for Continuing Medical Education (ACCME) to make more CME activities available for MOC credit. The second is a recent announcement on ABIM's decision to not require practice assessment through 2018.

In fall 2015, responding to a call from physicians and medical societies to create a more flexible, streamlined process to combine continuing medical education (CME) activities with MOC requirements, ABIM and ACCME announced a partnership focused on providing ABIM board-certified physicians with access to more accredited CME activities that meet ABIM's MOC requirements. As this new partnership with ACCME expands, the number of options will continue to grow. ABIM currently accepts more than 600 CME activities for MOC credit. This includes 121 options within pulmonary disease, as well as many other options in internal medicine, critical care, and sleep medicine, among others. It is important to note that if you choose to maintain multiple certifications, the points you earn will apply to all certificates.

The other recent announcement is that ABIM **will not require** Practice Assessment, Patient Voice, and Patient Safety in its MOC program through December 31, 2018. This means that no physician will have their certification status changed for not having completed Practice Assessment, Patient Voice, and Patient Safety activities through December 31, 2018. Instead, ABIM will focus on efforts to improve these aspects of the MOC program with input from practicing physicians. ABIM will continue to provide MOC credit for quality improvement activities physicians choose to do that meet standards for MOC credit and will expand the list of these activities recognized for MOC credit.

Continued on following page

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Even with these changes, it is important to remember that the MOC program still remains in place. ABIM board-certified physicians still need to take and pass an exam every 10 years and earn 100 MOC points every 5 years as well as complete some MOC activity every 2 years to participate in the program.

These changes, along with several other significant programmatic changes over the last 2 years, were based on input we have heard from you and your medical societies.

We encourage you to visit the Transforming ABIM blog to learn more about all of the changes. Subscribe to the blog to receive updates about ABIM's ongoing discussions with the internal medicine and subspecialty community and upcoming opportunities to provide input.

To learn more about your specific requirements and deadlines or to check your certification status, sign in to ABIM's website to view your MOC status report.

We look forward to sharing more updates with you as we continue our work of ensuring the relevancy of MOC to pulmonary disease physicians across the country.

IN MEMORIAM

Dr. Arthur Kotch

Dr. Arthur Kotch, FCCP, passed away on December 6, 2015. He started his career as junior faculty in the Pulmonary Division at the University of Pennsylvania. He was then recruited to Danbury Hospital, in Danbury, Connecticut, where over the years, he built the Division of Pulmonary Medicine, the Department of Respiratory Care, a Pulmonary Rehabilitation Unit, and the first Sleep Center in the state of Connecticut. He was a pulmonary, critical care, and sleep medicine physician who combined an encyclopedic knowledge with a very humanistic approach to life, displaying the ultimate dedication to trainees and his patients, and amazing service to his hospital and the community. The American College of Chest Physicians extends its condolences to the Kotch family.

This information was kindly provided to CHEST by Dr. Octavian C. Ioachimescu, FCCP, who was a dear friend of Dr. Kotch.

This month in *CHEST*: Editor's picks

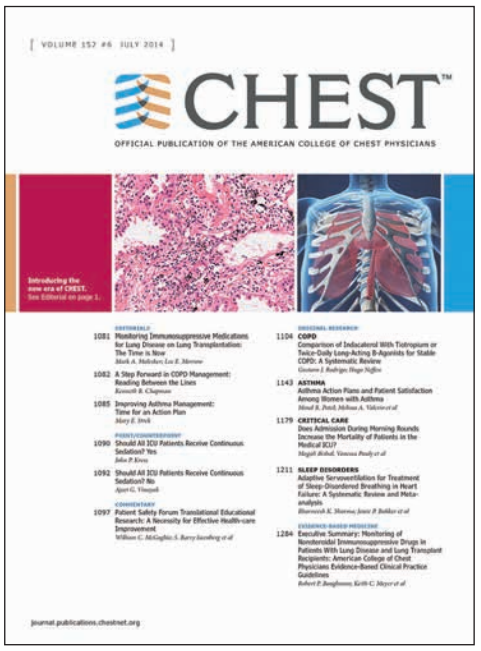
BY DR. RICHARD S. IRWIN, MASTER FCCP
EDITOR IN CHIEF, *CHEST*

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough: A Randomized Controlled Trial. *By Dr. A. E. Vertigan et al.*

Parenteral Prostanoid Use at a Tertiary Referral Center: A Retrospective Cohort Study. *By Dr. B. R. Hay et al.*

Health-care Provider Screening and Advice for Smoking Cessation Among Smokers With and Without COPD: 2009-2010 National Adult Tobacco Survey. *By Dr. G. L. Schauer et al.*

Is There Any Reliable Clinical Evidence to Suggest That Acthar Is More Effective Than Other Forms of Corticosteroids in Treating Sarcoidosis and Other Diseases It Is Being Marketed to Treat? *By Dr. M. Metersky (Correspondence)*



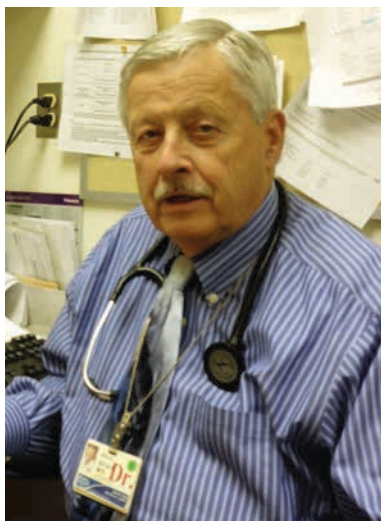
Finding Common Ground: Professionalism and Acthar Prescribing Practices (Editorial, G/W Metersky Correspondence at left). *By Dr. Don Liss et al.*

Giants in Chest Medicine – Dr. Leonardo M. Fabbri. *By Dr. P. J. Barnes*

Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: CHEST Guideline and Expert Panel Report. *By Dr. M. M. Wahidi et al.*

Catching up with our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new in their lives.



DR. KVALE

Dr. Paul Kvale, Master FCCP President, 2004-2005

Since my term as President of the American College of Chest Physicians, I have remained active with CHEST in several capacities, including serving as a reviewer for the McCaffree Community Service Awards and, currently, as Chair of the Compensation Committee.

I continued with research activities until the primary papers were published for the National Lung Screening Trial (NSLT) and the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trials were complete. I retired from active practice at Henry Ford Hospital at the end of June 2015. That was the 50th

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NAMDRC crystallizes its legislative and regulatory agendas for pulmonary medicine in 2016

BY PHIL PORTE
NAMDRC Executive Director

It is a presidential election year, and that usually signals a dearth of activity in Washington and on Capitol Hill. Recognizing that Congress hasn't been doing much at all for the past few years as acrimony reaches new heights, NAMDRC (the National Association for Medical Direction of Respiratory Care) is focusing on a limited number of issues that impact pulmonary medicine.

First, a recent study (A-02-1401013) by the HHS Office of the Inspector General (OIG) focused on one hospital in New Jersey, citing significant billing problems with its pulmonary (and cardiac) rehabilitation programs. The hospital was eventually required to repay the

NAMDRC continues to work with its sister societies to refine submissions to the CMS Coverage and Analysis Group to address issues related to home mechanical ventilation.

Centers for Medicare and Medicaid Services (CMS) over $115,000 for errant billing, most of which was traced back to flaws in the Individual Treatment Plan (ITP) and undocumented medical need.

After a direct conversation on this topic, CMS acknowledged that it was not aware of any broad focus on pulmonary rehabilitation programs and, indeed, the agency had no immediate plans to change its existing policies to provide more clarification for pulmonary rehabilitation programs. In fact, CMS encouraged NAMDRC to work with Medicare Administrative Contractors (MACs) in the event that we believed additional clarifications might be necessary/helpful. To that end, NAMDRC is encouraging the American Association of Cardiovascular & Pulmonary Rehabilitation (AACVPR) to take the lead, providing guidance to its members to ensure compliance with current CMS and MAC requirements.


MR. PORTE

Secondly, also related to pulmonary rehabilitation, NAMDRC and AACVPR may approach CMS for clarification regarding billing for G0424, the HCPCS (Healthcare Common Procedure Coding System) code for billing for pulmonary rehabilitation services provided in the hospital outpatient setting. Current regulations clearly permit billing of G0424 up to two times per day, but in a nuance in the hospital outpatient rate setting announcement, it appears that G0424 is considered a bundled service, with a cap of one billable unit per day. We are also working with the American Association for Respiratory Care (AARC) to determine the frequency of multiple uses of G0424 compared with single use and may approach CMS for clarification if broad inconsistencies are uncovered.

As an update, NAMDRC continues to work with its sister societies to refine submissions to the CMS Coverage and Analysis Group to address issues related to home mechanical ventilation and bilevel/RADs (respiratory assist devices). Home mechanical ventilation policies are outdated as Medicare contractors rely on a 2001 decision memo that, needless to say, does not reflect the state-of-the-art standard of care in 2016. According to CMS regulations, the primary pathway for such change is a reconsideration of the current National Coverage Determination (NCD) for home mechanical ventilation and a request for a new NCD to address bilevel/RADs.

The largest challenge facing the team working on these issues is the CMS expectation that in order to change current policy there must be well-documented, peer-reviewed support for change. And herein lies a notable problem—trying to prove negatives. On the home mechanical ventilation issue, there are obviously no randomized clinical trials that compare continued mechanical ventilation with frequency of death upon removal of mechanical ventilation. On the bilevel issue, for example, current CMS policy focuses, in part, on the need for a trial without a back-up rate, despite the absence of any research that focused on that specific issue. Again, trying to prove negatives, or at least the best way around it, is continuing to be the greatest challenge on this effort.

NAMDRC is encouraging the AACVPR to take the lead in providing guidance to its members to ensure compliance with current CMS and MAC requirements.

If one thinks about this issue in a genuine macro perspective, one has to look at the original authorizing legislation that permits coverage in these two related areas. While home mechanical ventilation is not referenced in the statute, iron lungs are,

Continued on page 52

CHEST Foundation introduces 2016 NetWorks challenge

The CHEST Foundation launched its 2016 NetWorks Challenge on March 1, adding creative and meaningful prizes for NetWorks and members of various levels of participation. The criteria for assigning winners and awards are members' contributions in three categories (there will be two winners for each category):

- First half winners (announced July 1):
  - o Total amount contributed by a NetWorks Steering Committee
- Second half winners (announced at the Monday morning opening session at the 2016 CHEST Annual Meeting):
  - o Highest percentage of participation by NetWorks Steering Committee
- Annual meeting challenge (announced after the annual meeting):
  - o Highest percentage of participation by NetWorks membership

With the creation of six travel awards and a clinical research grant related to the winning NetWorks' subspecialty, we've created a vehicle for all members to embrace the foundation's mission – to champion lung health and to help fellow colleagues support each other's personal and professional growth.

"Many people think of the CHEST Foundation as the philanthropic arm of the College, but it really serves a much greater role as a champion of pulmonary health. No matter which aspect of lung health is most important to you, the foundation is making an impact there. Giving to the foundation fosters the development of novel research, allows the provision of care to patients who might not otherwise receive it, and funds the creation of educational materials for both patients and their providers to improve the overall care of people with lung disease around the globe. And besides, it is a great way for me to thank CHEST for everything they have done for my own personal and professional growth over the last decade.

Even as a junior clinician, I made a point to give to the CHEST Foundation on an annual basis. Every gift, regardless of the amount, goes a long way to helping the foundation's mission."

– Dr. David A. Schulman, FCCP, Chair, Council of NetWorks

Visit chestnet.org/networkschallenge to learn more!

TAGRISSO™
osimertinib

A NEW TREATMENT OPTION
FOR PATIENTS WITH METASTATIC EGFR T790M MUTATION-POSITIVE NSCLC, AS DETECTED BY AN FDA-APPROVED TEST, WHO HAVE PROGRESSED ON OR AFTER EGFR TKI THERAPY

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- QTc interval prolongation occurred in TAGRISSO patients. Of the 411 patients in two Phase II studies, 0.2% were found to have a QTc greater than 500 msec, and 2.7% had an increase from baseline QTc greater than 60 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia
- Cardiomyopathy occurred in 1.4% and was fatal in 0.2% of 813 TAGRISSO patients. Left Ventricular Ejection Fraction (LVEF) decline >10% and a drop to <50% occurred in 2.4% of (9/375) TAGRISSO patients. Assess LVEF before initiation and then at 3 month intervals of TAGRISSO treatment. Withhold TAGRISSO if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)

Please see Brief Summary of complete Prescribing Information.

Visit TAGRISSOhcp.com for more information

AstraZeneca

Continued from page 50

and the inference is somewhat obvious. In the event that CMS might agree with our recommendations but argues that it does not have the legislative authority to implement those changes because of current limitations within the law, we might consider a legislative initiative to address that matter.

Of course, undertaking a legislative strategy to address coverage issues within Medicare is no small challenge. For example, in 1981 the then Health Care Financing Administration (HCFA) clearly stated, in writing, to NAMDRC that pulmonary rehabilitation was indeed a covered service. Some 20 years later, CMS declared that position no longer applicable, and it took several years of effort on Capitol Hill to create a specific benefit category for pulmonary rehab within the statute.

While no one is eager to take on such a large undertaking, NAMDRC has begun engaging some of the interested parties in preliminary discussions along the lines of "what if…" in the event that CMS conceptually agrees with our eventual recommendations, but claims there is no legislative authority to implement those recommendations.

CHEST World Congress 2016: Don't miss cutting-edge education or Shanghai's attractions

When you travel to Shanghai to attend CHEST World Congress 2016, April 15 - 17, don't miss a minute of the cutting-edge education sessions and simulation training. And, make some time to explore the great city of Shanghai. Knowing that your time may be limited, we came up with a list of some of the best restaurants and local activities in Pudong, the popular Shanghai district where the Shanghai International Convention Center is located.

Enjoy a walk or grab a cab to enjoy these nearby eats:

Upscale restaurants

Club Jinmao

86F, Grand Hyatt Hotel, No.88, Century Avenue, Pudong New Area

This is the highest local authentic Shanghai restaurant, located on the 86th floor. Diners will enjoy the seafood soup and other delicious dishes while appreciating the charming scenery of Pudong.

The House of Roosevelt / Bund 27

No.27 Zhongshan Dong Yi Lu. Vicinity: The Bund

This is one of the largest wine emporiums in Shanghai. With the largest wine list in Asia (3,800 labels), the nine-floor venue has a brasserie, wine cellar, rooftop terrace, and private members' club.

Whampoa Club

5F, No. 3, the Bund, No.3 Zhongshan Dong Yi Lu,, Huangpu District (near Guangdong Road)

Check out this famous luxury restaurant on the Bund. The chef is known for adding many novel ingredients to traditional cuisine, and you won't want to miss the smoked fish and the fried shrimp balls.

Moderately priced restaurants

Lang Yi Fang

5F, Super Brand Mall, No. 168, West Lujiazui Road, Pudong District (near West Yincheng Road)

The restaurant serves authentic Shanghai Benbang dishes at reasonable prices. The crab bean curd, smoked fish, and Babao Duck are its signature dishes.

Yang's Fry Dumpling

54-60 Wujiang Lu (near Nanjing Xi Lu)

The Yang's Fry chain is, if not the originator, then clearly the benchmark for Shanghai's homegrown pan-fried pork dumpling, the shengjian bao. They're a stone-cold Shanghainese street food classic and a cousin to Shanghai's more famous soup dumpling, the xiaolongbao.

Takumi

IFC Pudong, 4/F, 8 Shiji Da Dao

This Japanese robata and sake bar in the IFC Mall specializes in grilled meats and vegetables.

Looking for a quick excursion during a break in your education schedule? These nearby activities will

Continued on following page

CHEST World Congress 2016 | 世界胸科大会 CHINA Shanghai • April 15-17

Continued from previous page

offer you a glimpse into Shanghai's charm and history:

The Bund - a famous waterfront and regarded as the symbol of Shanghai for hundreds of years. It has been called a museum of international architecture. You can also find ritzy shopping and high-end restaurants and bars at this swanky attraction.

Huangpu River - Take in the bustling city and the local architecture from this enjoyable vantage point. There are boat tours available ranging from a quick ferry ride to 3-hour cruises.

The Oriental Pearl TV Tower - This high tower, at 1,536 feet, is the world's sixth and China's second tallest TV and radio tower. However, even more alluring than its height is its unique, attractive architectural design. Visitors travel up and down the tower in double-decker elevators and receive an introduction to the tower in English and Chinese.

Shanghai World Financial Center (SWFC) - The second tallest skyscraper in mainland China, this building aims to be a symbol of the world's finance. Visitors can enjoy sights of the city from the observatory or the Park Hyatt Hotel.

We know you'll enjoy Shanghai and CHEST World Congress 2016's extensive educational offerings. You'll receive relevant updates on patient care, and practice management strategies will offer insight, perspective, and inspiration you can seamlessly incorporate into your practice to stay at the forefront of clinical chest medicine.

Begin planning your trip to Shanghai now with help from Shanghai's tourism website, meet-in-shanghai.net. Learn more about CHEST World Congress 2016, and register today at chestworldcongress2016.org.

Continued from page 49

anniversary of employment at HFH, coincident with HFH celebrating its 100th founding anniversary. I continue to serve every couple of weeks with teaching sessions with the pulmonary fellows on a voluntary basis. This pro bono work is consistent with the objectives that I stated when I became President of CHEST.

My wife Susan and I have continued to travel internationally, now about one to two such trips each year. A river cruise in Portugal was the highlight in late 2014 and another on the Danube River from Budapest to Nurenberg was our itinerary in late 2015. We also spend about 6 weeks each year at our home on Hilton Head Island, South Carolina, and our intentions are to enjoy even more time there going forward.

Since I retired, I have enrolled as an undergraduate student at Wayne State University, taking a course in geology just "for fun." Geology is a field of science that I could not work into my schedule as a pre-med student, so now I have the time and opportunity. One of my grandsons has joined me as I returned to a childhood hobby of building flyable model airplanes. I golf with several friends twice a week, and I wish I still had the game that I had at age 25!! Susan and I will continue to travel and see things that we enjoy together.

2016 Education Calendar

Live Learning Courses

Advanced Clinical Training in Pulmonary Function Testing
April 9-10

Critical Care Ultrasonography: Integration Into Clinical Practice
May 5-7

Advanced Critical Care Echocardiography
June 2-4

Transesophageal Echocardiography (TEE)
June 5

Comprehensive Pleural Procedures
June 17-18

Difficult Airway Management
July 15-17

Mechanical Ventilation: Advanced Critical Care Management
July 29-31

Bronchoscopy Procedures for the Intensivist
August 6-7

Ultrasonography: Essentials in Critical Care
September 9-11

Cardiopulmonary Exercise Testing (CPET)
September 16-18

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 23-25

Critical Care Ultrasonography: Integration Into Clinical Practice
November 11-13

Ultrasonography: Essentials in Critical Care
December 2-4

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CHEST Board Review
Phoenix, Arizona
August 19-28

CHEST Annual Meeting
CHEST 2016
October 22-26
Los Angeles, California
LOS ANGELES OCTOBER 22 - 26

Calendar subject to change.
For most current course list and more information, visit chestnet.org/live-learning.

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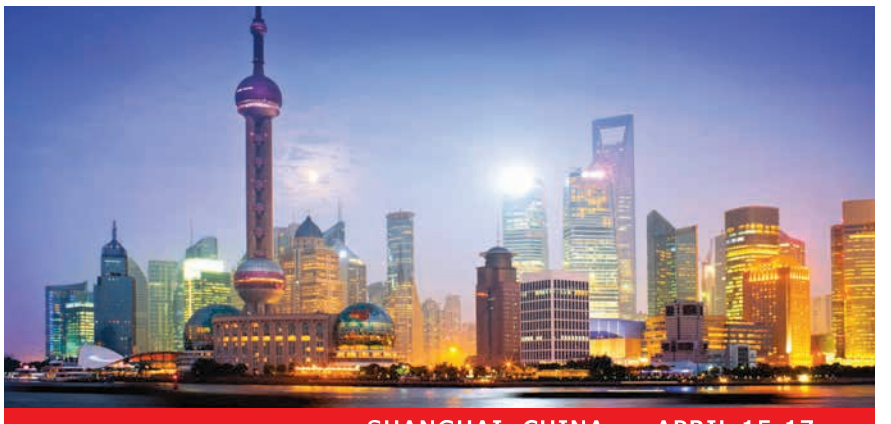

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‘Cautious optimism’ about MACRA implementation

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – Coming regulations to implement the MACRA legislation also could include sweeping reforms to meaningful use and quality reporting programs, said Dr. Steven J. Stack, president of the American Medical Association.

Dr. Stack expressed “cautious optimism” that the regulations would help doctors to return to focusing on treating patients and away from meeting the myriad of regulatory requirements that have piled up in recent years.

The AMA has been working closely with the Centers for Medicare & Medicaid Services and “very candidly and very constructively.” The agency has “demonstrated a willingness to reconsider things,” Dr. Stack said at the AMA National Advocacy Conference.

The regulations to implement MACRA (the Medicare Access and CHIP Reauthorization Act of 2015) “offers CMS an uncommonly robust opportunity to take things like [the Physician Quality Reporting System], meaningful use, value-based purchasing and reconceptualize, now that we have the opportunity under one rulemaking, to say how should all of these really work together,” Dr. Stack said.

Indeed, during a keynote address at the AMA conference, CMS Administrator Andy Slavitt said one of the goals for the agency this year was to simplify things for doctors.

“We must reduce burden and give physicians back more time to spend with patients,” Mr. Slavitt said. “Several years ago, we launched an initiative that is reducing regulatory burden and saving hospitals $3.2 billion over 5 years. But we are barely scratching the surface.

“We have a strategic effort this year designed to reduce burden and create efficiencies in the physician’s office,” Mr. Slavitt said.

He hinted that the MACRA regulations would be used to redefine how health IT is utilized, noting the emphasis will be on rewarding outcomes that technology helps achieve, rather than simply incentivizing the use of it; providing more flexibility to meet physician needs; leveling the playing field to allow more competition from vendors; and to address ongoing interoperability issues.

The concern Dr. Stack addressed during the press meeting was the ongoing opioid epidemic, one of the few things he expects to see legislative action on during this presidential election year.

He called for thoughtful, comprehensive solutions to addressing the problem so that it allows patients with a true medical need for chronic pain management to be able to continue to have access to needed prescription pain medications.

Arbitrary prescribing caps and other fixes that, on the surface, are simple and easy to implement, should be avoided, he said.

“Those kinds of approaches for this problem could have the really undesired consequences of rather than solving the problem,” Dr. Stack said, adding that they could drive even more people from prescription pills to heroin.

That “causes deaths far more rapidly than the other stuff, which takes tens of millions of Americans with legitimate chronic pain who are legitimately suffering and throwing them into horrific life problems without access to care they need.”

As an adjunct, Dr. Stack also addressed drug pricing, using naloxone, which is used to help patients experiencing and opioid overdose, as an example of a drug that has skyrocketed in price.

In looking at 5 years of drug prices in his state of Kentucky, naloxone has gone up from just over $4.50 a pill in 2010 to $38 a pill in 2015.

“If there is one thing that I will be absolutely clear on as a physician in the United States, this is not the time for the pharmaceutical industry to play games in the midst of an epidemic that taking over a quarter-million people’s lives over the documented course of this problem,” Dr. Stack said.

“This is the time for the pharmaceutical industry to do its part and make sure that naloxone is as cheap as water from a tap so that patients in need can get the care they need and have this life-saving drug. This is not a profiteering opportunity for anyone,” he added.

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Supreme Court: Fate of health care cases uncertain

BY ALICIA GALLEGOS
Frontline Medical News

The fate of several high-profile health care cases remains uncertain after the death of U.S. Supreme Court Justice Antonin Scalia.

The eight remaining justices will hear oral arguments on and weigh in on a range cases this term. Justice Scalia's death however, means the possibility of a tie vote in some cases, which could lead to conflicting case law across states.

"Most Supreme Court decisions are not decided on a 5-to-4 split, so presumably regular business will continue as to most of the cases they are deciding," said Timothy S. Jost, health law professor at Washington and Lee University in Lexington, Va. "However, for some of the most important cases in health care – like the abortion decision or the contraceptive decision – it was likely there was going to be a 5-to-4 split. Of those cases, the justices can either hold them over or vote, in which case there [could] be a 4-to-4 split."

If the court divides equally on a case, the lower court's decision is affirmed. But the case would not have a Supreme Court precedent, meaning the lower ruling would apply only in the circuit court's jurisdiction, said Eric J. Segall, a professor of law at Georgia State University, Atlanta.

In *Whole Woman's Health v. Cole*, also known as *Whole Woman's Health v. Hellerstedt,* for instance, a split would uphold an appellate decision that allowed abortion restrictions in Texas to go forward. In that case, the state is battling health providers over a mandate that abortion providers must have admitting privileges at a hospital within 30 miles and that abortion clinics must meet the same requirements as those of ambulatory surgical centers (ASCs). The 5th U.S. Circuit Court of Appeals ruled that the regulations do not impose an undue burden on a patient's right to get an abortion.

"If a 5-4 [Supreme Court decision] upheld those restrictions, that would be national law for the whole country, and it would be a huge deal," Mr. Segall said in an interview. "If it's a 4-4 tie, than in Texas and two other states, the Texas decision would still be good law, but it would have no effect outside that circuit."

In the case of *Zubik v. Burwell* however, a split vote would mean nationwide differences in how the Affordable Care Act's contraceptive mandate is applied, said Ilya Shapiro, a senior fellow in constitutional studies at the Cato Institute. The Zubik case centers on whether the ACA contraceptive-coverage mandate and its "accommodation" violates the Religious Freedom Restoration Act by forcing religious nonprofits to act in violation of their beliefs. The 8th U.S. Circuit Court of Appeals struck down the exception twice, ruling that forcing organizations to offer contraceptive coverage – even indirectly – violates their religious rights. The 8th Circuit's decisions are at odds with rulings by the 2nd and 5th Circuits.

Because of the conflicting lower court opinions, if the Zubik case

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JUSTICE ANTONIN SCALIA

were decided 4-4, "the regulation [would be] in place in parts of the country and not in others," Mr. Shapiro said in an interview. "That seems untenable. Cases like that especially, the court would likely delay the arguments that are currently scheduled until the next term."

Justices can decide whether to vote or rehear cases that were already heard with Justice Scalia in attendance, but are not yet decided. They can also dismiss or wait to address cases next term. Decisions that were made with Justice Scalia's vote, but were not yet published, will be void, Mr. Shapiro said. As for Justice Scalia's replacement, Mr. Shapiro noted that even if President Obama makes a nomination and it is confirmed by the Senate, it would be too late to consider cases this term.

Mr. Segall stressed that it's too early to tell how Justice Scalia's death will impact ongoing and future cases and the court as a whole.

"We don't really have a precedent for this," he said. "We've had vacancies before, but we've never had a vacancy in an election year where [the Court comprised] four conservative Republicans and four liberal Democrats. I think we should all step back. There are so many imponderables."

Supreme Court analysts predict the eight justices will announce their decisions – or lack thereof – during the last week of June.

Justice Scalia was known as the high court's most vocal conservative and was the longest-serving current justice on the court, hearing cases for 29 years.

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What's on the docket?

The Supreme Court is set to decide a number of significant health law cases this term. Here are some of the most pressing ones and the issues at stake.

Zubik v. Burwell

Argument date: March 23, 2016
The court will decide whether an accommodation under the ACA contraceptive mandate violates the Religious Freedom Restoration Act by forcing religious nonprofits to act in violation of their beliefs, when the government has not proved that this compulsion is the least restrictive means of advancing a compelling interest. The accommodation clause refers to an exception for organizations that oppose coverage for contraceptives but are not exempted entities such as churches. The plaintiffs argue the process serves as a trigger that enables contraceptive use and makes the groups complicit. The government argues the exception does not impose a burden on the groups and that courts should not disregard the interest of employees who may not share employers' religious beliefs.

Whole Woman's Health v. Cole

Argument date: March 2, 2016
Justices will weigh whether two Texas regulations place an undue burden on a woman's right to access an abortion. The regulations mandate that abortion providers have admitting privileges at a hospital within 30 miles of an abortion clinic in order to provide the service, and that all abortion clinics meet the same requirements as those of ambulatory surgical centers (ASCs). The plaintiffs, who are clinics and doctors, argue that both restrictions are unnecessary and limit access to abortion services. The Texas Department of State Health Services states the restrictions are reasonable and effective measures that raise the standard of care for abortion patients and ensure health and safety. The case is sometimes cited as *Whole Woman's Health v. Hellerstedt*.

Universal Health Services v. United States ex rel. Escobar

Argument date: To be determined
In question is whether the legal theory used by the federal government to bring False Claims Act (FCA) lawsuits is valid. The case centers on a patient who died after receiving care by Universal Health Services Inc. (UHS) in Lawrence, Mass. The patient's parents sued UHS under both the federal and state False Claims Act laws alleging that UHS providers were improperly licensed and made fraudulent government claims. The Supreme Court will answer whether the implied certification test for determining when claims "sufficiently plead falsity" under the FCA is constitutional and if so, if the relevant statute needs to explicitly state the conditions of payment with which the defendant allegedly failed to comply. Physician associations are concerned that a ruling for the plaintiff will expand the FCA's reach and increase false claim lawsuits against health providers.

Gobeille v. Liberty Mutual Insurance Company

Argument date: Dec. 2, 2015
The Supreme Court will decide whether a self-funded insurer must share certain information, such as claims and member data, with Vermont's all-payer database. The state argues the information is needed to improve the cost and effectiveness of health care and that an adverse ruling would chill reform efforts in other states with similar databases. Liberty Mutual, which maintains a self-insured health plan for its employees, argues that the Employee Retirement Income Security Act of 1973 (ERISA) preempts state statutes that provide for "all payer" health care databases, and that it does not have to supply the information. Analysts say the case will ultimately decide to what extent federal law can facilitate the centralized management of health care.

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PROFESSIONAL OPPORTUNITIES

CMS clarifies how to report overpayments

BY ALICIA GALLEGOS
Frontline Medical News

There is finally some clarity about how to report and return Medicare overpayments, under a final rule released by the Centers for Medicare & Medicaid Services Feb. 11.

The final regulation clarifies that health providers have identified an overpayment when they "have or should have, through the exercise of reasonable diligence, determined [they have] received an overpayment and quantified the amount of the overpayment."

CMS holds that large and small providers have a duty to ensure claims are accurate and appropriate and to report and return overpayments they have received.

Overpayments must be reported and returned only if identified within 6 years of the date the payment was received – down from the 10 years included in the proposed rule released in 2012. Physician organizations and other health care stakeholders had criticized the proposal, calling the 10-year time frame unreasonable and burdensome.

The revised definition of identification makes more sense for physicians, particularly that identification exists when providers have quantified the amount of the overpayment, said Scot T. Hasselman, a Washington health law attorney. In many cases, it takes time to decipher how much money is owed after discovering a potential overpayment, he said in an interview.

"This all goes to: When does the clock begin ticking for the 60 days?" he said. "The language in the final rule provides for a standard that is easier to apply.

The 6-year time frame is also more reasonable and will save practices money by limiting their audit obligations, Mr. Hasselman noted.

The final rule also allows the 60-day deadline for returning overpayments to be suspended if a provider requests an extended repayment schedule. In the past, "people could be in a real pickle if they didn't have the money to return," Mr. Hasselman said. "This [provision] is important, especially for smaller [practices] and physicians who may not have big credit lines or the cash flow of an institutional provider."

The final rule also clarifies how to report overpayments. Providers and suppliers must use an applicable claims adjustment, credit balance, self-reported refund, or another appropriate process to satisfy the obligation to report and return overpayments, the rule states. If a provider has reported a self-identified overpayment using the self-referral disclosure protocol managed by CMS or the self-disclosure protocol managed by the HHS Office of Inspector General (OIG), the provider is considered to be in compliance with the rule.

Refusing to allow scalable responses is unfortunate for practices unable to react robustly to overpayments.

MR. CLARK

It takes time to decipher how much money is owed after discovering a potential overpayment.

MR. HASSELMAN

But the final rule is not entirely positive, according to Houston-based health law attorney Michael E. Clark. Many health providers had requested clarification about the level of resources small providers are expected to devote to investigating potential overpayments. Commenters suggested CMS allow for more defined overpayment responses based on provider size and resources. The agency did not do so, saying that providers "large and small have a duty to ensure claims are accurate and appropriate and to report and return overpayments they have received."

Refusing to allow scalable responses is unfortunate for practices that do not have the ability to react to overpayments as robustly as larger chains, Mr. Clark said.

"The agency was unwilling to go that far," Mr. Clark said. "They're not going to give a lesser standard for smaller providers. They're going to look at the facts and circumstances. It gives [CMS] subjectivity, whereas doctors would rather have more clarification and objectivity."

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NETWORKS: Informatics, transplant, VTE in transgender women

Clinical Research NetWork

Utility of clinical informatics in current practice

With the increasing use of digital medical information and the resultant voluminous health-care data, there has been an increased demand for translating these data into meaningful knowledge that enhances population health outcomes. That is the role of clinical informatics, which is a discipline that resides at the intersection of three major domains: the health system, clinical care, and information technology.


DR. BASSILY-MARCUS

Clinical documentations, computerized physician orders entry, clinical decision support, data display, device integration, and e-prescription are common examples of the use of informatics in our daily practices. A document can be designed with pertinent links that are relevant to the clinician with built-in smart-data elements capturing data for future use. Order-sets can be utilized as part of care pathways to standardize the health-care delivery and to ensure compliance with quality metrics and regulatory requirements. Clinical decision support aims to improve safety. The visual display of specific data elements represents the basis for clinical dashboards and score cards for use in individual patient care. These clinical datasets can be used in disease management of populations, utilizing analytic tools that are necessary for population management. Automating scoring systems that facilitate identification of populations at risk is another example of informatics tools. The use of telemedicine, with its expanded categories, including tele-monitoring (e-ICU, tele-rounding, tele-homecare), tele-consultation, tele-visits, and tele-pharmacy, represents another growing application of informatics.

While the use of informatics has great opportunity toward optimization of health-care delivery, it comes with many challenges. These include cost (of designing, testing, analyzing, implementing), workflow changes, decreased bedside presence, alarm fatigue, data validation, data security, limited prognostication, difficulty in capturing unstructured data, challenging interoperability, and relatively slower technologic development compared with the rapidly increasing clinical demand. Clinical informatics is crucial and provides opportunities to enhance health-care delivery, yet its success is dependent on thoughtful analysis, design, and implementation.

Dr. Adel Bassily-Marcus, FCCP
Steering Committee Member

Transplant NetWork

Update: Referring and selecting candidates for lung transplantation

While there have been several recent therapeutic discoveries for patients with advanced heart and lung disease, transplantation remains an important treatment consideration. As the clinical course of most cardiopulmonary diseases may be highly variable and sometimes marked by acute and rapid deterioration, early referral for transplantation should be remembered. Early referral does not necessarily mean that a patient will immediately be placed on a transplant waiting list; rather, it allows time for transplant providers to evaluate a patient's candidacy and work with referring providers to optimize any comorbidities or other factors that may increase a candidate's mortality. Early referral allows more time for educating patients about transplant; monitoring disease status; determining the appropriate time for wait-listing; and fostering trust among patients, their caretakers, and the transplant team.

Recognizing the emergence of new data regarding the appropriate selection of patients for lung transplantation, the International Society of Heart and Lung Transplantation (ISHLT) recently updated their Consensus Report for the Selection of Lung Transplant Candidates (*J Heart Lung Transplant*. 2015;34:1-15). Unlike previous editions from 1998 and 2006, the current report highlights several novel issues affecting contemporary candidate selection, such as changes to lung allocation, use of mechanical ventilation and extracorporeal technology for bridging patients to transplant, pediatric and multiorgan transplantation, and the expansion of candidate selection criteria, including new limits of age, comorbidities, and underlying recipient infections. Also addressed is the selection of candidates for re-transplantation, a procedure more commonly considered now for some recipients with graft dysfunction. Using this updated report, providers can more capably identify and refer patients who are most likely to benefit from transplantation.

Dr. Keith M. Wille, FCCP
Steering Committee Member

Women's Health NetWork

Thromboembolic risk in transgender women

Recently, the binary concept of gender has been challenged and definitions have undergone evolution. The estimated 700,000 people in the United States who are transgender do not have adequate access to well-informed health care (Rubin. *The Lancet*. 2015;386[9995]:727).


DR. BANERJEE

Gender identity disorder is often treated with hormonal therapy in order to suppress endogenous hormonal phenotype and amplify desired traits (Hembree et al. *J Clin Endocrinol Metab.* 2009;94:3132). The endocrine guidelines recommend targeting a physiologic range for hormone therapy so as to minimize risk of thrombotic events.

Venous thromboembolism (VTE) is the major complication of male to female transsexuals (van Kesteren et al. *Clin Endocrinol.* 1997;47[3]:337). Earlier observational studies found a 6% to 8% or up to a 20-fold increased risk of VTE in transwomen treated with oral ethinyl estradiol. This product is associated with increased coagulation (Toorians et al. *J Clin Endocrinol Metab.* 2003;88[12]:5723), and the risk has decreased since implementation of newer formulations and transdermal routes of estrogen (van Kesteren et al) (Gooren et al. J *Clin Endocrinol Metab.* 2008;93[1];19). In the largest and most recent cohort studied, transwomen taking various preparations of hormonal therapy had increased incidence of VTE (5.1%) (Wierckx et al. 2013. doi: 10.1530/EJE-13-0493). Of those who suffered VTE, approximately half were within the first year of treatment and most were smokers.


DR. LAPINSKY

Limited available research into VTE risk during hormone therapy in the transgender patient requires thoughtful consideration of risks and benefits, paying attention to the important role hormones play in the identity of these women. There is an increased need for education for health-care providers to better understand specific challenges faced by populations not falling within the traditional cultural paradigm.

Dr. Debasree Banerjee,
Dr. Stephen E. Lapinsky
Steering Committee Members

Additional Reading

2011 Williams Institute report. http://williamsinstitute.law.ucla.edu/ wp-content/uploads/Gates- How-Many-People-LGBT- Apr-2011.pdf

Injustice at Every Turn report. www.thetaskforce.org/static_html/ downloads/reports/reports/ntds_full.pdf

WorldProfessional Association for Transgender Health

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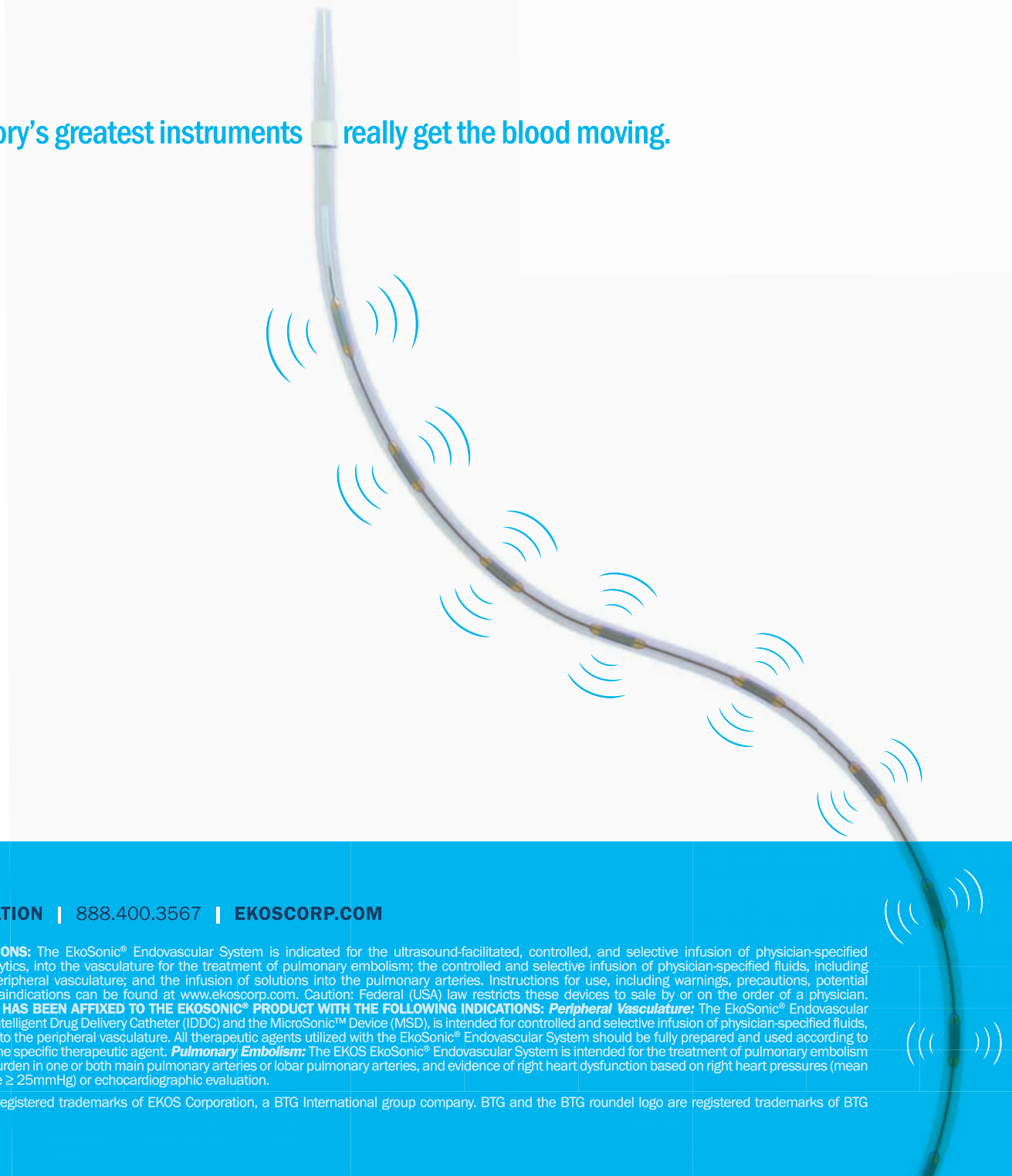

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