COUGH DIAGNOSIS
CHEST expert panel with two new guidelines // **9**

CARDIONEPHRODIABETOLOGY
Navigating the landscape of SGLT2 inhibitors and GLP-1 RAs // **14**

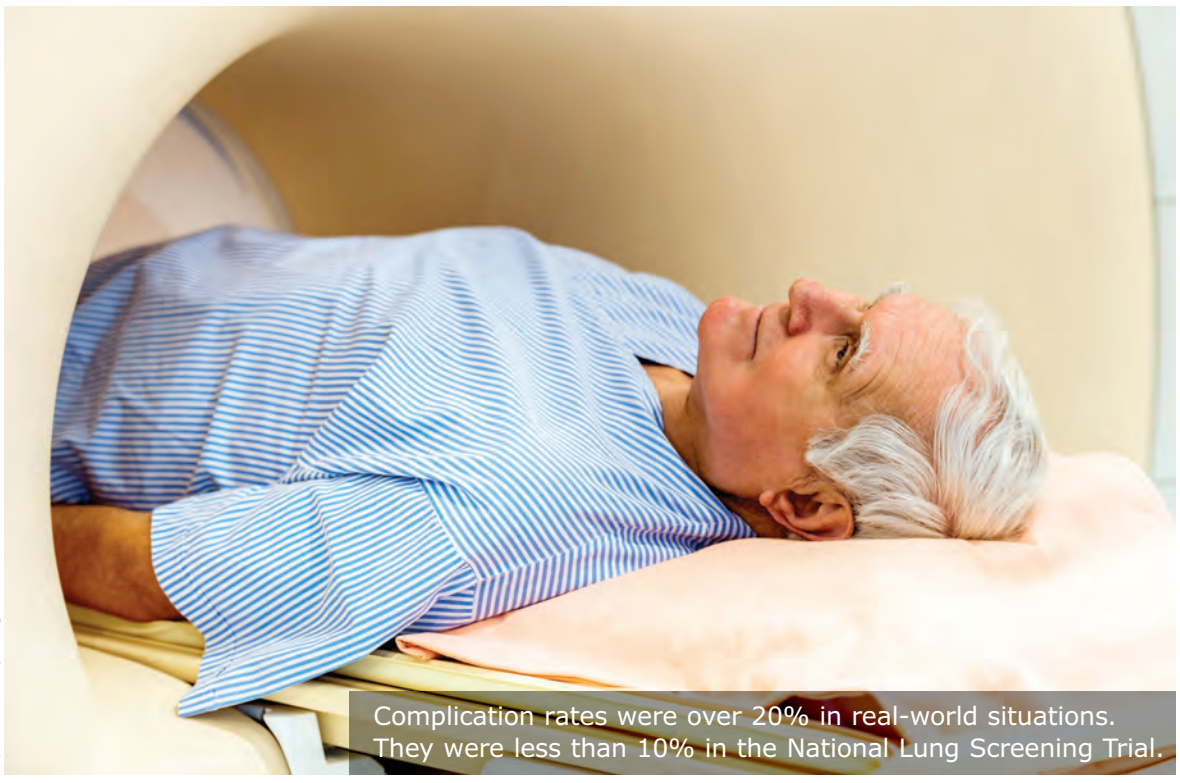
PULMONARY PERSPECTIVES®
CTEPH, the 'fixable' form of PH that you don't want to miss // **38**

CRITICAL CARE COMMENTARY
Team dynamics and renal replacement therapy in the ICU // **47**

VOL. 14 • NO. 2 • FEBRUARY 2019

CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



skynesher/Getty Images

Complication rates were over 20% in real-world situations. They were less than 10% in the National Lung Screening Trial.

In real-world setting, LDCT screen is linked to high complication risk

BY ANDREW D. BOWSER
MDedge News

The real-world rates of complications associated with diagnostic procedures that followed low-dose computed tomography (LDCT) for lung cancer screening were substantially higher, more than double, the rates that were seen in clinical trials of LDCT screening, a retrospective cohort study suggests.

Plus, those complications are potentially costly, based on the finding of the analysis of commercial and Medicare claims data for nearly 350,000 individuals.

The findings emphasize the importance of discussing the risk of adverse events and their costs as part of the shared decision-making process between physicians and patients before LDCT screening, researchers said in a report on their study in JAMA Internal Medicine.

"As the number of individuals seeking lung cancer screening with LDCT increases, so too will the number of individuals undergoing invasive diagnostic procedures as a result of abnormal findings," that may be incidental or false positive, said Jinhai Huo, MD, PhD, of the department of health services research, management, and policy at the University of Florida, Gainesville.

The study included 174,702 individuals who underwent an invasive diagnostic procedure as a

LDCT SCREENING // *continued on page 4*

More than 23% of antibiotic prescriptions 'inappropriate'

BY RICHARD FRANKI
MDedge News

More than 23% of all antibiotic prescriptions filled in 2016 were medically unnecessary, and another 36% were questionable, according to an analysis of prescribing data for 19.2 million children and nonelderly adults.

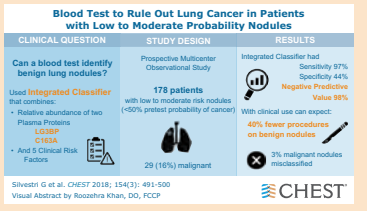
Based on the diagnosis codes for 15.5 million prescriptions filled that year, at least 3.6 million (23.2%) were "inappropriate" – prescribed for conditions for which an antibiotic is almost never recommended, such as acute upper respiratory conditions – and 5.5 million (35.5%) were "potentially inappropriate" – conditions such as acute sinusitis or otitis media, for which an antibiotic is only sometimes recommended, Kao-Ping Chua, MD, PhD, of the University of Michigan, Ann Arbor, and his associates reported in the BMJ.

Only 12.8% of filled prescriptions for the 39 oral antibiotics assessed were classified as "appropriate" under the investigators' scheme, which assigned an antibiotic appropriateness level to all 91,738 diagnostic codes in the 2016 ICD-10-CM. Finally, 28.5% of antibiotic fills were not associated with a recent diagnosis code, suggesting that they

ANTIBIOTIC PRESCRIBING // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST



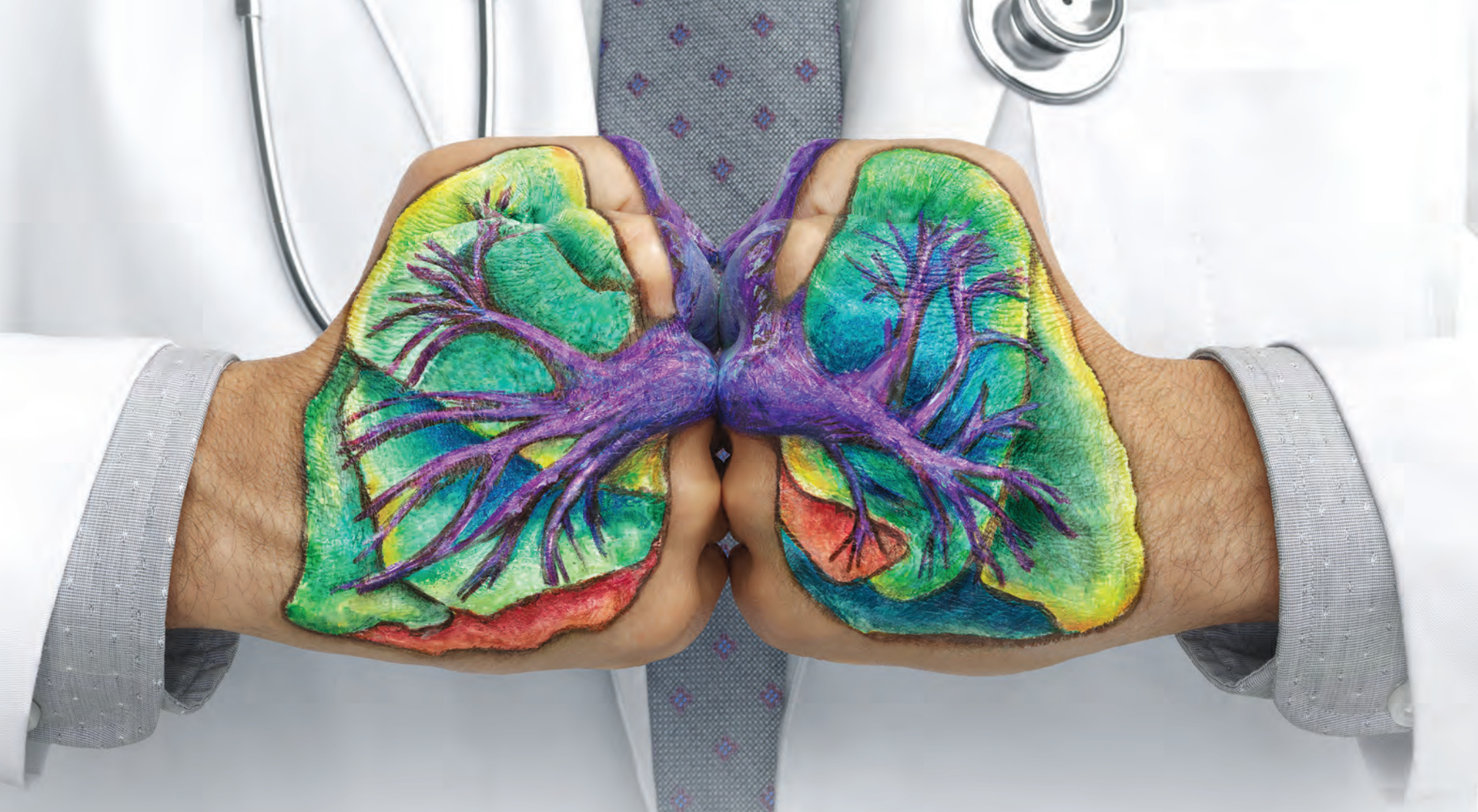
Visual abstracts enhance reader experience

Page 39

CHANGE SERVICE REQUESTED

CHEST Physician
10255 W Higgins Road,
Suite 280
Rosemont, IL 60018

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY



Indication

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

Select Important Safety Information

Elevated liver enzymes: Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3× ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels prior to initiating Esbriet, then monthly for the first 6 months, and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

Gastrointestinal (GI) disorders: Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, compared with 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary.

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

Drug Interactions:

CYP1A2 inhibitors: Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

CYP1A2 inducers: Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

Specific Populations:

Mild to moderate hepatic impairment: Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

Severe hepatic impairment: Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

Genentech

A Member of the Roche Group

WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.[1–3]

STUDIED IN A RANGE OF PATIENTS

Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[4]

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[1†]

COMMITTED TO PATIENTS

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

WORLDWIDE PATIENT EXPERIENCE

More than 37,000 patients have taken pirfenidone worldwide[4§]

Mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} <30 mL/min) renal impairment: Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

End-stage renal disease requiring dialysis: Esbriet is not recommended. Esbriet has not been studied in this patient population.

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when using Esbriet.

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

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

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

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

IPF=idiopathic pulmonary fibrosis.

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

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[1]

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

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

LDCT screening can lead to risky diagnostic procedures // continued from page 1

result of abnormal findings on lung cancer screening and 169,808 control subjects.

All individuals studied were between 55 and 77 years old, the targeted age range for lung cancer screening specified by the Centers for Medicare & Medicaid Services.

Complication rates were about twice as high in the real-world study as they were in the landmark National Lung Screening Trial (NLST), both for a younger cohort of individuals aged 55-64 years, and an older Medicare age group of individuals aged 65-77 years, Dr. Huo and his coinvestigators reported.

The estimated rate of complications was 22.0% (95% confidence interval, 21.7%-22.7%) in the younger age group, and even higher in the older age group, at 23.8% (95% CI, 23.0%-24.6%), according to investigators. By contrast, complication rates in the NLST were 9.8% and 8.5% for younger and older age cohorts, respectively.

The cost of managing postprocedural complications was higher than the cost of the diagnostic procedures.

Mean costs ranged from $6,320

for minor complications to $56,845 for major complications, they reported.

The most common invasive diagnostic procedure in the study cohort was a cytology test or biopsy in 26.1%, followed by bronchoscopy in 25.6%, according to study data. Another 5.4% of study subjects underwent thoracic surgery.

In a previous Medicare advisory committee meeting, some experts had expressed concern that complication rates in settings outside of the NLST would likely be higher than what was reported in that study, Dr. Huo and coauthors noted.

"Our findings echoed this concern," the researchers wrote.

The researchers reported no conflicts of interest. Their study was supported by the University of Texas MD Anderson Cancer Center, the University of Florida, the National Cancer Institute, and the National Institutes of Health.

chestphysiciannews@chestnet.org

SOURCE: Huo J et al. JAMA Intern Med. 2019 Jan 14.

VIEW ON THE NEWS

Patients need briefing on harms vs. benefits

"The conversations that are occurring about lung cancer screening are woefully inadequate and do not discuss harms," Rita F. Redberg, MD, wrote in an editorial note. Shared decision-making visits were made mandatory prior to lung cancer screening by the Centers for Medicare & Medicaid Services. That decision was made because of an evidence review suggesting a "low likelihood" that benefits of lung cancer screening would exceed harms in the Medicare population, Dr. Redberg wrote. Despite that, most Medicare beneficiaries are not having the required visit for shared decision making before they undergo the CT scan.

Of those Medicare beneficiaries who did have a shared decision-making visit, 40% opted out of screening, probably because they learned of the harms relative to the benefits during that visit, Dr. Redberg said.

"It is likely that patients' decisions not to undergo low-dose computed tomography for lung cancer screening are driven by the high false-positive rate, high chance of incidental findings, and subsequent need for invasive procedures, and small chance of benefit," she said in her comment.

Shared decision-making visits are also rarely happening in the privately insured population, as shown in previous research, Dr. Redberg noted.

She reported no conflicts of interest related to her Editor's Note, which appears in JAMA Internal Medicine (2019 Jan 14).

Dr. Redberg is with the department of medicine, University of California, San Francisco.

Greetings, readers!

BY DAVID A. SCHULMAN, MD, FCCP
CHEST Physician Editor in Chief

One year ago, I wrote in these pages with regard to my two main goals for *CHEST Physician* for 2018, namely allowing more space in our pages for leaders and members to express their views, and improving interactivity between the staff here and our readership to help us better craft a publication that met your needs.

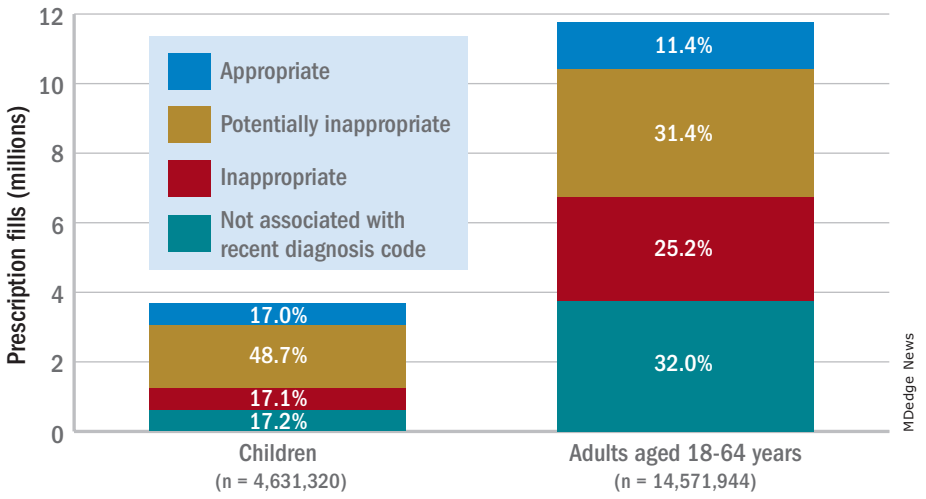
While I think we've met the first goal quite well, with a greater number of educational write-ups from our NetWork leadership and high-quality editorials and commentaries from other CHEST dignitaries, we have not yet heard much from the most important resource we have, our readers.

So for the coming year, I would welcome you to drop us a line every now and then. See something in our pages that you like, or with which you disagree? Is there something in the news relevant to pulmonary, critical care, or sleep medicine that you think we should have covered but did not?

Send us an email at chestphysiciannews@chestnet.org. I look forward to closer contact with you over the coming year.

Let's make *CHEST Physician* even better together!

Proportion of antibiotic prescription fills by appropriateness, 2016



Note: Based on data from the Truven MarketScan Commercial Claims and Encounters database.
Source: BMJ. 2019;364:k5092. doi: 10.1136/bmj.k5092

Antibiotic prescribing // *continued from page 1*

involved phone consultations that did not result in claims or visits that were paid out of pocket and did not make it into the Truven MarketScan Commercial Claims and Encounters database used in the study, the investigators said.

The three highest levels of inappropriate fills were 70.7% in office-based settings, 6.2% in urgent care centers, and 4.7% in emergency departments.

"The unacceptable scale of inappropriate antibiotic prescribing in the United States ... underscores the need to learn more about prescriptions that aren't justified by a diagnosis – or are written after no diagnosis at all," coinvestigator Jeffrey Linder, MD, of Northwestern University, Chicago, said in a written statement.

Prescriptions for children, who represented almost a quarter of all antibiotic fills, were less likely to be inappropriate than those for adults aged 18-64 years. Proportions for children were 17.1% inappropriate, 48.7% potentially inappropriate, and 17.0% appropriate, compared with 25.2%, 31.4%, and 11.4%, respectively, for adults, Dr. Chua and his associates said.

"This study shows how data and analytics can help us identify and understand important challenges facing the American health care system," said Gopal Khanna, director of the Agency for Healthcare Research and Quality, which funded the study. "We now need to use these data to spur change in the prescribing of these very common medications."

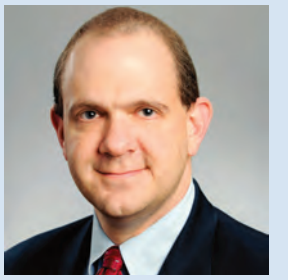
rfranki@mdedge.com

SOURCE: Chua K-P et al. BMJ. 2019;364:k5092. doi: 10.1136/bmj.k5092.

NEWS FROM CHEST // 38

CHEST NETWORKS // 50

***CHEST PHYSICIAN* IS ONLINE**
CHEST Physician is available at chestphysician.org.



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

CHEST® Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

EDITORIAL OFFICES 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

ADVERTISING OFFICES 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

Spending on medical marketing increased by $12.2 billion over the last 2 decades

BY STEVE CIMINO
MDedge News

Total spending on medical marketing in the United States increased from $17.7 billion in 1997 to $29.9 billion in 2016, according to an analysis of direct-to-consumer (DTC) and professional marketing for prescription drugs, disease awareness campaigns, health services, and laboratory tests.

"Increased medical marketing reflects a convergence of scientific, economic, legal, and social forces," wrote Lisa M. Schwartz, MD, and her coauthor, adding that, "although marketing expanded over 20 years, regulatory oversight remains relatively limited." Dr. Schwartz, then codirector of the Center for Medicine and Media at The Dartmouth Institute in Lebanon, N.H., died in November of 2018, after her work was accepted for publication in JAMA.

Dr. Schwartz and her coauthor, David Woloshin, MD, also of Dartmouth, reviewed consumer advertising and professional marketing data, along with searches of medical literature and business journals, to ascertain the quantity and impact of spending. The most money was spent on marketing to medical professionals, which increased from $15.6 billion in 1997 to $20.3 billion in 2016. In terms of percentages, the biggest increase was seen in DTC advertising: $2.1 billion in 1997 (11.9% of total spending) ballooned to $9.6 billion (32.1% of total spending).

These increases were not accompanied by corresponding regulatory efforts to limit influence or protect patients and consumers. In 2016, the Food and Drug Administration's Office of Prescription Drug Promotion received 97,252 promotional materials that drug companies submitted for review, compared with 34,182 in 1997, but violation letters for prescription drug advertising decreased from 156 to 11. In the same year, the FDA reviewed 41% of core materials – such as risk disclosures and key messages – for new drugs or indications prior to launch, a performance measure the coauthors called "critically important."

Marketing saw a remarkable 430% increase ($542 million to $2.9 billion) over the 2 decades, while health services spending increased by 90% ($1.2 trillion to $2.2 trillion).

In regard to disease awareness campaigns, 2004 guidance from the FDA on awareness advertising – including standards for unbranded campaigns and recommendations to avoid encouraging self-diagnosis and self-treatment – was withdrawn in 2015 and never replaced. The Federal Trade Commission, which has jurisdiction over unbranded advertising, has not taken regulatory action of its own; any FDA requests for investigation are unknown. In addition, these 2 decades have not seen state attorneys general initiate any action against deceptive consumer advertising, nor has the FTC acted against misleading laboratory test promotion.

"The FDA and FTC should establish and enforce standards for responsible disease awareness campaigns," the coauthors wrote, "including criteria to validate symptom quizzes (or banning them) and evidence-based strategies to minimize misconceptions that a drug can treat all symptoms of disease."

Overall, spending on medical marketing actually increased faster than did spending on health services overall. Marketing saw a remarkable 430% increase ($542 million to $2.9 billion) over the 2 decades, while health services spending increased by 90% ($1.2 trillion to $2.2 trillion).

One of the rare similarities from 1997 to 2016 was spending on marketing prescription drugs to physicians, typically through face-to-face meetings and hospital visits; this held steady at approximately $5 billion. However, spending on drug samples increased from $8.9 billion to $13.5 billion, while medical journal advertising declined drastically from $744 million to $119 million.

Spending on DTC marketing of prescription drugs increased across all therapeutic categories but three: cholesterol, allergy, and osteoporosis, each of which saw top-selling drugs either become over-the-counter or lose patent protection. Spending on drugs for diabetes/endocrine disease went from $27 million in 1997 to a whopping $725 million in 2016, followed by dermatology drugs ($67 million to $605 million) and pain/central nervous system drugs ($56 million to $542 million).

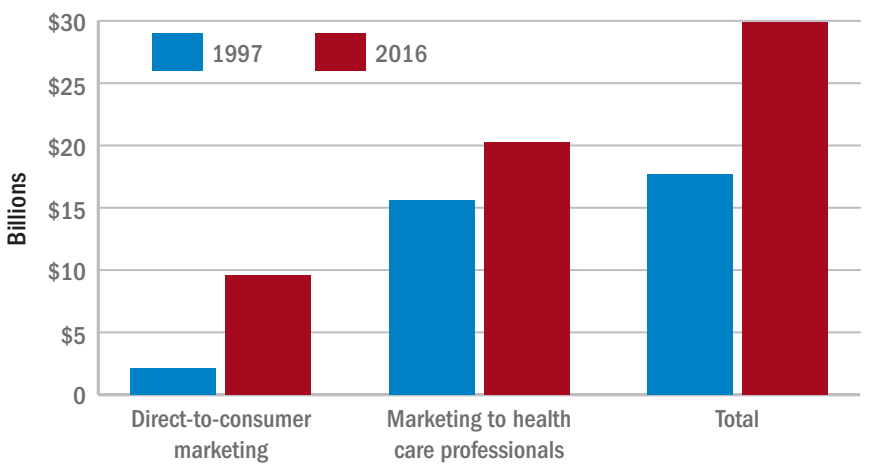
The coauthors shared potential limitations of their study, including the likelihood that they underestimated how much is actually spent on medical marketing. "Data on professional marketing (e.g., detailing) of laboratory tests, health services or devices, and pharmaceutical company spending on coupons or rebates, online promotion, and meetings and events could not be obtained," they noted. In addition, company marketing budgets often do not include additional expenses that should count toward this total, and any published literature on medical marketing's return on investment is largely based on observational data and cannot be fully relied upon.

The two coauthors previously served as medical experts in testosterone litigation and were cofounders of a company that provided data about the benefits and harms of prescription drugs, which ceased operations in December 2016. No other conflicts of interest were reported.

chestphysiciannews@chestnet.org

SOURCE: Schwartz LM et al. JAMA. 2019 Jan 8. doi: 10.1001/jama.2018.19320.

Spending on U.S. medical marketing, 1997 and 2016



Note: Based on data from Kantar Media (DTC) and from IQVIA Institute for Human Data Science, Open Payments, and company websites (professionals).

Source: JAMA. Jan 8 2019;321(1):80-96. doi: 10.1001/jama.2018.19320

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: These data did not surprise me in the least. I am certain that I am not the only health-care provider who has had to explain to patients why a drug or procedure that they saw on television or the internet is not indicated for their disease. Like many, I don't spend a great deal of time reading the advertisements in medical journals, but it is more difficult to avoid the profusion of promotion in other forms of media, especially television. Effective advertising is not meant to educate, but rather to persuade one to purchase a product, often with hyperbole. Unfortunately, lack of oversite by the Food and Drug Administration and the Federal Trade Commission will make our jobs just that much more difficult. I long for the days of free pens and note pads with no TV commercials.

INPULSIS-ON: Long-term nintedanib safe for IPF

BY AMY KARON
MDedge News

For patients with idiopathic pulmonary fibrosis, up to 68 months of treatment with nintedanib showed acceptable safety and tolerability and might have slowed disease progression, according to the results of the open-label INPULSIS-ON trial.

No new safety signals were identified among patients who continued nintedanib or who switched from placebo to the medication after completing one of the two 52-week phase 3 INPULSIS trials, reported Bruno Crestani, MD, of Hôpital Bichat, Paris, and his associates.

"Patients with idiopathic pulmonary fibrosis could use nintedanib over the long term to slow disease progression," they wrote in Lancet Respiratory Medicine.

Idiopathic pulmonary fibrosis patients often die or deteriorate because of acute declines in respiratory function. Nintedanib (Ofev) is an intracellular tyrosine kinase inhibitor approved for idiopathic pulmonary fibrosis in the United States in 2014, based on the results of the replicate randomized, placebo-controlled, double-blind, phase 3 INPULSIS trials, in which nintedanib (150 mg twice daily) was tolerable, showed an acceptable overall toxicity profile, and lessened the annual rate of decline in forced vital capacity (FVC), compared with placebo.

Idiopathic pulmonary fibrosis has a chronic trajectory, so data on long-term safety and efficacy were clearly desirable. "Results from the open-label extension of the [foundational] phase 2 TOMORROW trial [also] identified no new safety signals and suggested an effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis beyond 52 weeks; however, only 35 patients treated with nintedanib 150 mg twice daily entered the extension study," the researchers wrote.

The open-label INPULSIS-ON trial included 734 patients, which was 91% of the population that completed the INPULSIS trials. A total of 59% patients in the open-label trial continued nintedanib while the rest switched to nintedanib from placebo. With both cohorts considered, the median duration of exposure to nintedanib was 44.7 months.

Rates of major adverse cardiovascular events were 2.4 per 100 person-years of drug exposure among treatment initiators and 3.6 per 100 person-years among continuers. Rates of bleeding were 6.7 and 8.4 events per 100 person-years, respectively, while rates of myocardial infarction, using the broadest definition, were 0.7 and 1.3 events per 100 person-years, respectively. The most common adverse event was diarrhea, with 60.1 and 71.2 events per 100 person-years among treatment initiators and continuers, respectively. In all, 10% of treatment initiators and 5% of continuers stopped nintedanib because of diarrhea. A total of 14% of treatment initiators and 12% of continuers stopped treatment because of disease progression.

The adjusted annual rate of decline in FVC was −135.1 mL overall, −145 mL in nintedanib continuers, and −119.7 mL in nintedanib initiators, which resembled the findings of the INPULSIS trials.

Boehringer Ingelheim funded the study. Dr. Crestani disclosed grants and personal fees from Boehringer Ingelheim and other drug companies.

chestphysiciannews@chestnet.org

SOURCE: Crestani B et al. Lancet Respir Med. 2018 Sep 14. doi: 10.1016/S2213-2600(18)30339-4.

VIEW ON THE NEWS

Bias may compromise efficacy data

The study provides "invaluable safety data, including a very low incidence of cardiovascular events" among patients who received long-term nintedanib therapy for idiopathic pulmonary fibrosis, wrote Athol U. Wells, MD, in an editorial published alongside the study.

But the efficacy data were substantially more problematic, he said. "At first sight, the data seem to show that treatment benefits are sustained during long-term follow-up. However, this finding applied to patients completing 4 years of treatment. Approximately 70% of patients discontinued nintedanib [during the open-label extension trial]."

Death, probable treatment failure, or adverse events unrelated to idiopathic pulmonary fibrosis accounted for 62% of withdrawals from this study, and the investigators did not present FVC trends for these patients, he noted. This makes it difficult to know whether bias affected the efficacy results. Long-term stability or slow progression was seen in 30%-40% of patients, exceeding results from previous IPF cohorts, but "this finding, although encouraging, is clearly non-definitive."

The mortality data also were problematic because the trial excluded patients with major comorbidities and severe disease, and the researchers tracked vital status for only 6 weeks after patients withdrew from INPULSIS-ON, he said. "One cannot help but feel that a major opportunity was lost in this study and, equally, in the pirfenidone extension study. An intention-to-treat study design would have provided invaluable long-term efficacy data and should be prioritized in future."

Dr. Wells is with Royal Brompton Hospital in London. He disclosed personal fees from Boehringer Ingelheim, Intermune/Roche, Bayer, Actelion, and Raffo, outside the submitted work (Lancet Respir Med. 2018 Sep 14. doi: 10.1016/S2213-2600[18]30385-0).

In-hospital mortality higher in PAD patients with COPD

BY MARK S. LESNEY
MDedge News

Patients with peripheral arterial disease (PAD) and chronic obstructive pulmonary disease (COPD) have a 1.2-fold higher in-hospital mortality as do patients with PAD alone, Karsten Keller, MD, of the Johannes Gutenberg-University Mainz (Germany) and his colleagues wrote in Respiratory Medicine.

"Unexpectedly, this increase was not driven by [myocardial infarction] as the life-threatening acute presentation of [coronary artery disease], but rather was related to an increased risk for [pulmonary embolism] and a higher coprevalence of cancer." The researchers recommended that PAD inpatients with COPD be monitored more intensively, especially for potential pulmonary embolism and myocardial infarction.

Dr. Keller and his colleagues analyzed the German inpatient national database based on ICD codes. They identified 5,611,827 adult inpatients (64.8% men) diagnosed with PAD between January 2005 and December 2015, and of those, 13.6% also were coded for COPD. Overall, 277,894 PAD patients (5.0%) died in the hospital, Dr. Keller and his colleagues wrote.

The all-cause, in-hospital mortality was 6.5% in PAD patients with COPD, compared with 4.7% in patients with PAD alone (*P* less than .001). Cardiovascular events comprising pulmonary embolism, deep vein thrombosis, and myocardial infarction occurred more often in coprevalence with PAD and COPD.

In PAD patients, COPD was an independent predictor of in-hospital death (odds ratio, 1.16; 95% confidence interval, 1.15-1.17; *P* less than .001) as well as an independent predictor for PE (OR, 1.44; 95% CI, 1.40-1.49; *P* less than .001).

Coronary artery disease and heart failure were more common in PAD patients with COPD, as were cancer and renal insufficiency.

"Remarkably, PAD patients with COPD showed more frequently lower PAD stages than those without COPD. Especially, PAD stage IV was more prevalent in PAD patients without COPD (19.6% vs. 13.8%; *P* less than 0.001)," the authors wrote.

The German Federal Ministry of Education and Research funded the study, and the authors reported having no conflicts.

mlesney@mdedge.com

SOURCE: Keller K et al. Respir Med. 2019 Feb;147:1-6.

New CHEST expert panel advice on cough diagnosis

BY JIM KLING
MDedge News

FROM THE JOURNAL *CHEST*® ▪ The CHEST Expert Cough Panel has released two new expert guidelines, one aimed at adult outpatients with a cough likely related to influenza or pneumonia and one for pertussis-associated cough in adults and children.

Upper and lower respiratory tract infections are a common reason for primary care visits. A cough caused by influenza or pneumonia represents an opportunity to intervene for a significant benefit. The recommendations were published in the journal *CHEST*®. The panel drafted recommendations based on available evidence and graded them using the CHEST grading system. The grading is based on the strength of the recommendation (either strong or weak) and a rating of the overall quality of the body of evidence. Where available evidence was weak, but guidance was still warranted, a weak suggestion was developed and graded 2C. Recommendations based on consensus in cases of insufficient clinical evidence are labeled "ungraded consensus-based statement."

Pneumonia or influenza?

In adult outpatients with acute cough, the clinical signs of pneumonia include cough, dyspnea, pleural pain, sweating/fevers/shivers, aches and pains, temperature greater than or equal to 38°C, tachypnea, and new and localizing chest examination signs. When pneumonia is suspected to cause acute cough, C-reactive protein (CRP) should be measured. A CRP value higher than 30 mg/L bolsters the case for pneumonia, whereas a CRP value of lower than 10 mg/L, or between 10 mg/L and 50 mg/L in the absence of dyspnea and daily fever, makes pneumonia less likely.

The guidelines recommend against routine measurement of procalcitonin for outpatient adults suspected to have pneumonia. For adults with acute cough and abnormal vital signs believed to be secondary to pneumonia, the guidelines call for a chest x-ray.

Routine microbiological testing need not be performed in suspected pneumonia, but it should be considered if the results could guide or lead to a change in therapy.

When pneumonia is suspected but imaging is unavailable, empiric antibiotics should be used in concordance with local and national guidelines. If imaging turns up negative, antibiotics should not be used. However, if there is no clinical or radiographic evidence of pneumonia, antibiotics should not be used routinely.

Finally, adult patients with acute cough and suspected influenza should begin antiviral treatment within 48 hours of the start of symptoms.

Pertussis

Pertussis has significant morbidity and mortality, with infants being particularly vulnerable, and it is highly contagious. Although antibiotics will not affect the course of the disease, they should be administered as quickly as possible in order to prevent further spread. This puts pressure on the clinician to make a treatment decision before further testing is available.

A prespecified meta-analysis found high sensitivity and low specificity for paroxysmal cough (sensitivity, 93.2%; specificity, 20.6%) and absence of fever (sensitivity, 81.8%; specificity, 18.8%). The study found low sensitivity and high specificity for inspiratory whoop (sensitivity, 29.8%; specificity, 79.5%) and posttussive vomiting (sensitivity, 32.5%; specificity, 77.7%). In children, the review found that posttussive vomiting was moderately sensitive (60.0%) and specific (66.0%).

In adult patients with acute cough (less than 3 weeks' duration) or subacute cough (3-8 weeks), the new guidelines recommend that physicians consider four key characteristics: the presence of recurrent, prolonged coughing episodes with an inability to breathe during the spell (paroxysmal); posttussive vomiting; inspiratory whooping; and presence of fever.

In acute or subacute cough, if the patient has a fever (body temperature greater than 98.6° F or 37.6° C) or does not have a paroxysmal cough, pertussis is unlikely. On the other hand, posttussive vomiting or an associated inspiratory whooping sound suggests pertussis.

Children with a cough lasting fewer than 4 weeks (acute) should be assessed for paroxysmal cough, posttussive vomiting, and inspiratory whooping. A cough associated with any of these characteristics may be caused by pertussis.

chestphysiciannews@chestnet.org

SOURCES: Moore A et al. CHEST. 2019 Jan;155:147-154; Hill A et al. CHEST. 2019 Jan;155:155-167.

Prescribed opioids raise pneumonia risk

BY MARK S. LESNEY
MDedge News

Prescribed opioids were associated with an increase in community-acquired pneumonia in patients with and without HIV infection, according to results of a large database study.

People living with HIV (PLWH) appeared to have a greater community-acquired pneumonia (CAP) risk at lower opioid doses and particularly with immunosuppressive opioids compared with uninfected patients, although the difference was not significant, E. Jennifer Edelman, MD, of Yale University, New Haven, Conn., and her colleagues wrote in JAMA Internal Medicine.

The researchers performed a nested case-control study of 25,392 participants (98.9% men; mean age, 55 years) in the Veterans Aging Cohort Study from Jan. 1, 2000, through Dec. 31, 2012.

Dr. Edelman and her colleagues compared the characteristics of 4,246 CAP cases with those of 21,146 uninfected controls in the sample. They also compared cases and controls by HIV status, and ran models stratified by HIV status and formally checked for an interaction between prescribed opioid characteristics and HIV status.

In unadjusted logistic regression analysis, prescribed opioids were associated with increased odds of CAP, with the greatest risk observed with currently prescribed opioids, compared with past prescribed opioids or no opioids.

Prescribed opioids remained associated with CAP in the adjusted models for past unknown or nonimmunosuppressive (adjusted odds ratio, 1.24; 95% confidence interval, 1.09-1.40) and past immunosuppressive opioid use (aOR, 1.42; 95% CI, 1.21-1.67). For currently prescribed opioids, nonimmunosuppressive or unknown, the aOR was 1.23 (95% CI, 1.03-1.48). For currently prescribed immunosuppressive opioids, the aOR was 3.18 (95% CI, 2.44-4.14).

Currently prescribed high-dose opioids were associated with the greatest CAP risk, followed by medium- and then by low-dose opioids, whether immunosuppressive or not.

With regard to the effect of HIV status in stratified, adjusted analyses, CAP risk tended to be greater among PLWH with current prescribed opioids, especially immunosuppressive opioids, compared with uninfected patients. However, the difference was not statistically significant.

Although the researchers stated that a limitation of their study was an inability to prove causality or rule out respiratory depression (vs. immunosuppression) as the cause of the increased CAP risk, "the observed effects of opioid immunosuppressive properties and CAP risk lend support to our hypothesis that opioids have clinically relevant immunosuppressive properties."

Dr. Edelman and her colleagues were not able to determine whether patients took their prescribed medications appropriately and to assess whether the patients took nonmedically prescribed opioids. Also, because men made up such a large portion of the study population, it is unclear whether the results are generalizable to women.

"Health care professionals should be aware of this additional CAP risk when they prescribe opioids, and future studies should investigate the effects of opioids prescribed for longer durations and on other immune-related outcomes," wrote Dr. Edelman and her colleagues. "Understanding whether mitigating the risk of prescribed opioids for CAP is possible by using a lower dose and nonimmunosuppressive opioids awaits further study."

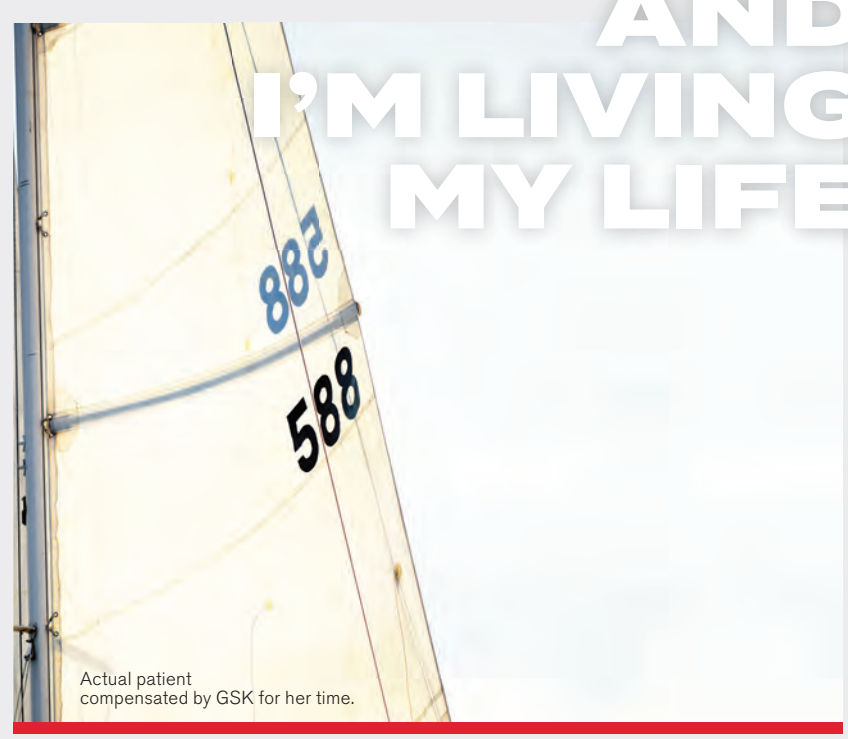
They advised attempting to modify other factors known to affect CAP risk, including smoking and lack of vaccination.

Several U.S. government agencies and Yale University provided funding for the study. The authors reported that they had no conflicts.

mlesney@mdedge.com

SOURCE: Edelman EJ et al. JAMA Intern Med. 2019 Jan 7. doi: 10.1001/jamainternmed.2018.6101.

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



#1 prescribed biologic indicated for severe eosinophilic asthma*—27,000 patients and counting[1†]

*Source: IQVIA - NPA™ audit: 12 mo. TRX data ending 7/18 (All rights reserved).

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

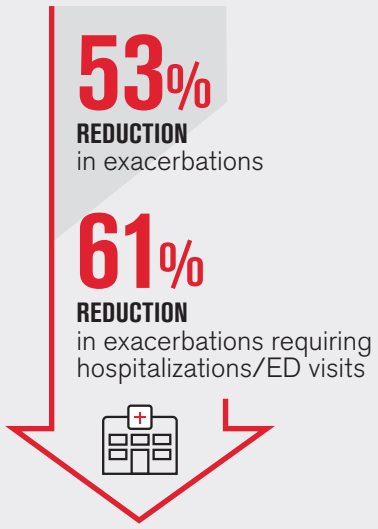
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms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

Parasitic (Helminth) Infection

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

Choose NUCALA:

Powerful Protection From Exacerbations[2‡]



Powerful Reduction in OCS Dose[3]

Lasting Evidence[1]

Only anti-interleukin 5 (IL-5) with a

4.5-year

open-label study that evaluated safety and efficacy

MENSA (Trial 2)[2]: 32-week study comparing NUCALA 100 mg to placebo, each added to SOC in 576 patients with severe eosinophilic asthma (SEA). **Primary Endpoint Results:** Frequency of exacerbations. NUCALA: 0.83/year, placebo: 1.74/year; *P*<0.001). **Secondary Endpoint Results:** Frequency of exacerbations requiring hospitalization and/or ED visit; NUCALA: 0.08/year; placebo: 0.20/year; *P*=0.02.

SIRIUS (Trial 3)[3]: 24-week study comparing NUCALA 100 mg to placebo in 135 patients with SEA receiving prednisone 5-35 mg (or equivalent) per day and regular use of high-dose ICS and 1 other controller. **Primary Endpoint Results:** Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control vs placebo; *P*=0.008.

COLUMBA[1]: 4.5-year open-label study assessing the safety, immunogenicity, and efficacy of NUCALA 100 mg added to asthma controller therapy in 347 patients with SEA.

‡Worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalizations and/or emergency department (ED) visits; for patients on maintenance oral/systemic corticosteriods, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

Standard of care (SOC)=regular treatment with high-dose inhaled corticosteroids (ICS) and at least 1 other controller with or without oral corticosteroids (OCS).

Learn more at **KnowNucalaHCP.com**

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207. **3.** Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371:1189-1197.

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

Printed in USA. 1007315R0 September 2018

Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience in Severe Asthma

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.3 Immunogenicity

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

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

6.4 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

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

(continued on next page)

(continued from preceding page)

8 USE IN SPECIFIC POPULATIONS (cont'd)

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

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

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.
Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.
Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

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

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

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

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

Manufactured by
GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Printed in USA. 1007315R0 September 2018

Leveraging CV, renal benefits of new diabetes drugs

BY MITCHEL L. ZOLER
MDedge News

CHICAGO – When the first results from a large trial that showed profound and unexpected benefits for preventing heart failure hospitalizations associated with use of the antihyperglycemic sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin came out – a little over 3 years ago – the general reaction from clinicians was some variant of "Could this be real?"


Dr. Braunwald

Since then, as results from some five other large, international trials have come out showing similar benefits from two other drugs in the same SGLT2-inhibitor class, canagliflozin and dapagliflozin, as well as results showing clear cardiovascular disease benefits from three drugs in a second class of antihyperglycemics, the glucagonlike peptide–1 receptor agonists (GLP-1 RAs), the consensus among cardiologists became: "The cardiovascular and renal benefits are real. How can we now best use these drugs to help patients?"

This change increasingly forces physicians to become more comfortable prescribing these two classes of antihyperglycemic drugs. During a talk at the American Heart Association scientific sessions, Eugene Braunwald, MD, arguably the top thought leader in cardiology, coined a new name for the medical subspecialty that he foresees navigating this overlap between diabetes care and cardiovascular disease prevention: diabetocardiology (although a more euphonic alternative might be cardiodiabetology, while the more comprehensive name could be cardionephrodiabetology).

"I was certainly surprised" by the report in 2015 from the EMPA-REG OUTCOME trial (N Engl J Med. 2015 Nov 26;373[22]:2117-28), said Dr. Braunwald, professor of medicine at Harvard Medical School in Boston. "Now we have three trials," with the addition of the CANVAS trial for canagliflozin (N Engl J Med. 2017 Aug 17;377[7]:644-57) and the DECLARE-TIMI 58 trial (N Engl J Med. 2018 Nov 10. doi:10.1056/NEJMoa1812389) for dapagliflozin at the AHA meeting in November.

"We are in the midst of two pandemics: heart failure and type 2 diabetes. ... We have to learn how to deal with this," said Dr. Braunwald, and the evidence now clearly shows that these drugs can help with that.

As another speaker at the meeting, Javed Butler, MD, a heart failure specialist, observed in a separate talk, "Heart failure is one of the most common, if not the most common, complications of patients with diabetes." This tight link between heart failure and diabetes makes cardiovascular mortality "the number one cause of death" in patients with diabetes, said Dr. Butler, professor and chair of medicine at the University of Mississippi in Jackson.

"Thanks to the cardiovascular outcome trials, we now have a much broader and deeper appreciation of heart failure and renal disease as integral components of the cardiovascular-renal spectrum in people with diabetes," said Subodh Verma, MD, a professor at the University of Toronto and cardiac surgeon at St. Michael's Hospital in Toronto. Dr. Braunwald spelled out in his talk some of the interrelationships of diabetes, heart failure, and renal dysfunction that together produce a downward-spiraling vicious circle for patients, a pathophysiological process that clinicians can now short-circuit with a SGLT2 inhibitor.

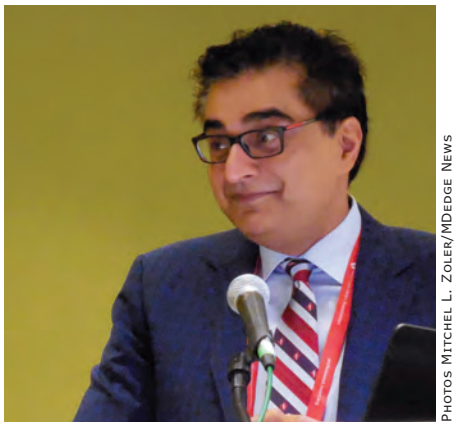
Outcome trials show the way

In the context of antihyperglycemic drugs, the "cardiovascular outcome trials" refers to a series of large trials mandated by the Food and Drug Administration in 2008 to assess the cardiovascular disease effects of new agents coming onto the U.S. market to treat type 2 diabetes mellitus (T2DM). By the time Dr. Verma spoke at the AHA meeting, he could cite reported results from 12 of these trials: 5 different drugs in the GLP-1 RA class, 4 drugs in the dipeptidyl peptidase-4 (DPP-4) inhibitor class, and 3 drugs from the SGLT2 inhibitor class. Dr. Verma summed what the findings have shown.

The four tested DDP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin) consistently showed neutrality for the primary outcome of major adverse cardiovascular disease events (MACE), constituted by cardiovascular disease death, MI, or stroke.

The five tested GLP-1 RAs (albiglutide, exenatide, liraglutide, lixisenatide, and semaglutide) showed a mixed pattern of MACE results that seemed to be linked with the subclass the drug fell into. The two exedin-4–based drugs, exenatide and lixisenatide, each showed a statistically neutral effect for MACE, as well as collectively in a combined analysis. In contrast, three human GLP-1–based drugs, albiglutide, liraglutide, and semaglutide, each showed a consistent, statistically significant MACE reduction in their respective outcome trials, and collectively they showed a highly significant 18% reduction in MACE, compared with placebo, Dr. Verma said. Further, recent analysis by Dr. Verma that used data from liraglutide treatment in the LEADER trial showed the MACE benefit occurred only among enrolled patients treated with liraglutide who had established atherosclerotic cardiovascular disease (ASCVD). Patients enrolled in the trial with only multiple risk factors (in addition to having T2DM) but without established ASCVD showed no significant benefit from liraglutide treatment for the MACE endpoint, compared with control patients.


Dr. Javed Butler


Dr. Subodh Verma

PHOTOS MITCHEL L. ZOLER/MDEDGE NEWS

Recently a press-release announcement of results from a sixth GLP-1 RA, dulaglutide, in the REWIND trial of MACE outcomes suggested that a drug in this class could have a broader effect. The majority, 69%, of the 9,901 patients with T2DM enrolled in REWIND had risk factors but not established ASCVD at enrollment. A Nov. 5, 2018, statement from the company developing this drug, Lilly, reported that the study overall produced a statistically significant reduction in MACE, although it provided no additional details. As the released noted, this made REWIND the first trial to show a MACE benefit from a drug in the GLP-1 RA class in patients without established ASCVD.

The MACE outcome results from the three SGLT2 inhibitor trials showed a similar pattern as liraglutide: In patients with established ASCVD, the drugs individually each produced a MACE reduction, although dapagliflozin just missed having a statistically significant reduction. Collectively, the three drugs showed a statistically significant, 14% relative risk reduction for MACE, compared with control patients. But among patients with multiple risk factors only, but without established ASCVD, included in two of the three trials (CANVAS and DECLARE-TIMI 58), the results showed both individually and collectively a neutral MACE effect.

But unlike the other antihyperglycemic drugs tested in the cardiovascular outcome trials, the SGLT2 inhibitors have shown two additional, highly important secondary outcomes: a consistent reduction in hospitalization for heart failure and a consistent reduction in renal-disease progression.

A meta-analysis of the three SGLT2 inhibitor trials published coincident with the release of the DECLARE-TIMI 58 results showed that, for the outcome of either cardiovascular death or hospitalization for heart failure, the SGLT2 inhibitors collectively showed a significant 29% relative decrease in this incidence among patients with a history of heart failure, and a significant 21% relative decrease among patients without history of heart failure (Lancet. 2018 Nov 10. doi: 10.1016/S0140-6736[18]32590-X). Among the subset of patients with established ASCVD, treatment with a SGLT2 inhibitor across all three trials showed a significant 16% relative risk reduction, and in the subset with multiple risk factors but no established ASCVD, the two SGLT2 inhibitors collectively produced a 16% relative cut in cardiovascular death or heart failure hospitalization with a *P* value of .06. Finally, the Lancet meta-analysis showed that,

for a combined endpoint that reflected renal worsening, the SGLT2 inhibitors showed a significant relative reduction of about 45% in both the subgroup of patients with established ASCVD and in the subgroup of those with just risk factors.

"This is a big step forward for patients with multiple risk factors and diabetes but without ASCVD, that both renal disease and hospitalization for heart failure are sensitive" to the SGLT2 inhibitors, Dr. Verma noted. "We see renal protection and reduction of heart failure hospitalization across both primary and secondary prevention patients, with no need to distinguish them based on ASCVD." In contrast, he noted, the MACE benefit from the SGLT2 inhibitors seems limited to patients with ASCVD. The day before making this point in a talk during the meeting, Dr. Verma had published the same message in a commentary (Lancet. 2018 Nov 10. doi: 10.1016/S0140-6736[18]32824-1).

Although the "nomenclature of primary versus secondary prevention is appropriate for atherosclerotic outcomes, it is likely to be inappropriate for a person with type 2 diabetes who is at risk of hospitalization for heart failure and renal disease," Dr. Verma wrote.

What it means for clinicians

The upshot of all of these cardiovascular outcome trial results from the past 3 years has been a new appreciation of how antihyperglycemic drugs can have cardiovascular and renal benefits that transcend their effects on glycemia. The evidence has put the SGLT2 inhibitors and GLP-1 RAs on track to challenge, and potentially displace, metformin as the top drug to prescribe for patients with T2DM.

Clinicians should realize that they should prescribe SGLT2 inhibitors and selected GLP-1 RAs "as early as metformin in patients with established ASCVD," said Dr. Verma. "For patients with recalcitrant atherosclerotic disease and a history of MI and ischemia, I'd primarily treat with a GLP-1 RA. In a patient with left ventricular dysfunction or evidence of heart failure, I'd use an SGLT2 inhibitor. But it's not a fight between these two. You could treat a patients with type 2 diabetes with both classes," although the practicality of this approach is limited by the high cost of these drugs.

The SGLT2 inhibitors "should now be considered as first-line therapy after metformin in most people with type 2 diabetes, irrespective of whether or not they have established atherosclerotic vascular disease, chronic kidney disease, or heart failure," he and his associates wrote.

"What I struggle with the most is how we prioritize and individualize secondary-prevention therapies based on risk for ischemia and heart failure. Some therapies [the SGLT2 inhibitors] are predominantly for heart failure prevention, and some [the GLP-1 RAs] are primarily for ischemia. How do we choose when a patient cannot afford to take both? Does a combination of a SGLT2 inhibitor and a GLP-1 RA offer the greatest CVD benefit? We need to test this in a trial. And will metformin be displaced as first-line treatment?" Dr. Verma asked.

"The day will probably come when, for maximal protection, you treat with both classes. But right now we're forced to choose because of the cost," said John McMurray, MD, professor of cardiology at the University of Glasgow, at the meeting.

As to specifically which SGLT2 inhibitor to prescribe, "they all look pretty much the same" in the newly published meta-analysis, Dr. Mc-

Continued on following page

Continued from previous page

Murray said, although he noted that safety differences among agents in the class remain possible.

"For patients similar to those studied in the three SGLT2 inhibitor trials, clinicians should use one of these drugs to reduce the risk for

Mitchel L. Zoler/MDedge News

Dr. John McMurray

incident heart failure, irrespective of their effect on MACE," said Dr. Butler. Reducing the risk for incident heart failure and of progressive renal dysfunction are two new goals for antihyperglycemic therapy that now overlay the long-standing goals of controlling glycemia and reducing cardiovascular disease risk and the more recent goals of cutting cardiovascular disease mortality and cutting the risk for a MACE event.

A current limitation for practice is that the none of the three drug companies that market the tested SGLT2-inhibitor drugs has sought regulatory approval for an indication of reducing the risk for heart failure hospitalization. Despite that, "these drugs should be used for renal protection and reducing heart failure hospitalizations," Dr. Butler said. "We need to start thinking about this and not get lost thinking about only their MACE effect because, when you focus on MACE, there is a competition between the SGLT2 inhibitors and the GLP-1 RA. If we think of GLP-1 RAs as drugs to prevent MACE, and SGLT2 inhibitors as drugs that primarily prevent heart failure and renal dysfunction, then there is no competition. Perhaps combined treatment is where we need to go," he said in an interview.

But the enthusiasm that experts have for wider use of these drugs is not necessarily matched among many community physicians.

David J. Becker, MD, is an example of the clinicians who appreciate the growing evidence that supports wider use, but remain uneasy about applying this evidence in practice.

Dr. Becker, associate director of the Preventive and Integrative Heart Health Program of the Temple Heart and Vascular Institute in Philadelphia, writes a column for the Philadelphia Inquirer on medical care. In a December 2018 piece, he said "like most cardiologists, I 'don't do diabetes' – because it's not my expertise.

Dr. Becker

The new drugs, however, mean I need to learn more" about treating these patients. "The problem: There are so many of these medications that they present a bewildering choice."

Dr. Becker cited barriers to prescribing these drugs:

- High cost, with prices that run close to $20/day for each drug.
- A thicket of names and choices that "lead to confusion and paralysis," which has been exacerbated by "advertising wars."
- Physicians usually defer to endocrinologists to prescribe these drugs, but most patients with T2DM aren't seen by endocrinologists. The result: "Few doctors prescribe them."

The cardiovascular disease benefits of these drugs have not been adequately promoted. Until that changes, "cardiologists like me will not realize their importance," Dr. Becker concluded.

Dr. Braunwald placed the onus for managing this emerging facet of diabetes largely outside the scope of endocrinology.

"We can't call in a consultant every time we have a patient with diabetes," he said. Training of cardiologists now needs to include treating patients with diabetes, Dr. Braunwald advised, just as 30 years ago when cardiologists had to become more familiar with blood clotting to better manage thrombotic disease.

Dr. Braunwald has been a consultant to Cardurion, Myokardia, and Sanofi; an adviser to Endcardia; and has received research funding from AstraZeneca, Daiishi Sankyo, and Novartis. Dr. Butler has been a consultant or adviser to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Merck, Novartis, Novo Nordisk, and Sanofi. Dr. Verma has received honoraria and research funding from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Merck, Novartis, NovoNordisk, Sanofi, and Valeant. Dr. McMurray has received research funding from 12 companies. Dr. Becker had no disclosures.

mzoler@mdedge.com

Secondhand vaping linked to asthma exacerbations

BY M. ALEXANDER OTTO
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Just like exposure to secondhand smoke, exposure to secondhand aerosols from e-cigarettes is associated with an increased risk of asthma exacerbations in children, according to a review of the 11,830 kids with asthma in the 2016 Florida Youth Tobacco survey.

Every year, the Florida Department of Health surveys public school children aged 11-17 years about various tobacco issues. In 2016, almost 12% of the asthmatic children in the survey said they vaped. Almost half were exposed to secondhand smoke, and a third reported exposure to secondhand vaping aerosols within the past 30 days. Overall, 21% reported an asthma attack in the past 12 months.

Using data from the Florida survey, the investigators crunched the numbers and found that secondhand aerosol exposure increased the odds of an asthma attack by 27%, independent of exposure to secondhand smoke and whether children smoked or vaped themselves (adjusted odds ratio, 1.27; 95% confidence interval, 1.11-1.47).

"Health professionals may wish to counsel asthmatic youth and their families regarding the potential risks of ENDS [electronic nicotine delivery system] use and exposure to ENDS aerosols." Providers "may also consider including ENDS aerosol exposure as a possible trigger in asthma self-management/action plans and updating asthma home environment assessments to include exposure to ENDS aerosols," said investigators led by medical student Jennifer Bayly, a research fellow at the National Institute on Minority Health and Health Disparities in Bethesda, Md.

About 4% of adults in the United States and 11% of high school students vape, and almost 10% of U.S. adolescents reported living with an ENDS user in 2014. Given the data, "it is likely that a substantial number of asthmatic youth are exposed," the investigators said.

The study adds to a growing body of evidence linking e-cigarettes to asthma. There's moderate evidence for increased cough and wheezing in adolescents who use e-cigarettes, plus an association with e-cigarette use and increased asthma exacerbations. The new study, however, is likely the first to look specifically at secondhand exposure among asthmatic children. Ingredients in vaping aerosols, including flavorings, propylene glycol, and vegetable glycerin, are physiologically active in the lungs, and may be lung irritants.

Overall, about half of the respondents were female, and two-thirds were 11-13 years old. About a third identified as Hispanic, a third as white, and just over a fifth as black. Three-quarters of the sample lived in large or midsized metropolitan areas, and close to two-thirds in stand-alone homes. Participants were considered exposed to secondhand aerosols if they reported that in the past month they were in a room or car with someone who was vaping.

The work was funded by the National Institutes of Health. The investigators had no disclosures.

aotto@mdedge.com

SOURCE: Bayly J et al. CHEST. 2018 Oct 22. doi: 10.1016/j.chest.2018.10.005.

Off label drugs used for ADHD sleep problems common

BY THERESE BORDEN
MDedge News

Sleep problems in children with attention-deficit/hyperactivity disorder are treated with a variety of medications, many off label for sleep and unstudied for safety and effectiveness in children, based on a study of Medicaid prescriptions.

"Sleep disorders coexist with attention-deficit/hyperactivity disorder (ADHD) for many children and are associated with neuropsychiatric, physiologic, and medication-related outcomes," Tracy Klein, PhD, of Washington State University, Vancouver, and her colleagues wrote in the Journal of Pediatric Health Care.

These patients can have sleep-disordered breathing and behavioral issues occurring around bedtime. Adverse effects of the stimulant and nonstimulant medications used to treat ADHD can include sleep disturbance, delayed circadian rhythm, insomnia, and somnolence. Yet, research on sleep problems in children with ADHD and prescribing patterns is scanty, they said.

Dr. Klein and her colleagues used 5 years of pharmacy claims for children aged 3-18 years in Oregon insured through Medicaid and with a provider diagnosis of ADHD. The number of 30-day prescriptions was measured. The medications were classified as controlled or uncontrolled as determined by Title 21 of the U.S. Controlled Substances Act.

The data yielded 14,567 prescriptions for 2,518 children for a 30-day supply of medication known to potentiate sleep but off label for children. Children aged 3-11 years comprised about 38% of these patients. Some children were prescribed more than one of these medications. Medications specifically on label for sleep but not indicated for children were not included. Those medications indicated for comorbid conditions and those indicated for ADHD that specifically cause somnolence were excluded.

The uncontrolled medications prescribed in this sample were amitriptyline, doxepin, hydroxyzine, low-dose quetiapine, and trazodone. The controlled medications identified were clonazepam and lorazepam, and phenobarbital.

Most of the prescriptions (63.8%) went to older children aged 12-18 years and most prescriptions (66.3%) went to males. The most commonly prescribed noncontrolled medication was trazodone (5,190 prescriptions), followed by hydroxyzine (2,539), and quetiapine (2,402). The most frequently prescribed controlled medication was clonazepam (2,145), followed by lorazepam (534).

Specialist prescribers wrote most of the prescriptions for this patient group, but no differences were found in prescribing patterns.

Dr. Klein and her colleagues noted that 871 unique children were prescribed 5,190 30-day–supply prescriptions for trazodone, including 23 children under age 5. Trazodone is a serotonin modulator indicated for the treatment of major depressive disorder, but has not been studied for safety and efficacy in children and has no Food and Drug Administration indication for children. "Hydroxyzine, quetiapine, and amitriptyline also were prescribed for a large number of children, including some for children as young as 3 years, despite lack of approval for use to induce to sleep and increased potential for significant adverse reactions in children," they wrote.

Prescribers may receive pressure from families to "do something" for their children, who may be disruptive day and night. "Prescribers may be unaware that trazodone, which is commonly used in practice, has never been approved for treatment of insomnia in children or adults. Insurance may not adequately fund other options, such as extensive behavioral therapy," she said in an interview.

These medications come with some risk for children, Dr. Klein noted. "Developmentally, [children] may be unable to verbally express the side effects they are feeling and may therefore be subject to a drug to treat a drug side effect, especially if their reaction to it is behavioral." There is also potential for unanticipated drug interactions between off-label medications prescribed for sleep and drugs prescribed to treat ADHD.

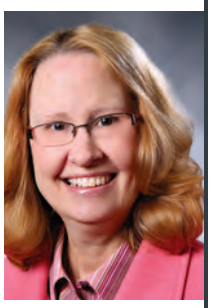
The researchers reported having no disclosures.

tborden@mdedge.com

SOURCE: Klein T et al. J Pediatr Health Care. 2018 Jan 8. doi: 10.1016/j.pedhc.2018.10.002.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: ADD and ADHD are important problems to deal with, but pediatricians and family practice physicians frequently don't have enough education on how to deal with sleep issues that may co-exist. Sleep hygiene can also be a problem that physicians may "medicate" instead of providing education on decreased screen time, for example. Pediatric pulmonologists who treat sleep-disordered breathing or board-certified pediatric sleep physicians are happy to receive referrals for these patients to help figure out how to treat sleep issues safely.



Guideline-concordant antibiotic treatment for pediatric CAP still unlikely in nonchildren's hospitals

BY LUCAS FRANKI
MDedge News

Guideline-concordant antibiotic treatment for pediatric community-acquired pneumonia (CAP) was significantly less likely in a nonchildren's hospital, according to new research.

"This gap is concerning because approximately 70% of children hospitalized with pneumonia receive care in nonchildren's hospitals," wrote Alison C. Tribble, MD, of C. S. Mott Children's Hospital, University of Michigan, Ann Arbor, and her associates. The report is in JAMA Pediatrics.

Data were collected from the Pediatric Health Information System (children's hospitals) and Premier Perspectives (all hospitals) databases and included a total of 120,238 children aged 1-17 years diagnosed with CAP between Jan. 1, 2009, and Sept. 30, 2015. Before the publication of the new guideline in October 2011, the probability of receiving what would become guideline-concordant antibiotics was 0.25 in children's hospitals and 0.06 in nonchildren's hospitals.

By the end of the study period, the probability of receiving guideline-concordant antibiotics for pediatric CAP was 0.61 in children's hospitals and 0.27 in nonchildren's hospitals. Without the interventions, the probabilities would have been 0.31 and 0.08, respectively. The rate of growth over the 4-year postintervention period was similar in both children's and nonchildren's hospitals.

"Studies in children's hospitals have suggested that local implementation efforts may be important in facilitating guideline uptake. Nonchildren's hospitals likely have fewer resources to lead pediatric-specific efforts, and care may be influenced by adult CAP guidelines," the authors noted.

No conflicts of interest were reported.

lfranki@mdedge.com

SOURCE: Tribble AC et al. JAMA Pediatr. 2018 Dec 10. doi: 10.1001/jamapediatrics.2018.4270.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: I am obviously biased, since I am employed at a children's hospital. This is a robust study reported out of the University of Michigan that bears attention!

LAIV4 less effective against aggressive influenza virus strain

BY JEFF CRAVEN
MDedge News

The quadrivalent live attenuated influenza vaccine (LAIV4) was less effective against the influenza A/H1N1pdm09 virus in children and adolescents across multiple influenza seasons between 2013 and 2016, compared with the inactivated influenza vaccine (IIV), according to research published in the journal Pediatrics.

With regard to other strains, there was similar effectiveness against influenza A/H3N2 and influenza B with LAIV4 and IIV vaccinations. "In contrast to findings of reduced LAIV4 effectiveness against influenza A/H1N1pdm09 viruses, our results suggest a possible but nonsignificant benefit of LAIV4 over IIV against influenza B viruses, which has been described previously," wrote Jessie R. Chung, MPH, from the influenza division at the Centers for Disease Control and Prevention in Atlanta, and her colleagues.

The researchers performed an analysis of five different studies where vaccine effectiveness was examined for LAIV4 and IIV in children and adolescents aged 2-17 years from 42 states.

The analysis included data from the U.S. Influenza Vaccine Effectiveness Network (6,793 patients), a study from the Louisiana State University Health Sciences Center (3,822 patients), the Influenza Clinical Investigation for Children (3,521 patients), Department of Defense Global, Laboratory-Based, Influenza Surveillance Program (1,935 patients), and the Influenza Incidence Surveillance Project (1,102 patients). The researchers sourced current and previous season vaccination history from electronic medical records and immunization registries.

Of patients vaccinated across all seasons, there was 67% effectiveness against influenza A/H1N1pdm09 (95% confidence interval, 62%-72%) for those who received the IIV and 20% (95% CI, −6%-39%) for LAIV4. Among patients who received the LAIV4 vaccine, there was a significantly higher likelihood of influenza A/H1N1pdm09 (odds ratio, 2.66; 95% CI, 2.06-3.44) compared with patients who got the IIV vaccine.

The Influenza Clinical Investigation for Children was funded by MedImmune, a member of the AstraZeneca Group. Two of the researchers are employees of AstraZeneca. The other authors reported having no conflicts of interest.

chestphysiciannews@chestnet.org

SOURCE: Chung JR et al. Pediatrics. 2018. doi: 10.1542/peds.2018-2094.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The American Academy of Pediatrics (AAP) provides yearly updates for influenza vaccinations in the United States. For the 2018-2019 season, the AAP recommends inactivated influenza vaccine as the first choice, either in the inactivated trivalent form (IIV3) or the inactivated quadrivalent form (IIV4). The AAP is very specific in regards to usage of the live attenuated influenza vaccine, LAIV4, also called FluMist® Quadrivalent. The AAP states, "LAIV4 should be used for children who would not otherwise receive an influenza vaccine, if the child is at least 2 years old and healthy with no underlying chronic medical condition."[1]

REFERENCE

1. AAP Red Book Updates 2018 "Recommendations for Prevention & Control of Influenza in Children 2018-2019.

Jet nebulizer beats breath-enhanced

BY JIM KLING
MDedge News

In children with moderate to severe acute asthma, albuterol delivered by a conventional jet nebulizer led to more improvement in forced expiratory volume in 1 second (FEV_1) than delivery via a breath-enhanced nebulizer.

One previous study has compared the two types of nebulizers in children with acute asthma. It showed that the new technology is noninferior to the older device, but it had a small sample size and did not examine spirometry data.

Mike Gardiner, MD, of the University of California, San Diego, and Matthew H. Wilkinson, MD, of the University of Texas Southwestern at Austin, conducted a randomized, observer-blind study of the effectiveness of the two nebulizers. The results were published in the Journal of Pediatrics.

At a large pediatric emergency department, researchers randomized 107 children (aged 6-18 years) with moderate to severe asthma exacerbations to one or the other nebulizer.

Children treated with the conventional jet nebulizer had a greater improvement in FEV_1 (+13.8% vs. +9.1% of predicted; $P = .04$). The improvements were similar in a subgroup analysis of 57 subjects who met ATS/ERS (American Thoracic Society/ European Respiratory Society) spirometry guidelines (+14.5% vs. +8.5% of predicted; $P = .03$). There were no significant differences in side effects, Pediatric Asthma Score, Pediatric Asthma Severity Score, ED length of stay, or admission rate.

The study was funded by the University of Texas Southwestern. The authors had no conflicts of interest.

chestphysiciannews@chestnet.org

SOURCE: Gardiner M, Wilkinson MH. J Pediatr. 2019;204:245-9.

BREO has better formulary coverage nationally than Symbicort

Individual access may vary by geography and plan benefit design.
Source: Managed Markets Insight & Technology, LLC, database as of August 2018.

4 Million
More Unrestricted **Commercial** Lives Than Symbicort

2 Million
More Unrestricted **Medicare Part D** Lives Than Symbicort

"Unrestricted coverage" means reimbursement from a health plan without accompanying step edits or prior authorizations. Commercial lives calculation does not include patient lives associated with Indian Health Services or Department of Veterans Affairs.

BREO has the best unrestricted Medicare Part D formulary coverage in its class

"Best unrestricted formulary coverage" defined by percent of Medicare Part D lives with unrestricted formulary coverage for BREO 96% vs ADVAIR 88%, AirDuo 7%, Dulera 22%, and Symbicort 90%. Total covered lives on Medicare Part D plans.

What you need to know about this formulary information:

Formulary status may vary and is subject to change. Formulary comparisons do not imply comparable indications, safety, or efficacy. This is not a guarantee of partial or full coverage or payment. Consumers may be responsible for varying out-of-pocket costs based on an individual's plan and its benefit design. Each plan administrator determines actual benefits and out-of-pocket costs per its plan's policies. Verify coverage with plan sponsor or Centers for Medicare & Medicaid Services. Medicare Part D patients may obtain coverage for products not otherwise covered via the medical necessity process.

Nationally, BREO Unrestricted Commercial Coverage 165 Million; Symbicort Unrestricted Commercial Coverage 161 Million. Medicare Part D BREO Unrestricted Lives covered 39 Million; Symbicort 37 Million.

100% of eligible commercially insured patients pay no more than $10 a month:

A coupon for eligible patients to pay no more than $10 for each prescription for up to 12 months of BREO (30-day supplies). Patients CANNOT use this coupon offer if they are Medicare eligible or government program participants. For coupon eligibility purposes, all those 65 or older will be considered Medicare eligible. Please see the savings offer for complete rules and eligibility.

BREO ELLIPTA was developed in collaboration with INNOVIVA

To learn more about BREO, visit www.SavingsforBREO.com

BREO ELLIPTA
(fluticasone furoate 100, 200 mcg and vilanterol 25 mcg inhalation powder)

Synthetic opioids drive spike in fatal overdoses

BY RANDY DOTINGA
MDedge News

New federal statistics suggest that the opioid epidemic in the United States is evolving as physicians crack down on the use of prescription painkillers: Fatal drug overdose deaths rose by 12% from 2016 to 2017, boosted by a wave of fatalities linked to illicit synthetic opioids like fentanyl that are now linked to an estimated 60% of opioid-related deaths.

"Overall, the overdose epidemic continues to worsen, and it has grown increasingly complex by coinvolvement of prescription and illicit drugs," Lawrence Scholl, PhD, MPH, and his associates at the Centers for Disease Control & Prevention wrote in the Morbidity and Mortality Weekly Report.

The new statistics provide more evidence that 2017 marked "a sharp increase in what has characterized as the third wave of the opioid epidemic," said drug and health policy researcher Stephen Crystal, PhD, of Rutgers University, New Brunswick, N.J., in an interview. He was referring to a wave that experts believe started in 2013 amid a spike in U.S. overdose deaths from fentanyl and other synthetic opioids.

The new report analyzes fatal drug overdose data from 2013 to 2017. According to the findings, the total number of those overdoses rose to 70,237 in 2017, up from 63,632 in 2016. The highest drug overdose death rates in 2017 were in West Virginia, followed by Ohio, Pennsylvania, and the District of Columbia.

Some statistics did not change much from 2016 to 2017: About two-thirds of the drug overdose deaths were linked to opioids in both years, and the death rate of cases linked to prescription drugs and heroin remained steady.


US DEA

However, the percentage of fatal overdose cases linked to synthetic opioids grew 45% from 2016 to 2017. Overall, 60% of opioid-related fatal overdoses in 2017 involved synthetic opioids.

The report identifies increases in several areas from 2016 to 2017. Opioid-related drug overdose deaths among black people rose by 25%, and data from 34 states and the District of Columbia found the highest increases in death rates in North Carolina (29%), Ohio (19%), and Maine (19%).

In regard to deaths linked to synthetic opioids specifically, the highest death rates in 2017 were in West Virginia (37 per 100,000), Ohio (32 per 100,000), and New Hampshire (30 per 100,000).

"Part of what we're seeing in these increased numbers are individuals who have pain, can't get prescribed opioids, and turn to street drugs," Dr. Crystal said, adding that "abruptly cutting patients off is not good, and leaving patients with a lot of untreated pain is not good. If people are going to be discontinued [from opioids] or have their doses reduced, the taper needs to be done very slowly and carefully."

Also, the death rates of cases linked to cocaine and psychostimulants (such as methamphetamine) jumped by more than a third in 2017.

The report had limitations, including that details about drug use were missing from 12% (2016) and 15% (2017) of death certificates in fatal overdose cases. By state, the percentages of those death certificates that included drug information ranged from as little as 55% to 99%.

The report points to early data from 2018 suggesting that the number of annual drug overdose deaths may be leveling off – although it says more analysis is needed to confirm the trend.

Dr. Crystal reported no relevant disclosures.

chestphysiciannews@chestnet.org

SOURCE: Scholl L et al. MMWR. 2019 Jan 4;67(5152):1419-27.

App aims to detect respiratory failure in opioid overdoses

BY RANDY DOTINGA
MDedge News

A smartphone app seeks to detect the first moments of an overdose-related respiratory crisis and summon help before it's too late.

The ultimate goal is "to provide a harm reduction system that can automatically connect naloxone-equipped friends and family or emergency medical services to help prevent fatal overdose events," Rajalakshmi Nandakumar, and her associates wrote in the study, published in Science Translational Medicine.

An estimated 70,000 people in the United States died from drug overdoses in 2017, according to a 2018 data brief from the Centers for Disease Control and Prevention.

"We're hoping a device that most people carry around could be transformed into technology that could save your life in an overdose," said anesthesiologist Jacob E. Sunshine, MD, of the University of Washington, Seattle, and coauthor of the study. The app, which builds on previous work aimed at detecting disordered breathing in sleep apnea, uses a "short-range active sonar system" to detect respiration in a person within the distance of about 3 feet.

The app's microphone detects an "audio reflection" of the tone after it bounces off a nearby person's body and then analyzes it to calculate the distance to the person's chest. "We're able to use those distances to measure when someone is taking a breath, and when they're not taking a breath," said Dr. Sunshine.

If a disordered breathing pattern is detected, the app is designed to send a text message with a GPS-pinpointed location to a prespecified contact. The app also could be set to call 911.

In the study, the investigators tested the app's algorithm at a supervised injection facility – a space designed to allow users to inject illicit drugs safely – in Vancouver. They tested the app on 94 drug users as they injected themselves; half of the users "experienced clinically important respiratory depression," and two needed to be treated by clinic staff for overdose, the researchers wrote.

The app detected cessation of breathing for 10 seconds or longer 95.9% of the time (95% confidence interval, 86.0%-99.5%) with 97.7% specificity (95% CI, 88.2%-99.9%). However, the app was less adept at identifying respiratory depression (respiratory rate equal to or less than 7 breaths per minute): The investigators reported 87.2% sensitivity (95% CI, 74.2%-95.1%) and 89.3% specificity (95% CI, 76.9%-96.4%).

The app's algorithm also was tested on patients undergoing anesthesia. It correctly detected disordered breathing in 19 of 20 patients.

It's not clear how the app would work in environments full of breathing people and, potentially, pets. Since it needs to be able to bounce audio signals off a user's chest, the app will not work if a phone is in a pocket or if a user is face down, turns around, or wanders off.

However, the app can detect sudden changes in motion, Dr. Sunshine said, and investigators are developing a way to require users to check in with the app in certain situations that might signal trouble.

The next steps are to refine the app's user interface and figure out how to connect it to the 911 emergency-response system, Dr. Sunshine said. Meanwhile, researchers have created a company to develop the product. "We're going to do additional development through that entity and seek [Food and Drug Administration] approval," Dr. Sunshine said. The investigators do not plan to charge users for the product.

The study was funded by the Foundation for Anesthesia Education and Research, the National Science Foundation, and the University of Washington's Alcohol and Drug Abuse Institute. The researchers are inventors on a provisional patent application related to the project, and all have equity stakes in a company that is developing the technology.

chestphysiciannews@chestnet.org

SOURCE: Nandakumar R et al. Sci Transl Med. 2019 Jan 9;11(474). doi: 10.1126/scitranslmed.aau8914.

Topical mupirocin decolonizes *S aureus* in NICU infants

BY MARK S. LESNEY
MDedge News

Application of the topical antibiotic mupirocin to multiple body sites was reported to be safe and efficacious in eradicating *Staphylococcus aureus* (SA) colonization on infants in the neonatal intensive care unit (NICU), according to researchers at the University of Maryland, Baltimore.

PERBOGE/THINKSTOCK

Karen L. Kotloff, MD, and her colleagues conducted a phase 2 multicenter, open-label, randomized trial to assess the safety and efficacy of intranasal plus topical mupirocin in eradicating SA colonization.

"Staph aureus is a leading cause of sepsis in young children admitted to the NICU. Sepsis, which is systemic infection, can be fatal in infants. Thus, preventing these infections is very important in managing risk for babies in the NICU who are fragile and struggling with multiple medical problems," Dr. Kotloff said in a press release from the university.

Infants in the NICU at eight study centers who were less than 24 months old underwent serial screening for nasal SA. Infants colonized with SA were randomly assigned to receive 5 days of mupirocin versus no mupirocin to the intranasal, periumbilical, and perianal areas.

Treatment effects were assessed on day 8 (primary decolonization) and day 22 (persistent decolonization) for all three body areas.

Primary decolonization occurred in 62/66 (93.9%) of treated infants and 3/64 (4.7%) of the control infants (*P* less than .001).

Persistent decolonization was seen in 21/46 (45.7%) of treated infants compared with 1/48 (2.1%) of the controls (*P* less than .001).

"This multicenter trial supervised by Dr. Kotloff provides strong support for a safe strategy to minimize *Staphylococcus aureus* infections in some of the most at-risk patients in any hospital, premature babies," said E. Albert Reece, MD, who is dean of the University of Maryland School of Medicine.

He made his comments on the study in a press release from the university.

mlesney@mdedge.com

SOURCE: Kotloff KL et al. Pediatrics. 2019. doi: 10.1542/peds.2018-1565.

Alcohol, distress high with REM sleep behavior disorder

BY ERIK GREB
MDedge News

Alcohol consumption and psychological distress are associated with possible REM sleep behavior disorder (RBD), according to a population-based cohort study published in Neurology. In addition, the results replicate previous findings of an association between possible RBD and smoking, low education, and male sex.

The risk factors for RBD have been studied comparatively little. "While much is still unknown about RBD, it can be caused by medications or it may be an early sign of another neurologic condition like Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy," according to Ronald B. Postuma, MD, an associate professor at McGill University, Montreal. "Identifying lifestyle and personal risk factors linked to this sleep disorder may lead to finding ways to reduce the chances of developing it."

To assess sociodemographic, socioeconomic, and clinical correlates of possible RBD, Dr. Postuma and his colleagues examined baseline data collected between 2012 and 2015 in the Canadian Longitudinal Study on Aging (CLSA), which included 30,097 participants. To screen for possible RBD, the CLSA researchers asked patients, "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep [e.g., punching, flailing your arms in the air, making running movements, etc.]?" Participants answered additional questions to rule out RBD mimics. Patients with symptom onset before age 20 years, positive apnea screen, or a diagnosis of dementia, Alzheimer's disease, parkinsonism, or Parkinson's disease were excluded from analysis.

> *"Identifying lifestyle and personal risk factors linked to this sleep disorder may lead to finding ways to reduce the chances of developing it."*

In all, 3,271 participants screened positive for possible RBD. After the investigators excluded participants with potential mimics, 958 patients (about 3.2% of the total population) remained in the analysis. Approximately 59% of patients with possible RBD were male, compared with 42% of controls. Patients with possible RBD were more likely to be married, in a common-law relationship, or widowed.

Participants with possible RBD had slightly less education (estimated mean, 13.2 years vs. 13.6 years) and lower income, compared with controls. Participants with possible RBD retired at a slightly younger age (57.5 years vs. 58.6 years) and were more likely to have retired because of health concerns (28.9% vs. 22.0%), compared with controls.

In addition, patients with possible RBD were more likely to drink more and to be moderate to heavy drinkers than controls; they were also more likely to be current or past smokers. Antidepressant use was more frequent and psychological distress was greater among participants with possible RBD.

When the investigators performed a multivariable logistic regression analysis, the associations between possible RBD and male sex and relationship status remained. Lower educational level, but not income level, also remained associated with possible RBD. Furthermore, retirement age and having reported retirement because of health concerns remained significantly associated with possible RBD, as did the amount of alcohol consumed weekly and moderate to heavy drinking. Sensitivity analyses did not change the results significantly.

One of the study's limitations is its reliance on self-report to identify participants with possible RBD, the authors wrote. The prevalence of possible RBD in the study was 3.2%, but research using polysomnography has found a prevalence of about 1%. Thus, the majority of cases in this study may have other disorders such as restless legs syndrome or periodic limb movements. Furthermore, many participants who enact their dreams (such as unmarried people) are likely unaware of it. Finally, the researchers did not measure several variables of interest, such as consumption of caffeinated products.

"The main advantages of our current study are the large sample size; the systematic population-based sampling; the capacity to adjust for diverse potential confounding variables, including mental illness; and the ability to screen out RBD mimics," the authors concluded.

egreb@mdedge.com

SOURCE: Postuma RB et al. Neurology. 2018 Dec 26. doi: 10.1212/WNL.0000000000006849.

PAP decreased levels of Alzheimer biomarker

BY MICHELE G. SULLIVAN
MDedge News

Soluble amyloid-beta in cerebrospinal fluid (CSF) decreased when subjects with obstructive sleep apnea used a positive airway pressure device with good adherence, suggesting that improving sleep could reduce the risk of Alzheimer disease in this population.

The small decrease in cerebrospinal amyloid-beta 40 (Ab40) and Ab42 hints at decreased neuronal release of the neurotoxic protein, wrote Yo-El S. Ju, MD, and her colleagues. The report was published online in Annals of Neurology.

Alzheimer disease (AD) biomarker studies typically find decreased CSF levels associated with increased Ab brain plaques. But before plaques form, increased soluble Ab in CSF is a risk factor for aggregation. Thus, higher soluble Ab levels in mid-life may suggest a risk of later Ab pathology, wrote Dr. Ju of Washington University, St. Louis.

"We tested individuals without any AD pathology as assessed by Ab42 [in CSF], a highly sensitive biomarker of amyloid plaques," Dr. Ju and her coauthors wrote. "This means our study findings can be extrapolated to the large population of people with OSA [obstructive sleep apnea], many of whom are middle-aged or younger, and have many years to accrue benefit from AD risk reduction. ... The effect of OSA on SWA [slow-wave activity], Ab, and possibly tau, is a probable proximal step in a cascade whereby OSA increases the risk of AD."

The researchers recruited 35 subjects with mild to severe OSA and without abnormal Ab levels in CSF. Subjects used auto-titrating positive airway pressure (PAP) for 1-4 months; 18 were sufficiently compliant to be included in the analysis (more than 4 hours on more than 70% of 30 preceding nights as recorded by the machine). CSF was obtained after a baseline polysomnogram and after the treatment period lasting 1-4 months.

Of the 18 analyzed patients, 7 had mild OSA and 11 had moderate to severe OSA. They were an average of nearly 57 years old with a mean body mass index of 30.4 kg/m^2; 7 patients had hypertension.

PAP treatment was effective, indicated by a normalized apnea-hypopnea index and decreased time in hypoxemia. Total sleep time and sleep efficiency were unchanged, but slow-wave activity did increase. As expected, hourly arousals and time in hypoxemia decreased, and hypoxic nadir shifted from an oxygen saturation of 82.5% to 91%.

"As a group, there was no significant change in Ab with treatment," the researchers wrote. But a correlational analysis found that "greater improvement in OSA was associated with greater decrease in Ab40 and Ab42. Additionally, we found that change in tau negatively correlated with OSA improvement."

The team suggested a two-factor model to explain the relationship between OSA and Ab levels. "Due to decreased SWA, there would be relatively increased release of Ab into the [interstitial fluid]. However, as OSA severity worsens, pressure effects of obstructive respiratory events impede the clearance of Ab and tau out of the interstitial space, resulting in lower levels in the CSF and an inverse U-shaped curve. In this model, a small improvement in OSA may result in an increase in Ab or tau, whereas a larger improvement in OSA – that ameliorates both SWA and clearance mechanisms – will result in a decrease in Ab and tau."

The project was funded in part by Philips-Respironics, which provided the devices, and by the National Institutes of Health. Philips-Respironics had no input or role in any other part of the study. The authors had no financial disclosures.

msullivan@mdedge.com

SOURCE: Ju YS et al. Ann Neurol. 2018 Dec 31. doi: 10.1002/ana.25408.

New hypopnea criteria ID unique OSA patient subset

BY ANDREW D. BOWSER
MDedge News

The latest recommended criteria for hypopnea define a distinct group of patients who report substantial daytime sleepiness but with no significant cardiovascular risk, investigators reported in a retrospective, cross-sectional analysis.


Dr. Won

The number of obstructive sleep apnea (OSA) diagnoses increased by nearly 13% when using the 2012 American Academy of Sleep Medicine (AASM) criteria of at least 3% desaturation or arousal, instead of the 2007 criteria of at least 4% desaturation. While cardiovascular disease risk did not appear to be elevated in those with an OSA diagnosis based on the newer, more inclusive criteria, the OSA diagnosis remained a risk factor for arrhythmias in this group of patients, reported Christine H.J. Won, MD, of Yale University, New Haven, Conn., and her colleagues.

"Our findings suggest [that] a more inclusive hypopnea definition alters OSA severity categorization, identifies a new symptomatic group of patients with predominantly mild OSA without increased cardiovascular odds, and does not ameliorate the increased odds predicted by severe OSA for arrhythmias," the investigators wrote in the Journal of Clinical Sleep Medicine.

The analysis by Dr. Won and her colleagues included 1,400 veterans who had polysomnography for suspected sleep-disordered breathing. Of those veterans, two-thirds (932; 66%) had an OSA diagnosis based on at least 4% desaturation criteria. With the newer criteria of at least 3% desaturation or arousal, another 175 OSA diagnoses were captured out of the remaining 468 previously negative studies, meaning that more than 37% of those patients would be recategorized as having OSA, Dr. Won and her coauthors said.

Compared with individuals with OSA classified by the older, more restrictive criteria, the 175 individuals in this "new OSA" group were younger and less likely to be obese. Compared to individuals without OSA, the new OSA group had more disrupted sleep architecture, worse oxygen saturations, and more self-reported sleepiness on the Epworth Sleepiness Scale.

Adding in the new OSA group redistributed disease severity, with a relative increase of 21.4% for mild and 21.3% for moderate OSA, but just 15.3% for severe OSA.

This is thought to be the first study to describe a unique group of patients who escape OSA diagnosis based on the at least 4% desaturation criteria but are captured with at least 3% desaturation or arousal criteria.

"It would also be important to assess whether treatment in any of these groups leads to improved cardiovascular health, or whether treatment of the [new OSA] group leads to improved daytime sleepiness or quality of life," they said.

The researchers reported no conflicts of interest. Their work was performed at the Veterans Affairs Healthcare System in West Haven, Conn., Indianapolis, and Cleveland.

chestphysiciannews@chestnet.org

SOURCE: Won CHJ et al. J Clin Sleep Med. 2018 Dec 15;14(12):1987-94.

VIEW ON THE NEWS

Useful take on varying hypopnea definitions

The study by Won and colleagues provides a "useful perspective" on how hypopnea is defined by including outcome data based on the two different scoring criteria, according to Kenneth R. Casey, MD, MPH, FCCP, and Rachna Tiwari, MBBS.

Results of the study suggest a rationale for using both the 2007 American Academy of Sleep Medicine hypopnea criteria based on ≥4% desaturation, and the updated 2012 AASM criteria based on ≥3% desaturation or arousal in the evaluation of polysomnography results, Dr. Casey and Dr. Tiwari said in a commentary accompanying the study.

"This perspective may ultimately be the solution to the confusion caused by competing functional definitions of hypopnea," they said in the commentary published in the Journal of Clinical Sleep Medicine.

The 2007 recommended criteria of ≥4% desaturation seemed reasonable based on available evidence at the time, but was not rigorously based by today's standards, the authors said.

At that time, they also proposed the new alternative criteria based on ≥3% desaturation or an arousal, which in 2012 became elevated to a recommended rule. However, the previous recommended rule was kept to accommodate patients who required Centers for Medicare & Medicaid Services reimbursement, according to Dr. Casey and Dr. Tiwari.

Subsequent studies demonstrated "significant differences" in apnea-hypopnea index results, depending on which scoring criteria were used, they added.

"This confusing, vacillating definition has created a rather bizarre, and perhaps unsettling, situation wherein the severity of the diagnosis of sleep-disordered breathing, and perhaps its presence or absence, is determined by the patient's insurance coverage," they said in the commentary.

Dr. Casey and Dr. Tiwari are with the University of Wisconsin and William S. Middleton Memorial Veterans Hospital, both in Madison. They reported no conflicts of interest related to their editorial, which appears in the Journal of Clinical Sleep Medicine.

Data link severe sleep apnea and aggressive melanoma

BY HEIDI SPLETE
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Severe sleep-disordered breathing was significantly associated with more aggressive skin cancer in a study of 443 adults published in the journal CHEST.

Sleep-disordered breathing has been associated with cancer risk and mortality, but no large studies have examined the association in specific cancers, wrote Miguel Angel Martinez-Garcia, MD, of La Fe University and Polytechnic Hospital, Valencia, Spain, and his colleagues.

The researchers conducted a sleep study of 443 adults with melanoma within 6 months of their diagnoses. Overall, patients with more severe sleep apnea were nearly twice as likely to have aggressive melanoma, defined as a Breslow index greater than 1 mm.

Patients with greater than 15.6 events per hour or in the DI4% tertile (more than 9.3 desaturations per hour) were approximately twice as likely (1.94 and 1.93 times, respectively) to have a more aggressive melanoma as were those with less severe sleep apnea, after adjustment for age, gender, body mass index, and melanoma location.

The average age of the patients was 60 years, 51% were male, and the average time between the melanoma diagnosis and the sleep study was 82 days.

Sleep symptoms were not significantly different between the patients with aggressive or less aggressive melanoma. However, in addition to more severe sleep apnea, those with aggressive melanoma were significantly more likely to be older, male, and have a higher BMI than were those with less aggressive disease.

The association with sleep apnea was significant in patients younger than 55 years only if their Breslow index was greater than 2 mm, the researchers said.

The study was supported in part by Fondo de Investigation Sanitaria, SEPAR, Red Respira, and Sociedad Valenciana de Neumología.

The researchers had no financial conflicts to disclose.

chestphysiciannews@chestnet.org

SOURCE: Martinez-Garcia MA et al. Chest. 2018. doi: 10.1016/j.chest.2018.07.015.

Instead of choosing an ICS/LABA,

START BREAKING TRADITION

Start appropriate symptomatic patients with COPD on ANORO for dual bronchodilation

THE GOLD 2019 REPORT

- **Continues to emphasize the role of LAMA/LABA for patients with COPD[1]**
- **Does not include ICS/LABA as initial treatment for many patients[1]**

ANORO was studied in patients with moderate or worse COPD.

ANORO is for the once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

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

START WITH ANORO FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION VS AN ESTABLISHED ICS/LABA[2]

Nearly 2x the lung function improvement vs ADVAIR[2]

LS mean change from baseline in weighted mean FEV_1 (0-24 hours) on Day 84

1.8x IMPROVEMENT

Study DB2114930[2]

74 mL Difference (*P*<0.001)
ANORO **165 mL (n=353)**
ADVAIR **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101 mL Difference (*P*<0.001)
ANORO **213 mL (n=349)**
ADVAIR **112 mL (n=348)**

The indication for ANORO differs from the indication for ADVAIR in that ANORO is not indicated for reducing COPD exacerbations.

Studied in patients with moderate to severe COPD (GOLD 2 or 3).[2]

What would almost 2x the lung function improvement mean for your patients?

Learn more at **StartWithANORO.com**

Description of studies[2,3]: The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of ADVAIR 250 mcg/50 mcg (administered via the DISKUS inhaler) were evaluated in two 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

Primary endpoint: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LS=least squares.

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO should not be used more often or at higher doses than recommended or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Caution should be exercised when considering the coadministration of ANORO with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO if such reactions occur.

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors as increased systemic exposure to vilanterol and cardiovascular adverse effects may occur. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- ANORO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

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

References: 1. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. 2019 report. www.goldcopd.org. Accessed November 27, 2018. **2.** Donohue JF, Worsley S, Zu C-Q, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015; 109(7):870-881. **3.** Data on file, GSK.

Visit StartWithANORO.com

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

ANORO ELLIPTA was developed in collaboration with INNOVIVA

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

ANORO ELLIPTA **BRIEF SUMMARY**

(umeclidinium and vilanterol inhalation powder), for oral inhalation

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 1 5.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.

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

5.2 Deterioration of Disease and Acute Episodes

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

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

When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

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

5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting Beta$_2$-agonists

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

5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.5 Paradoxical Bronchospasm

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

5.6 Hypersensitivity Reactions

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

5.7 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full prescribing information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.9 Worsening of Narrow-Angle Glaucoma

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

5.10 Worsening of Urinary Retention

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

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

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

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials

The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

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

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial

In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

6.2 Postmarketing Experience

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

Cardiac Disorders

Palpitations.

Eye Disorders

Blurred vision, glaucoma, increased intraocular pressure.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

Nervous System Disorders

Dysgeusia, tremor.

Psychiatric Disorders

Anxiety.

Renal and Urinary Disorders

Dysuria, urinary retention.

Respiratory, Thoracic, and Mediastinal Disorders

Dysphonia, paradoxical bronchospasm.

(continued on next page)

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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

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

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

Nonteratogenic Effects

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

ANORO ELLIPTA

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

Umeclidinium

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

Vilanterol

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

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

Umeclidinium

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

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

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

Vilanterol

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death

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

Not for Acute Symptoms

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

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

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

Tell patients they should not stop therapy with ANORO ELLIPTA without healthcare provider guidance since symptoms may recur after discontinuation.

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

Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

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

Paradoxical Bronchospasm

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

Risks Associated with Beta-agonist Therapy

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ANORO ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 10/2017 ANR:5BRS

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

Poor-prognosis cancers linked to highest suicide risk in first year

BY ANDREW D. BOWSER
MDedge News

Suicide risk significantly increases within the first year of a cancer diagnosis, with risk varying by type of cancer, according to investigators who conducted a retrospective analysis representing nearly 4.7 million patients.

Risk of suicide in that first year after diagnosis was especially high in lung and pancreatic, while by contrast, breast and prostate cancer did not increase suicide risk, reported the researchers, led by Hesham Hamoda, MD, MPH, of Boston Children's Hospital/Harvard Medical School, and Ahmad Alfaar, MBBCh, MSc, of Charité–Universitätsmedizin Berlin.

That variation in suicide risk by cancer type suggests that prognosis and 5-year relative survival play a role in increasing suicide rates, according to Dr. Hamoda, Dr. Alfaar, and their coauthors.

"After the diagnosis, it is important that health-care providers be vigilant in screening for suicide and ensuring that patients have access to social and emotional support," they wrote in a report published in Cancer.

Their analysis was based on 4,671,989 patients with a diagnosis of cancer in the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2014. Out of 1,005,825 of those patients who died within the first year of diagnosis, the cause of death was suicide for 1,585, or 0.16%.

Overall, the risk of suicide increased significantly among cancer patients versus the general population, with an observed-to-expected (O/E) ratio of 2.51 per 10,000 person-years, the investigators found. The risk was highest in the first 6 months, with an O/E mortality of 3.13 versus 1.8 in the latter 6 months.

"After the diagnosis, it is important that health-care providers be vigilant in screening for suicide and ensuring that patients have access to social and emotional support."

The highest ratios were seen for lung cancer, with an O/E ratio of 6.05, and pancreatic cancer, with a ratio of 8.01, and the researchers found in further analysis.

Significant increases in suicide risk were also seen for colorectal cancer (2.08) and melanoma (1.45), though rates were not significantly different versus the general population for breast (1.23) and prostate (0.99), according to the reported data.

Suicide risk was relatively high for any cancer with distant metastases (5.63), though still significantly higher at 1.65 in persons with localized/regional disease, the data show.

The increased suicide risk persisted more than 1 year after the cancer diagnosis, though not to the degree observed within that first year, they added.

Most patients with suicide as a cause of death were white (90.2%) and male (87%). Nearly 60% were between the ages of 65 and 84 at the time of suicide.

Social support plays an integral role in suicide prevention among cancer patients, the researchers noted.

Previous studies suggest that support programs may decrease suicide risk by making patients better aware of their prognosis, receptive to decreased social stigma, or less likely to have stress related to cost of care, they said.

"Discussing the quality of life after diagnosis, the effectiveness of therapy, and the prognosis of the disease and maintaining a trusting relationship with health care professionals all decrease the likelihood of suicide immediately after a diagnosis of cancer," they said.

Dr. Hamoda, Dr. Alfaar, and their coauthors reported no conflicts of interest. Funding for the study came in part from the German Academic Exchange Service (Dr. Alfaar).

chestphysiciannews@chestnet.org

SOURCE: Saad AM et al. Cancer. 2019 Jan 7. doi: 10.1002/cncr.31876.

VIEW ON THE NEWS

Jacques-Pierre Fontaine, MD, FCCP, comments: This article highlights the significantly increased risk of suicide in the first year after diagnosis in patients with generally poor prognosis cancers, such as lung and pancreatic cancer, as compared with the general population or even compared with patients with cancers associated with a better prognosis, such as breast and prostate cancers. Therefore, special emphasis must be placed on suicide prevention for this cohort of patients.

Self-reporting extends lung cancer survival

BY WILL PASS
MDedge News

Patients with nonprogressive, metastatic lung cancer who report symptoms through a weekly, web-based monitoring system may survive longer than those who undergo standard imaging surveillance, according to a recent French study.

Self-reporting may notify care providers about adverse effects or recurrence earlier than imaging, suggested lead author, Fabrice Denis, MD, PhD, of Institut Inter-régional de Cancérologie Jean Bernard in Le Mans, France, and his colleagues. Findings were published in a letter in JAMA.

In 2017, a similar, single-center study showed that web-based symptom reporting could improve survival in patients undergoing chemotherapy. The lead investigator on that trial was Ethan Basch, MD, who coauthored the present publication.

The current, prospective study involved 121 patients treated at five centers in France between June 2014 and December 2017. Eligibility required a diagnosis of nonprogressive, metastatic lung cancer, including stage III or IV non–small cell or small cell disease. Patients were treated with antiangiogenic therapy, chemotherapy, immunotherapy, or tyrosine kinase inhibitors.

skynesher/Getty Images

Patients in the control group had standard follow-up with imaging every 3-6 months. In contrast, the patient-reported outcomes (PRO) group completed a weekly online survey of 13 common symptoms between follow-up visits. If patients reported symptoms that matched with predefined criteria for severity or worsening, then the treating oncologist was notified.

When an 18-month interim analysis showed significant survival advantage in the PRO group, recruitment was stopped, and control patients were moved to the PRO group. After 2 years of follow-up, 40 patients (66.7%) in the control group had died, compared with 29 patients (47.5%) in the PRO group. Before censor for crossover, median overall survival (OS) was 22.5 months in the PRO group, compared with 14.9 months in the control group ($P = .03$). Censoring for crossover widened the gap between groups by more than a month (22.5 vs. 13.5 months; $P = .005$).

"A potential mechanism of action is that symptoms suggesting adverse events or recurrence were detected earlier," the investigators concluded.

The study was funded by SIVAN Innovation. Investigators reported financial affiliations with AstraZeneca, SIVAN Innovation, Ipsen, Roche, the National Cancer Institute, Lilly, and others.

SOURCE: Denis F et al. JAMA. 2019 Jan 22;321(3):306-7.

More benefit to chemoradiation in earlier SCLC

BY TED BOSWORTH
MDedge News

In response to chemoradiation, patients with stage I or II small cell lung cancer (SCLC) have a significantly longer overall survival than do those with stage III disease, according to a post hoc analysis of a randomized trial of chemoradiation in patients with early stages of SCLC.

The fact that overall survival is better in stage I and II than in stage III SCLC isn't surprising. But the data confirm that stage I and II SCLC respond differently to chemoradiation than does stage III, providing a benchmark for safety and efficacy, according to the study authors.

The phase 3 CONVERT trial, from which the data were drawn, randomized patients with limited-stage SCLC to twice-daily (45 Gy in 30 fractions) or once-daily (66 Gy in 33 fractions) radiation after initiating cisplatin-etoposide chemotherapy (Lancet Oncol. 2017 Aug;18[8]:1116-25). Additional prophylactic cranial irradiation was permitted for those with an indication.

Contrary to the researcher's hypothesis, once-daily radiation was not more effective for the primary outcome of overall survival in CONVERT, which limited enrollment to patients with local disease but did not stratify outcomes by SCLC stage. The purpose of the new post hoc analysis was to compare outcomes in those early-disease SCLC patients stratified by stage, which the authors noted is now recommended by several guidelines.

At 5 years, 49% of the stage I/II patients were alive, compared with 28% of the stage III patients.

Because there were only four patients in CONVERT with stage I SCLC, those with either stage I or II SCLC, totaling 86 patients, were combined and then compared with the 423 with stage III SCLC.

At baseline, there were no significant differences between stage I/II and III groups for median age, smoking history, Eastern Cooperative Oncology Group performance status, or dyspnea score at baseline. Similar proportions of patients completed the planned therapy.

However, the median survival was twice as long in the stage I/II group, compared with those with stage III SCLC (50 vs. 25 months), producing a hazard ratio for this outcome of 0.60 (P = .001). At 5 years, 49% of the stage I/II patients were alive, compared with 28% of the stage III patients (P = .001).

Other outcomes, such as progression-free survival at 5 years (47% vs. 26%; P = .003) also favored those with earlier-stage disease.

The incidence of adverse events associated with chemoradiation was not significantly different for the two groups, with the exception of acute esophagitis, which was less frequent in patients with earlier-stage disease.

"The low incidence of severe toxic effects is a valid rationale to consider future radiotherapy dose intensification trials to improve outcomes" in patients with stage I/II disease, according to study author Ahmed Salem, MB, ChB, of the University of Manchester (England), and his coinvestigators.

The data from the post hoc analysis support guideline recommendations to stage even early and local SCLC when evaluating response to therapy in clinical trials, noted Howard (Jack) West, MD, of Swedish Cancer Institute, Seattle, in an accompanying editorial (JAMA Oncol. 2018 Dec 6. doi: 10.1001/jamaoncol.2018.5187). Dr. West suggested that such staging information might be useful when counseling patients about treatment options.

"These results imply that we may do our patients a disservice by dispensing with clinically relevant staging information that can lead to a more refined assessment of prognosis and optimal treatment," Dr. West wrote.

chestphysiciannews@chestnet.org

SOURCE: Salem A et al. JAMA Oncol. 2018 Dec 6:e185335. doi: 10.1001/jamaoncol.2018.5335.

No link between sex and survival on checkpoint inhibitors in latest meta-analysis

BY ANDREW D. BOWSER
MDedge News

Men and women with cancer may derive a similar survival benefit from immune checkpoint inhibitor therapy, results of a recent meta-analysis suggest.

Both men and women had an overall survival benefit from immunotherapy versus standard of care therapy, with no significant difference between the sexes, according to authors of this meta-analysis, which included 23 randomized clinical trials comprising nearly 14,000 patients. Of the 23 trials, 13 were studies of non–small cell lung cancer and small cell lung cancer that included nearly 7,000 patients.

The findings, reported in JAMA Oncology, contrast with those of another recent analysis, which suggested that men had a greater advantage of receiving immunotherapy versus standard of care than women did.

"We found no evidence that sex should be considered when deciding whether to offer immunotherapy to patients with advanced cancers," said Christopher J.D. Wallis, MD, PhD, of the University of Toronto, and his coauthors said in their report.

The present meta-analysis was based on a "more contemporary and comprehensive" literature search strategy than the earlier one, according to Dr. Wallis and his coinvestigators.

Specifically, they considered immunotherapy agents not included in the previous analysis, added seven new studies published since the previous analysis, and excluded three trials that compared immunotherapy agents, rather than comparing immunotherapy with standard of care, they explained in their report.

Their resulting meta-analysis included a total of 9,322 men and 4,399 women, most of whom were in their 70s. Overall, they found that immune checkpoint inhibitor therapy offered a statistically significant overall survival advantage versus standard systemic therapy, with a hazard ratio of 0.75 (95% confidence interval, 0.70-0.81; P less than .001).

That overall survival advantage was found for both men, with a hazard ratio of 0.75 (95% CI, 0.69-0.81; P less than .001) and women, at 0.77 (95% CI, 0.67-0.88; P = .002), investigators further reported. There was no statistically significant difference in overall survival advantage between men and women, both overall (P = 0.60) and in subgroup analyses that accounted for tumor type, line of treatment, and prevalence of women in the study.

The previous meta-analysis, published in the Lancet, found an overall survival hazard ratio of 0.72 for men receiving checkpoint inhibitors and 0.86 for women receiving checkpoint inhibitors (P = .0019), prompting those investigators to conclude that the magnitude of benefit was sex-dependent and that different immunotherapeutic approaches may be needed for men versus women.

Dr. Wallis reported no disclosures related to the study. Study coauthors provided disclosures related to Merck, AstraZeneca, Bristol-Myers Squibb, Illumina, Tempus, Novartis, Eli Lilly, Fate, Incyte, MedImmune, Pfizer, Roche/Genentech, Xcovery, Fate Therapeutics, Genocea, and Iovance.

chestphysiciannews@chestnet.org

SOURCE: Wallis CJD et al. JAMA Oncol. 2019 Jan 3. doi:10.1001/jamaoncol.2018.5904.

VIEW ON THE NEWS

Jacques-Pierre Fontaine, MD, FCCP, comments: This more robust and updated meta-analysis disproves the previously accepted notion that immunotherapy with checkpoint inhibitors was more effective in men as compared with women. Although identifiable genetic mutations are more frequent in women, the immunotherapeutic approach and its expected efficacy is no different between men and women.

DUPIXENT®
(dupilumab) Injection
200mg · 300mg

NOW APPROVED
IN MODERATE-TO-SEVERE ASTHMA

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

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

DUPIXENT is the **first and only dual inhibitor of IL-4 and IL-13 signaling**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

Visit **DUPIXENTASTHMAHCP.COM**

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia, which may be associated with a reduction of oral corticosteroids. Cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

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

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

SANOFI GENZYME

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in asthma patients are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Please see brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

Visit DUPIXENTASTHMAHCP.COM

REGENERON

US-DAS-1243

DUPIXENT® (dupilumab) injection, for subcutaneous use **Rx Only**
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

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

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*

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.

Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT plus TCS to placebo plus TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4):

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 1: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy[a]		DUPIXENT + TCS[b]	
	DUPIXENT 300 mg Q2W[c] N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W[c] + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis[d]	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis[e]	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection[f]	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

[a] Pooled analysis of Trials 1, 2, and 4

[b] Analysis of Trial 3 where subjects were on background TCS therapy

[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks

[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3):

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject). The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median

increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal MIs, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

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

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3)]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

Safety and efficacy in pediatric patients (<18 years of age) with atopic dermatitis have not been established.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3)]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License # 1760; Marketed by sanofi-aventis U.S. LLC, (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) /DUPIXENT is a registered trademark of Sanofi Biotechnology/ Issue Date: October 2018 US-DUP-1104

HIPAA compliance: Learn from these three cases

BY ALICIA GALLEGOS
MDedge News

Data security experts say three HIPAA violations that resulted in significant fines by the Office for Civil Rights (OCR) in 2018 hold important lessons for health professionals about safeguarding records and training staff in HIPAA compliance.

Read on to learn how the cases unfolded and what knowledge practices can gain from the common HIPAA mistakes.

Who? Allergy Associates of Hartford, Conn.
What happened? A patient contacted a local television station to complain about a dispute between herself and a physician at Allergy Associates. The disagreement stemmed from the office turning away the patient because she allegedly brought her service animal, according to a Nov. 26, 2018, announcement by the Department of Health & Human Services. The reporter contacted the doctor in question for a news story and, in responding, the physician disclosed protected patient information to the reporter.


Ms. Mitchell

What else? An OCR investigation determined that a privacy officer with Allergy Associates had instructed the physician not to respond to the media about the complaint or to respond with "no comment"; that advice was disregarded. The practice then failed to discipline the physician or take any corrective action following the disclosure, according to the OCR.
How much? The OCR imposed a $125,000 fine on the practice and a corrective action plan that includes 2 years of OCR monitoring.
Lessons learned: Had the practice disciplined the physician or taken corrective action after the disclosure, the OCR may not have penalized the group so severely, according to Jennifer Mitchell, a Cincinnati-based health law attorney and vice chair of the American Bar Association eHealth, Privacy, & Security Interest Group.

"In my opinion, the government levied these penalties because the provider did not sanction the doctor," Ms. Mitchell said in an interview. "Health care entities need to take proper steps to remediate and, at a minimum, hold their workforce responsible for their behavior and ensure that it won't happen again."

The case emphasizes the need to train team members on media protocols and to ensure that protected health information is not mistakenly released. In addition to implementing policies and procedures, practices must also be willing to discipline health professionals when violations occur.

"A health care provider's natural inclination is to defend themselves if they are being accused by a patient," she said. "However, under the HIPAA rules, health care providers have to understand that they are prohibited from making such public statements about any patient."


MARKLEVANT/GETTY IMAGES

Who? Advanced Care Hospitalists of Lakeland, Fla.
What happened? Advanced Care Hospitalists (ACH) received billing services from an individual who represented himself to be affiliated with a Florida-based company named Doctor's First Choice Billing. A local hospital later notified ACH that patient information, including names and Social Security numbers, were viewable on the First Choice website. ACH identified at least 400 patients affected by the breach and reported the breach to the OCR. However, ACH later determined that an additional 8,855 patients may have been affected and revised its OCR notification.
What else? During its investigation, the OCR found that the hospitalist group had never entered into a business associate agreement for billing services with First Choice, as required by HIPAA, and that the practice also failed to adopt any policies regarding business associate agreements until 2014, according to a Dec. 4, 2018, announcement from HHS.
How much? The OCR fined the practice $500,000 and also imposed a robust corrective action plan that includes an enterprise-wide risk analysis and the adoption of business associate agreements. Roger Severino, OCR director, called the case especially troubling because "the practice allowed the names and Social Security numbers of thousands of patients to be exposed on the Internet after it failed to follow basic security requirements under HIPAA."
Lessons learned: The case illustrates the importance of having a business associate agreement in place for all third parties that may have access to protected health information, said Clinton Mikel, a Farmington Hills, Mich., health law attorney specializing in HIPAA compliance.

Under HIPAA, a business associate is defined as a person or entity, other than a member of the workforce of a covered entity, who "performs functions or activities on behalf of, or provides certain services to, a covered entity that involve access by the business associate to protected health information."

HIPAA requires that covered entities enter into contracts with business associates to ensure appropriate safeguarding of protected health information.

"If your business associate has a breach, your practice must report the breach to OCR and your patients," Mr. Mikel said in an interview. "The OCR will then investigate your practice and your relationship with the business associate. Just because the breach and fault clearly happened elsewhere, you will still be investigated, and could face a penalty if HIPAA requirements weren't met."

Who? Filefax of Northbrook, Ill.
What happened? The OCR opened an investigation after receiving an anonymous complaint that medical records obtained from Filefax, a company that provided storage, maintenance, and delivery of medical records for health professionals, were left unmonitored at a shredding and recycling facility. OCR's investigation revealed that a person left the records of 2,150 patients at the recycling plant and that the records contained protected health information, according to an HHS announcement. It is unclear if the person worked for Filefax.
What else? The OCR discovered that, in a related incident, an individual who obtained medical records from Filefax left them unattended in an unlocked truck in the Filefax parking lot.
How much? The OCR imposed a $100,000 fine on Filefax. The company is no longer in business; however, a court-appointed liquidator has agreed to properly store and dispose of the remaining records.
Lessons learned: Although the case did not involve a health provider, the circumstances are applicable to physicians, particularly when practices move or close, Mr. Mikel said. In some cases, a former patient may contact a shuttered practice only to learn their record cannot be located, or worse, that a breach has occurred.

"[Such a case is] ripe for a patient to complain to OCR," he said. "OCR doesn't care if you're closed or retired, they're going to look."

HIPAA requires that covered entities apply appropriate administrative, technical, and physical safeguards to protect the privacy of protected health information in any form when moving or closing. The safeguards must prevent prohibited uses and disclosures of protected health information in connection with the disposal of such information, according to the rule. The HHS provides guidance for the disposing of medical records; further, the American Academy of Family Physicians has created a checklist on closing a practice that addresses the transferring of medical records.

Without taking the correct measures, doctors may end up drawing scrutiny from OCR and face a potential fine if violations are found, experts said.

"Covered entities and business associates need to be aware that OCR is committed to enforcing HIPAA regardless of whether a covered entity is opening its doors or closing them," Mr. Severino of the OCR said in a statement. "HIPAA still applies."

chestphysiciannews@chestnet.org

Hospital Readmissions Reduction Program may be doing more harm than good

BY GREGORY TWACHTMAN
MDedge News

A Medicare program aimed at lowering readmissions to hospitals could be having an adverse effect on mortality.

Results from a retrospective cohort study of hospitalizations for heart failure, acute myocardial infarction, and pneumonia in Medicare beneficiaries aged 65 years and older between April 1, 2005, and March 31, 2015 (covering the period before and after the Medicare Hospital Readmissions Reduction Program was announced in April 2010 and implemented in October 2012), found an increase in 30-day postdischarge mortality among heart failure and pneumonia patients.

"Most concerning, however, is the possibility that the relationship between the HRRP and postdischarge mortality for heart failure and pneumonia is causal, indicating that the HRRP led to changes in quality of care that adversely affected patients," Rishi Wadhera, MD, Harvard Medical School, Boston, and his colleagues wrote in a report published Dec. 25, 2018, in JAMA.

They looked at 8.3 million hospitalizations for heart failure, acute MI, and pneumonia, among 7.9 million patients alive at the time of discharge. There were roughly 270,000 deaths within 30 days of discharge for heart failure; 128,000 for acute MI; and 246,000 for pneumonia.

For trends, the timing was divided into four periods: two prior to the announcement of the HRRP (April 2005–September 2007 and October 2007–March 2010); a third covering the time when the HRRP was announced (April 2010–September 2012); and the fourth when HRRP was implemented (October 2012–March 2015).

Among patients discharged with heart failure, 30-day mortality was rising even before the announcement of the HRRP, by 0.27% from the first period to the second period. That baseline trend continued when the HRRP was announced, by 0.49%, from the second period to the third. The difference in change between those periods was 0.22%. After implementation, 30-day mortality increased by 0.52%, with a difference in change from the third period of 0.25%.

In pneumonia patients, postdischarge mortality was stable before HRRP, but increased after HRRP, by 0.26%, with a difference in change from the second period to the third period of 0.22%. After implementation, the 30-day postdischarge mortality was 0.44%, with a difference in change of 0.40%.

Acute MI was a different story. Postdischarge mortality decreased significantly after the implementation of the HRRP, by 0.22%. The difference in change was –0.26%.

The authors suggested that, "although hospitals that reduce readmissions also appear to reduce mortality, this hospital-level concordance does not reflect the change in readmissions and mortality at the level of the patient population, which is arguably of greater importance to individual patients and to public health."

gtwachtman@mdedge.com

SOURCE: Wadhera R et al. JAMA. 2018 Dec 25. doi: 10.1001/jama.2018.19232.

VIEW ON THE NEWS

Changes needed to hospital readmissions program

Evidence in this study shows that, while the Hospital Readmissions Reduction Program may be succeeding in reducing hospital admissions, little evidence is available to show that it is having a positive effect on patient outcomes.

The Centers for Medicare & Medicaid Services needs to reexamine the program and find alternative methods that are both effective at reducing hospital readmissions while at the same time protecting patients from unintentional harm, including death.

Gregg C. Fonarow, MD, University of California Medical Center, Los Angeles, in an editorial published in JAMA (Dec 25 2018. doi: 10.1001/jama.2018.19325).

PULMONARY PERSPECTIVES®

Chronic thromboembolic pulmonary hypertension: The "fixable" form of PH that you don't want to miss

BY SONJA BARTOLOME, MD

Chronic thromboembolic pulmonary hypertension (CTEPH) is an elevation in pulmonary vascular resistance (PVR) resulting from chronic, "scarred-in" thromboembolic material partially occluding the pulmonary arteries. This vascular obstruction, over time, results in failure of the right ventricle and early mortality.

CTEPH was first characterized in an autopsy series from the Massachusetts General Hospital in 1931. On these postmortem examinations, it was noted that the affected patients had large pulmonary artery vascular obstruction, but also normal pulmonary parenchyma distal to this vascular obstruction and extensive bronchial collateral blood flow (Means J. *Ann Intern Med*. 1931;5:417). Although this observation set the groundwork for the theory that surgically removing the vascular obstruction to this preserved lung tissue could improve the condition of these patients, it would take until the mid-20th century until imaging and cardiac catheterization techniques allowed the recognition of the disease in real time.

CTEPH is thought to begin with an acute pulmonary embolus, but in approximately 3.4% of patients, rather than resolving over time, the thrombus will organize and incorporate into the pulmonary artery intimal layer (Simonneau G, et al. *Eur Respir Rev*. 2017;26:160112) A history of venous thromboembolism in a patient with persistent dyspnea should spur a screening evaluation for CTEPH; 75% of patients with CTEPH have a history of prior known acute pulmonary embolus, and 56% of patients report a prior diagnosis of deep venous thrombosis. An acute pulmonary embolus will fibrinolyse early with the vast majority of the vascular obstruction resolving by the third month. Therefore, if the patient continues to report a significant exercise limitation after 3 months of therapeutic anticoagulation therapy, or has concerning physical exam signs, a workup should be pursued.

The initial evaluation for CTEPH begins with a transthoracic echocardiogram (TTE) and ventilation/perfusion (V/Q) scintigraphy. A retrospective study comparing V/Q scan and multidetector CT scan revealed that V/Q scanning had a sensitivity and specificity of 97% and 95% for CTEPH, while CTPA had good specificity at 99% but only 51% sensitivity (Tunariu N, et al. *J Nuc Med*. 2007;48[5]:680). If these are abnormal, then right-sided heart catheterization and invasive biplane digital subtraction pulmonary angiography are recommended.

These studies confirm the diagnosis, grade its severity, and allow an evaluation for surgically accessible vs distal disease. Some CTEPH centers utilize additional imaging techniques, such as magnetic resonance angiography, optical resonance imaging, spectral CT scanning with iodine perfusion images, and intravascular ultrasound. These modalities and their place in the diagnostic algorithm are under investigation.

The goal of the initial evaluation process is to determine if the patient can undergo surgical pulmonary thromboendarterectomy (PTE), because in experienced hands, this procedure ensures the best long-term outcome for the patient. The first pulmonary thromboendarterectomy was performed at the University of California San Diego in 1970. Because the disease involves the intimal layer of the pulmonary artery, the surgery had to involve not just removal of the intravascular obstruction but also a pulmonary artery intimectomy. Surgical mortality rates were high in the initial experience. In 1984, a review of 85 worldwide cases reported an average mortality rate of 22%, and as high as 40% in some centers (Chitwood WR, Jr, et al. *Clin Chest Med*. 1984;5[3]:507).

Dr. Bartolome

Over the ensuing years, refinements in surgical technique, the utilization of deep hypothermia and cardiac arrest during the procedure, development of new surgical instruments, and standardization of surgical selection and postoperative care have improved surgical mortality to <5% in experienced centers. Long-term outcomes of successful PTE surgery remain good, with 90% 3-year survival vs 70% for those who do not undergo surgery and are medically treated. Importantly, 90% of postoperative patients report functional class I or II symptoms at 1 year (Condliffe R, et al. *Am J Reslpir Crit Care Med*. 2008:177[10];1122). Because of this difference in early mortality and symptoms, PTE surgery remains the treatment of choice for CTEPH.

Despite the advances in PTE surgery, some patients are not operative candidates either due to surgically inaccessible disease or due to comorbidities. In 2001, Feinstein and colleagues described a series of 18 CTEPH cases treated with balloon pulmonary angioplasty (BPA). Promising hemodynamics effects were reported; however, the procedure had an unacceptable complication rate in which 11 patients developed reperfusion lung injury, 3 patients required mechanical ventilation, and 1 patient died.

In the ensuing years, Japanese and Norwegian groups have independently developed and improved techniques for BPA. The procedure is done in a series of sessions (average four to six), 1 to 4 weeks apart, where small (2-3 mm) balloons are directed toward distal, diseased pulmonary vessels. Common complications include reperfusion injury, vessel injury, hemoptysis, and, more rarely, respiratory failure. Still, early experience suggests this procedure decreases pulmonary vascular resistance over time, improves right ventricular function, and improves patients' symptoms (Andreassen A, et al. *Heart*. 2013;99[19]:1415). The experience with this procedure is limited but growing in the United States, with only a handful of centers currently performing BPAs and collecting data.

Lifelong anticoagulation, oxygen, and diuretics for right-sided heart failure are recommended for patients with CTEPH. The first successful large phase III medication study for CTEPH was the CHEST-1 trial published in 2013 (Ghofrani et al. *N Eng J Med*. 2013;369:310). This was a multicenter, randomized, placebo-controlled trial of the soluble guanylate cyclase stimulator riociguat. The study enrolled 261 patients with inoperable CTEPH or persistent pulmonary hypertension after surgery. The primary end point was 6-minute walk distance at 12 weeks. The treatment group showed a 46 m improvement ($P<.001$). Secondary end points of pulmonary vascular resistance, NT-proBNP level, and functional class also improved. This pivotal trial led to the FDA approval of riociguat for inoperable or persistent postoperative CTEPH.

MERIT-1, a phase II, randomized placebo-controlled double trial of macitentan (an oral endothelin receptor antagonist) was recently completed. It enrolled 80 patients with inoperable CTEPH. The primary endpoint was pulmonary vascular resistance at week 16, expressed as a percentage of baseline. At week 16, the patients in the treatment arm had a PVR 73% of baseline vs 87.2% in the treatment group. This medication is not yet FDA-approved for the treatment of inoperable CTEPH (Ghofrani H, et al. *Lancet Respir Med*. 2017;5[10]:785-794).

Pulmonary hypertension medication has been postulated as a possible way to "pretreat" patients before pulmonary thromboendarterectomy surgery, perhaps lowering preoperative pulmonary vascular resistance and surgical risk. However, there are currently no convincing data to support this practice, and medical treatment has been associated with a possible counterproductive delay in surgery. A phase II study including CTEPH patients with high PVR for preoperative treatment with riociguat vs placebo is currently enrolling to determine if "induction" treatment with medication prior to surgery reduces risk or delays definitive surgery.

Occasionally, patients are found who have persistent thrombus but not pulmonary hypertension. Chronic thromboembolic disease (CTED) is a recently coined term describing patients who have chronic thromboembolism on imaging but have normal resting hemodynamics. Whether CTED represents simply unresolved clot that will never progress to CTEPH or is an early point on the continuum of disease not well-defined and a controversial topic among experts.

At many centers, patients with CTED and symptoms will undergo exercise testing to look

Continued on following page

Visual abstracts enhance journal readers' experience

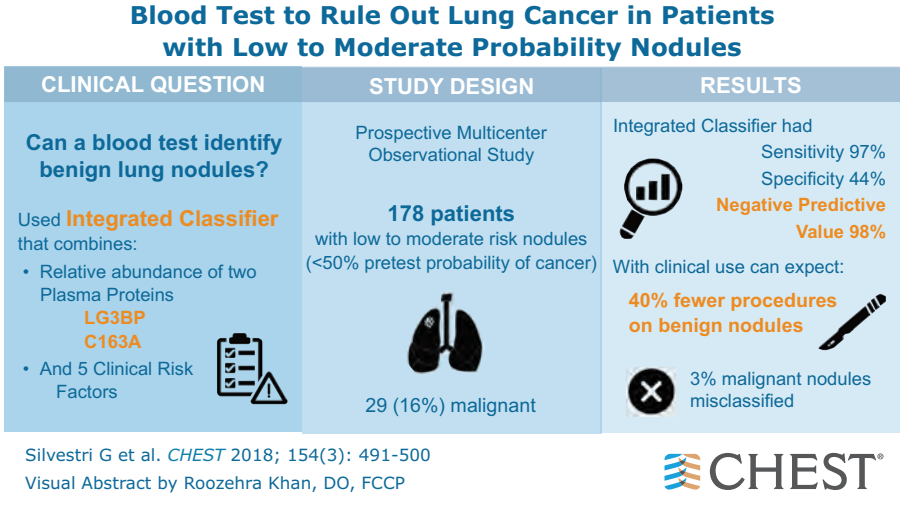
BY LISBETH MAXWELL
Managing Editor, CHEST

Physicians' time is decreasingly their own, and, yet, keeping abreast of clinical literature is increasingly more important. The journal *CHEST*® has introduced a new feature aimed at easing that task and broadening the reach of journal content: visual abstracts.

"It's become apparent that *CHEST* needs to make its content even more accessible, as well as available across many platforms," said Christopher Carroll, MD, FCCP, the journal's Web and Multimedia (WMM) Editor. "So we put together a Web and Multimedia team to take on that task.

At the direction of *CHEST* Editor in Chief Richard Irwin, MD, Master FCCP, Dr. Carroll assembled a team to help carry out an ambitious multimedia strategy (see box). Dr. Irwin charged the Web and Multimedia editorial team with not only extending the reach of journal content but also enhancing readers' engagement with and understanding of it.

"Our first project was the development of visual abstracts, a type of infographics used to distill the key points of a research abstract into an easily digested graphic form," says Dr. Carroll, who also is research director of pediatric critical care at Connecticut Children's Medical Center, Hartford, and a professor of pediatrics at the University of Connecticut School of Medicine, Farmington.



This is an example of the new infographics being introduced. A full gallery of all the visual abstracts so far is available at https://journal.chestnet.org/infographics.

The first visual abstracts were posted to accompany two articles in the July 2018 issue of *CHEST*. With the exception of August 2018, every issue since has been enhanced with infographics.

The visual abstracts are available through a number of vehicles: the journal's website (https://journal.chestnet.org/), the journal's mobile app (https://journal.chestnet.org/content/mobileaccessinstructions), and social media platforms such as Facebook (https://www.facebook.com/accpchest/) and Twitter (https://twitter.com/accpchest).

"Our goal with the infographics is to promote the exciting research *CHEST* publishes and to get readers to click through and read the entire article," says Dr. Carroll. "So far, we're happy with our results—and we're looking forward to even greater reach in 2019."

CHEST Web and Multimedia Section:

Editor
Christopher Carroll, MD, MS, FCCP, Hartford, CT

Assistant Editors
Yonatan Y. Greenstein, MD, FCCP, Newark, NJ
Roozehra Khan, DO, FCCP, Los Angeles, CA
Dominique J. Pepper, MD, MBChB, MHSc, Bethesda, MD.

Continued from previous page

for exercise induced pulmonary hypertension or an increase in dead space ventilation as a cause of their symptoms. A retrospective series of carefully chosen CTED patients who underwent PTE surgery reported improvements in symptoms and overall quality of life, without increased complications (Taboada D, et al. *Eur Respir J*. 2014 44[6]:1635). The operation carries risk, however, and further work into the epidemiology and prognosis of CTED is required before operative intervention can be recommended.

In conclusion, CTEPH is a disease that rarely occurs after an acute PE but when undiagnosed and untreated portends a poor prognosis. The definitive treatment for this disease is surgical PTE, but to achieve the best outcomes, this procedure needs to be performed at expert centers with multidisciplinary team experience. Patients who are poor operative candidates or with surgically inaccessible disease may be considered for balloon pulmonary angioplasty. For patients without more curative options, medication improves exercise tolerance. The field of CTEPH has been rapidly expanding over the last decade, leading to better patient outcomes and more treatment options.

Dr. Bartolome is Associate Professor, Pulmonary and Critical Care Medicine; Director, CTEPH Program; and Associate Director, PH Program; UT Southwestern Medical Center, Dallas, Texas.

Meet the CHEST President-Designate

Steven Q. Simpson, MD, FCCP, is a pulmonologist and intensivist with an extensive background in sepsis and in critical care quality improvement. Dr. Simpson acts as a CHEST Regent-at-Large of the Board of Regents, board liaison for the Guidelines Oversight Committee, sits on numerous board task forces and subcommittees and is a member of the CHEST SEEK Critical Care Medicine Editorial Board. He will serve as CHEST President for the 2020-2021 term.

Dr. Simpson is Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Kansas. He is also senior advisor to the Solving Sepsis initiative of the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services.

He has conducted research in all areas of severe sepsis, including molecular and cellular mechanisms, translational, quality improvement, and computer modeling studies.

He was a founder in 2005 of the Midwest Critical Care Collaborative, a multidisciplinary and interprofessional collaborative effort to improve the quality of critical care services throughout the Midwest.

In 2007, he initiated the Kansas Sepsis Project, a statewide program to improve severe sepsis care and outcomes via continuing education both in sepsis and in quality improvement principles and via interprofessional collaborations. Dr. Simpson is an author of the 2016 and 2020 updates of the Surviving Sepsis Campaign Guidelines. He is a member of the board of directors and Chief Medical Officer of Sepsis Alliance, a nationwide patient information and advocacy organization.


Dr. Simpson

During his tenure at the University of New Mexico, he contributed to the discovery of a particular form of sepsis, the hantavirus pulmonary syndrome, and published numerous papers on the clinical description, the hemodynamic description, and the approach to supportive care for patients with the syndrome, including extracorporeal hemodynamic and oxygenation support.

Dr. Simpson has authored over 180 scientific articles, book chapters, editorials, abstracts and electronic media publications. He was awarded the 2009 Eli Lilly Distinguished Scholar in Critical Care Medicine Award of the American College of Chest Physicians and the 2013 Roger C. Bone Memorial Lecture in Critical Care Medicine, which recognizes career contributions to the field. He has also been recognized as a Distinguished CHEST Educator in 2017 and 2018.

IMPACT TRIAL

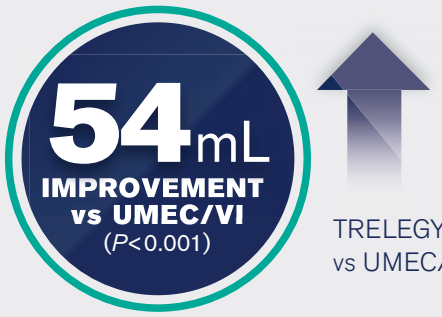
10,000+ PATIENTS. 52 WEEKS. 1 LANDMARK STUDY.

TRELEGY significantly improved lung function vs FF/VI (an ICS/LABA) and vs UMEC/VI (a LAMA/LABA)

IN PATIENTS WITH A HISTORY OF COPD EXACERBATIONS

SECONDARY ENDPOINT: CHANGE FROM BASELINE IN TROUGH FEV_1 AT MONTH 12[1,2]

TRELEGY (n=3366) 94 mL
vs FF/VI (n=3060) -3 mL



TRELEGY (n=3366) 94 mL
vs UMEC/VI (n=1490) 40 mL

STUDY DESCRIPTION[1,2]

Results of a 12-month, randomized, double-blind, parallel-group study in 10,355 patients with COPD (mean age: 65 years) with a history of moderate or severe COPD exacerbations. At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 45.5% and a mean postbronchodilator FEV_1/FVC ratio: 0.47. Treatment with TRELEGY (n=4145) once daily resulted in statistically significant differences in the co-primary endpoints of reduction in the annual rate of on-treatment moderate to severe exacerbations at Week 52 compared to patients treated with FF/VI 100/25 (0.91 vs 1.07, 15% reduction; *P*<0.001; n=4133) and with UMEC/VI 62.5/25 (1.21, 25% reduction; *P*<0.001; n=2069).

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

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol.

INDICATION FOR TRELEGY

- TRELEGY is for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for reducing exacerbations in patients with a history of exacerbations. TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

IMPORTANT SAFETY INFORMATION FOR TRELEGY

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- TRELEGY is not for treatment of asthma. LABA monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.

TRELEGY significantly improved quality of life in patients with a history of COPD exacerbations

SIGNIFICANT IMPROVEMENT IN QOL BASED ON SYMPTOMS, ACTIVITIES, AND IMPACT ON DAILY LIFE

Patients taking TRELEGY were more likely to show an improvement in quality of life total score at 1 year vs FF/VI and vs UMEC/VI as measured by the SGRQ.*

- SGRQ is a validated, respiratory disease–specific, patient-reported instrument across symptoms, activities, and impact on daily life domains.[2,3]

Responder rate* was statistically significantly greater for TRELEGY.[2]

TRELEGY 42% vs **FF/VI 34%**
(odds ratio: 1.41; 95% CI: 1.29, 1.55; *P*<0.001)

TRELEGY 42% vs **UMEC/VI 34%**
(odds ratio: 1.41; 95% CI: 1.26, 1.57; *P*<0.001)

*Response defined as a decrease in SGRQ total score from baseline of 4 or more. SGRQ for COPD (SGRQ-C) was used and results were then converted to SGRQ for reporting purposes.
CI=confidence interval; QOL=quality of life; SGRQ=St George's Respiratory Questionnaire.

IMPORTANT SAFETY INFORMATION FOR TRELEGY (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of ICS, like fluticasone furoate.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of ICS in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

Please see additional Important Safety Information for TRELEGY on the following page.

Please see Brief Summary of Prescribing Information, including Patient Information, for TRELEGY following this ad.

gsk | INNOVIVA

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

IMPORTANT SAFETY INFORMATION FOR TRELEGY (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density have been observed with long-term administration of products containing ICS. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of ICS or inhaled anticholinergics; therefore, monitoring is warranted.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo + FF/VI) reported in two 12-week clinical trials with umeclidinium + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).
- Additional adverse reactions (≥1% incidence) reported in subjects taking TRELEGY in a 52-week trial included upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Please see additional Important Safety Information for TRELEGY on the previous pages.

Please see Brief Summary of full Prescribing Information, including Patient Information, for TRELEGY, following this ad.

References: 1. Data on file, GSK. **2.** Lipson DA, Barnhart F, Brealy N, et al; for the IMPACT Investigators. Once-daily single-inhaler triple vs dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. **3.** Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med*. 1991; 85(suppl B):25-31.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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

BRIEF SUMMARY

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

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

1 INDICATIONS AND USAGE

TRELEGY is indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. TRELEGY ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

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

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

Available data from clinical trials in subjects with COPD do not suggest an increased risk of death with use of LABA in patients with COPD.

5.2 Deterioration of Disease and Acute Episodes

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

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

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

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

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

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

5.4 Local Effects of Inhaled Corticosteroids

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

5.5 Pneumonia

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

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was <1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.

In a 52-week trial of subjects with COPD (N=10,355), the incidence of pneumonia was 8% for TRELEGY ELLIPTA (n=4,151), 7% for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 5% for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Fatal pneumonia occurred in 12 of 4,151 patients (0.35 per 100 patient-years) receiving TRELEGY ELLIPTA, 5 of 4,134 patients (0.17 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (0.29 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (<0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression

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

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

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

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

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

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses

Continued on next page

of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

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

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

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions, Including Anaphylaxis

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

5.12 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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

In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction (MI), non-fatal acute MI, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for TRELEGY ELLIPTA (n=4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 2.2 per 100 patient-years for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving TRELEGY ELLIPTA, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving umeclidinium/vilanterol.

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

5.13 Reduction in Bone Mineral Density

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

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

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

5.15 Worsening of Urinary Retention

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

5.16 Coexisting Conditions

TRELEGY, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.17 Hypokalemia and Hyperglycemia

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

6 ADVERSE REACTIONS

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

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1)]*
- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular effects *[see Warnings and Precautions (5.12)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.14)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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

The safety of TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol and a 52-week long-term trial of TRELEGY ELLIPTA compared with the fixed-dose combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol *[see Clinical Studies (14)]*.

Trials 1 and 2

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based on the two 12-week trials.

Continued on next page

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

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

Trial 3 - Long-term Safety Data

A 52-week trial (Trial 3) evaluated the long-term safety of TRELEGY ELLIPTA compared with the fixed-dose combinations of fluticasone furoate/vilanterol 100 mcg/25 mcg and umeclidinium/vilanterol 62.5 mcg/25 mcg. A total of 10,355 subjects with COPD with a history of moderate or severe exacerbations within the prior 12 months were randomized (2:2:1) to receive TRELEGY ELLIPTA, fluticasone furoate/ vilanterol, or umeclidinium/vilanterol administered once daily in a double-blind clinical trial (mean age: 65 years, 77% white, 66% male across all treatments) *[see Clinical Studies (14)]*.

The incidence of adverse reactions in the long-term trial were consistent with those in Trials 1 and 2. However, in addition to the adverse reactions shown in Table 1, adverse reactions occurring in ≥1% of the subjects treated with TRELEGY ELLIPTA (n=4,151) for up to 52 weeks also included upper respiratory tract infection, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, oral candidiasis *[see Warnings and Precautions (5.4)]*, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

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

8.2 Lactation

Risk Summary

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

8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. In Trial 3, 2,265 subjects aged 65 years and older, of which 565 subjects were aged 75 years and older, were administered TRELEGY ELLIPTA. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

Fluticasone Furoate/Vilanterol

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

Umeclidinium

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

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

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

10.1 Fluticasone Furoate

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

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

10.2 Umeclidinium

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

10.3 Vilanterol

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

17 PATIENT COUNSELING INFORMATION

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

Not for Acute Symptoms

Inform patients that TRELEGY is not meant to relieve acute symptoms of COPD, and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled,

Continued on next page

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation *(cont'd)*

short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

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

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

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

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

Instruct patients not to use other LABA.

Local Effects

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

Pneumonia

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

Immunosuppression

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

Hypercorticism and Adrenal Suppression

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

Paradoxical Bronchospasm

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

Hypersensitivity Reactions, Including Anaphylaxis

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

Reduction in Bone Mineral Density

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

Ocular Effects

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

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

Worsening of Urinary Retention

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

Risks Associated With Beta-agonist Therapy

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

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 04/2018 TRL:3BRS

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

Trademarks are owned by or licensed to the GSK group of companies.

©2018 GSK group of companies or its licensor.
Printed in USA. 1006084R0 August 2018

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

CRITICAL CARE COMMENTARY

Renal replacement therapy in the ICU: Vexing questions and team dynamics

BY JAVIER A. NEYRA, MD, MSCS; AND CAROLINE E. HAUSCHILD, RN, BSN

More than 5 million patients are admitted to ICUs each year in the United States, and approximately 2% to 10% of these patients develop acute kidney injury requiring renal replacement therapy (AKI-RRT). AKI-RRT carries high morbidity and mortality (Hoste EA, et al. *Intensive Care Med.* 2015;41:1411) and is associated with renal and systemic complications, such as cardiovascular disease. RRT, frequently provided by nephrologists and/or intensivists, is a supportive therapy that can be lifesaving when provided to the right patient at the right time. However, several questions related to the provision of RRT still remain, including the optimal timing of RRT initiation, the development of quality metrics for optimal RRT deliverables and monitoring, and the optimal strategy of RRT de-escalation and risk-stratification of renal recovery. Overall, there is paucity of randomized trials and standardized risk-stratification tools that can guide RRT in the ICU.


Dr. Neyra


Ms. Hauschild

Current vexing questions of RRT deliverables in the ICU

There is ongoing research aiming to answer critical questions that can potentially improve current standards of RRT.

What is the optimal time of RRT initiation for critically ill patients with AKI?

Over the last 2 years, three randomized clinical trials have attempted to address this important question involving heterogeneous ICU populations and distinct research hypotheses and study designs.

Two of these studies, AKIKI (Gaudry S, et al. *N Engl J Med.* 2016;375:122) and IDEAL-ICU (Barbar SD, et al. *N Engl J Med.* 2018;379:1431) yielded no significant difference in the primary outcome of 60-day and 90-day all-cause mortality between the early vs delayed RRT initiation strategies, respectively (Table 1). Further, AKIKI showed no difference in RRT dependence at 60 days and higher catheter-related infections and hypophosphatemia in the early initiation arm. It is important to note that IDEAL-ICU was stopped early for futility after the second planned interim analysis with only 56% of patients enrolled (main hypothesis was that early RRT initiation reduced 90-day all-cause mortality by 10%).

In contrast, the ELAIN trial (Zarbock A, et al. *JAMA.* 2016;315:2190) showed a significant 90-day mortality reduction (39% vs 55%), reduced RRT need (9 days vs 25 days), and reduced length of stay (51 days vs 82 days) favoring early RRT initiation strategy.

A larger study (STARRT-AKI) addressing this question with a more pragmatic approach (incorporating clinical judgment and equipoise among intensivists and nephrologists for patient eligibility) is underway. However, it is possible that STARRT-AKI will not provide a definitive answer for the inevitable search for implementing RRT initiation protocols in the ICU. Therefore, the scientific community may need to redirect the research focus to risk-stratification tools that can assist in the identification of patients who could benefit from early RRT initiation through an individualized approach rather than a standardized protocol.

How can RRT deliverables in the ICU be effectively and systematically monitored?

The provision of RRT to ICU patients with AKI requires an iterative adjustment of the RRT prescription and goals of therapy to accommodate changes in the clinical status with emphasis in hemodynamics, multiorgan failure, and fluid overload (Neyra JA. *Clin Nephrol.* 2018;90:1). The utilization of static and functional tests or point-of-care ultrasonography to assess hemodynamic variables can be useful. Furthermore, the implementation of customized and automated flowsheets in the electronic health record can facilitate remote monitoring. It is, therefore, essential that the multidisciplinary ICU team develops a process to monitor and ensure RRT deliverables. In this context, the standardization and monitoring of quality metrics (dose, modality, anticoagulation, filter life, downtime, etc) and the development of effective quality management systems are critically important. However, big multicenter data are direly needed to provide insight in this arena.

How can renal recovery be assessed and RRT effectively de-escalated?

The continuous examination of renal recovery in ICU patients with AKI-RRT is mostly based on urine output trend and, if feasible, interdialytic solute control. Sometimes, the transition from continuous RRT to intermittent modalities is necessary in the context of multiorgan recovery and de-escalation of care. However, clinical risk-prediction tools that identify patients who can potentially recover or already exhibit early signs of renal function recovery are needed. Current advances in clinical informatics can help to incorporate time-varying clinical parameters that may be informative for risk-prediction models. In addition, incorporating novel biomarkers of AKI repair and functional tests (eg, furosemide stress test, functional MRI) into these models may further inform these tools and aid the development of clinical decision support systems that enhance interventions to promote AKI recovery (Neyra JA, et al. *Nephron.* 2018;140:99).

Continued on following page

TABLE 1

Comparison between recent randomized clinical trials addressing early vs delayed initiation of RRT in critically ill patients with AKI

Characteristics	AKIKI Trial	ELAIN Trial	IDEAL Trial
Participating sites	31 (France)	1 (Germany)	29 (France)
Total number of participants	620	231	488
Early RRT definition	KDIGO stage 3	KDIGO stage 2	KDIGO stage 3
Delayed RRT definition	BUN >112, K >6, pH <7.15, pulmonary edema, oliguria for >72 h	<12 h KDIGO stage 3 or absolute indications	>48 h KDIGO stage 3 or absolute indications
Timing from randomization to initiation of RRT, median	2 h (early) vs 57 h (delayed)	6 h (early) vs 25.5 h (delayed)	7.6 h (early) vs 51.5 h (delayed)
SOFA score, mean	11	16	12
CKD, %	10	41	15
Septic shock, %	67	32	100
Surgical intervention, %	21	97	–
RRT modality at initiation	HD, SLED, or CRRT	CRRT	HD, SLED, or CRRT
Primary endpoint	60-day mortality	90-day mortality	90-day mortality
Mortality – Early, %	49	39	58
Mortality – Delayed, %	50	55	54
Received RRT in delayed arm, %	51	91	62

MDEDGE NEWS

Note: KDIGO = Kidney Disease: Improving Global Outcomes; HD = hemodialysis; SLED = sustained low efficiency dialysis.

Continued from previous page

Is post-AKI outpatient care beneficial for ICU survivors who suffered from AKI-RRT?
Specialized AKI survivor clinics have been implemented in some centers. In general, this outpatient follow-up model includes survivors who suffered from AKI stage 2 or 3, some of them requiring RRT, and tailors individualized interventions for post-AKI complications (preventing recurrent AKI, attenuating incident or progressive CKD). However, the value of this outpatient model needs to be further evaluated with emphasis on clinical outcomes (eg, recurrent AKI, CKD, readmissions, or death) and elements that impact quality of life. This is an area of evolving research and a great opportunity for the nephrology and critical care communities to integrate and enhance post-ICU outpatient care and research collaboration.

Interdisciplinary communication among acute care team members
Two essential elements to provide effective RRT to ICU patients with AKI are: (1) the dynamics of the ICU team (intensivists, nephrologists, pharmacists, nurses, nutritionists, physical therapists, etc) to enhance the delivery of personalized therapy (RRT candidacy, timing of initiation, goals for solute control and fluid removal/regulation, renal recovery evaluation, RRT de-escalation, etc.) and (2) the frequent assessment and adjustment of RRT goals according to the clinical status of the patient. Therefore, effective RRT provision in the ICU requires the development of optimal channels of communication among all members of the acute care team and the systematic monitoring of the clinical status of the patient and RRT-specific goals and deliverables.

Perspective from a nurse and quality improvement officer for the provision of RRT in the ICU
The provision of continuous RRT (CRRT) to critically ill patients requires close communication between the bedside nurse and the rest of the ICU team. The physician typically prescribes CRRT and determines the specific goals of therapy. The pharmacist works closely with the nephrologist/intensivist and bedside nurse, especially in regards to customized CRRT solutions (when indicated) and medication dosing. Because CRRT can alter drug pharmacokinetics, the pharmacist closely and constantly monitors the patient's clinical status, CRRT prescription, and all active medications. CRRT can also affect the nutritional and metabolic status of critically ill patients; therefore, the input of the nutritionist is necessary. The syndrome of ICU-acquired weakness is commonly encountered in ICU patients and is related to physical immobility. While ICU patients with AKI are already at risk for decreased mobility, the continuous connection to an immobile extracorporeal machine for the provision of CRRT may further contribute to immobilization and can also preclude the provision of optimal physical therapy. Therefore, the bedside nurse should assist the physical therapist for the timely and effective delivery of physical therapy according to the clinical status of the patient.

Clinical risk-prediction tools that identify patients who can potentially recover or already exhibit early signs of renal function recovery are needed.

The clinical scenarios discussed above provide a small glimpse into the importance of developing an interdisciplinary ICU team caring for critically ill patients receiving CRRT. In the context of how integral the specific role of each team member is, it becomes clear that the bedside nurse's role is not only to deliver hands-on patient care but also the orchestration of collaborative communication among all health-care providers for the effective provision of CRRT to critically ill patients in the ICU.

Dr. Neyra and Ms. Hauschild are with the Department of Internal Medicine; Division of Nephrology; Bone and Mineral Metabolism; University of Kentucky; Lexington, Kentucky.

Secure a CHEST Foundation research award

In anticipation of the 2019 CHEST Foundation grants cycle, opening in late February, CHEST Foundation staff sat down with 2017 CHEST Foundation Community Service grant winner, Sharon Armstead, RRT, Director of Clinical Education & Clinical Assistant Professor for the Department of Respiratory Care at Texas State University, to learn more about her project supporting respiratory asthma clinics in Guyana.

Sharon Armstead, RRT (second from right), and her students with members of the Georgetown Public Hospital Corporation (GPHC) COPD/Asthma Team in Guyana.

Ms. Armstead's program takes respiratory care students from her institution on a study abroad trip to Guyana with aims to educate Guyanese student populations about asthma and teach them self-management skills. Additionally, she and her students work alongside clinicians at Georgetown Public Hospital to host a mobile asthma clinic that provides asthma screenings and education for Guyanese students, the first of its kind at Texas State University.

This passion for supporting clinics in Guyana stems from a deeply personal place. "Guyana is my country of birth. I left when I was 14. I came back many years later realizing that I can give back to the county that gave me so much." Ms. Armstead shared.

"The CHEST Foundation grant opened doors for me that had never been opened before. Members of the community were very open to hearing what we had to say and receptive to the changes we suggested they make in their daily lives. The financial portion of the award allowed me to purchase additional spirometers for the asthma clinic, allowing for a whole new level of outpatient testing and outreach in the community."

In addition to the impact she and her students have in Georgetown, Ms. Armstead says opportunity provided to her students was life-changing for them. "To watch my students communicate with people in a different country really helps build their confidence as future clinicians." Her study program received a significant growth in attendance over the past few years. "When we first started doing this study abroad in Guyana, I only had 2 students interested… We took 14 respiratory care students to Guyana in 2017. It's really elevated this study abroad program at my institution."

The CHEST Foundation's grants cycle opens in late February. Visit our grants page (https://foundation.chestnet.org/grants/apply-for-a-grant/) to view the RFPs for our 2019 offerings and see a step-by-step walkthrough of how simple it is to apply for funding! Be a champion of lung health, and secure your research award today!

Staying CHEST-involved is easy with auto-renewal

CHEST now offers membership auto-renewal.

Keeping active membership status allows you to save hundreds of dollars on education courses, annual meeting registration, and board review courses. You also have access to the journal *CHEST*®, networking opportunities, and other products to help you advance in your profession. And, you receive 20 Participation Points when you opt in. You can opt in on your "My Account" page or by or calling +1 (224) 521-9800 to speak with CHEST's friendly help team.

CHEST NETWORKS

Five steering committees examine the literature

Clinical Pulmonary Medicine

Asthma-COPD overlap: An underappreciated phenotype of obstructive airway disease (OAD)

Asthma-COPD overlap (ACO) is a common yet underappreciated clinical entity within the complex OAD spectrum. Currently, there is no consensus criteria to define ACO; however, a roundtable consensus from an international group (Sin, et al. *Eur Respir J*. 2016; 48:664) suggests using major and minor criteria, with key features being airflow limitation, asthma history, and cigarette or biomass exposure. Several studies have shown that patients with ACO have severe disease, faster lung function decline, greater morbidity and mortality, and lower QoL (Alshabanat, et al. *PLoS One*. 2015;10:e0136065).

There is paucity of data on the pathophysiology, risk factors, and clinical management given exclusion of these patients from clinical trials of asthma and COPD. Indeed, clinicians and researchers now realize that ACO is an umbrella term for multiple subphenotypes, including patients who have predominant asthma with some COPD features and others with predominant COPD with some asthma features. Overall, IgE level, FeNO, sputum, and blood eosinophils are usually higher in ACO than in COPD and relatively similar compared with asthma (Kobayashi, et al. *Int J Chron Obs Pulmon Dis*. 2016; 11:2117).

Most recently, a longitudinal study looked at predictors of ACO among NY firefighters exposed to WTC dust (Singh, et al. *CHEST*. 2018; 154[6]:1301). Pre-exposure low lung function and elevated blood eosinophils and IL4 (T2 inflammatory cytokine) increased risk of developing ACO among those exposed to WTC dust. Further research is required to better understand the interaction of environmental exposure and risk factors in the pathophysiology of ACO. It may be more pragmatic to use the unifying term OAD, as originally proposed in the Dutch hypothesis, and further delineate how several phenotypes of airway disease can be classified by combining traditional approaches with molecular and genomic analysis.

Dr. Luthra

Dr. D'Annunzio

Munish Luthra, MD, FCCP
Steering Committee Member

Samantha D'Annunzio, MD
Steering Committee Member

Airways Disorders

Defining and treating early COPD: Can we make a difference?

There is growing evidence that early COPD—before currently accepted spirometric or symptomatic criteria are present—may be an important clinical entity. The primary pathobiologic mechanisms in early COPD development include both abnormal lung development and accelerated lung aging (Agustí. *Am J Respir Crit Care Med*. 2018;198[8]987).

Martinez and colleagues recently proposed defining early COPD as age <50 with 10+ pack-year smoking history and at least one of the following: (1) early airflow limitation (postbronchodilator FEV_1/FVC < lower limit of normal), (2) compatible CT scan abnormalities, (3) rapid decline in FEV_1 (≥60 mL/yr) that is accelerated relative to FVC (Martinez et al. *Am J Respir Crit Care Med*. 2018;197[12]:1540).

A novel multiresolution CT scan imaging protocol described by Koo and coworkers found that substantial loss of small airways— specifically the terminal and transitional bronchioles—occurs in patients with mild-to-moderate COPD even prior to the development of emphysema on CT scan. These findings show that significant destruction of the

Continued on following page

This month in the journal *CHEST*®

Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Giants in Chest Medicine – Atul C. Mehta, MBBS, FCCP
By Dr. J. K. Stoller

Screening Heroin Smokers Attending Community Drug Services for COPD.
By Dr. H. Burhan, et al.

The NHLBI LAM Registry: Prognostic Physiologic and Radiologic Biomarkers Emerge From a 15-Year Prospective Longitudinal Analysis.
By Dr. N. Gupta, et al.

Indwelling Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications.
By Dr. C. Kniese, et al.

Implications of the Revised Common Rule for Human Participant Research.
By Dr. E. G. DeRenzo, et al.

INDEX OF ADVERTISERS

Biomerieux Company
BioFire 52

Boehringer Ingelheim Pharmaceuticals, Inc.
Corporate 21

Genentech USA, Inc.
Esbriet 2-5

GSK group of companies
Nucala 10-13
Breo 19
Anoro 24-28
Trelegy 40-46

Respiratory Technologies, Inc.
Corporate 15

Sanofi and Regeneron Pharmaceuticals, Inc.
Dupixent 31-35

Continued from previous page

small airways has occurred prior to the development of mild COPD (Koo, et al. *Lancet Respir Med*. 2018;6:591).

Pharmacologic treatment for COPD is targeted at the reduction of symptoms and risk of exacerbation, as there remains no conclusive evidence that existing therapies modify long-term decline in lung function. It is unknown if pharmacotherapy for "early COPD" will alter the disease course. While not directly addressing this subset, information may be gleaned from trials on younger, more mild GOLD stage 1 or stage 2 patients.

The Tie-COPD trial, the largest powered study to date of mild-to-moderate COPD, found

Dr. Conroy

Dr. Blaivas

that among patients with GOLD stage 1 or 2 COPD treatment with tiotropium compared with placebo for 2 years resulted in significantly higher FEV_1 before bronchodilator use (between group difference of 157 mL) and slowed annual decline in FEV_1 after bronchodilator use (Zhou, et al. *N Engl J Med.* 2017;377[10]:923).

As our understanding of heterogeneity within COPD increases, striving for improved outcomes from our therapies—an impact on lung function in addition to symptom and exacerbation risk—may need to begin with the study of earlier treatment.

Megan Conroy, MD
Steering Committee
Fellow-in-Training

Allen J. Blaivas, DO, FCCP
Steering Committee Vice-Chair

Critical Care

Mechanical ventilation: One size fits all?

Mechanical ventilation (MV) is a life-saving intervention in the ICU, but it has been associated with numerous complications ranging from overuse of sedation, atelectasis, and baro or volutrauma. After 2000, it became well known that using a low tidal volume (VT) strategy (6 mL/kg predicted body weight, PBW) in patients with ARDS produced lower mortality and more ventilator-free days (*N Engl J Med.* 2000;342[18]:1301). In addition, a meta-analysis in 2012 demonstrated a lower relative risk

Dr. Disselkamp

Dr. Megri

of new lung injury, mortality, and pulmonary infections with low VT in non-ARDS patients (*JAMA.* 2012;308[16]:1651). However, the included studies varied widely in their use of VT (9-12 mL/kg), duration of MV, and in mixed settings (ICU or operating room).

Recently, a large randomized clinical trial compared the effect of low (4-6 mL/kg, PBW) vs intermediate (8-10 mL/kg, PBW) VT ventilation strategy in non-ARDS ICU patients. Interestingly, the study concluded that there is no significant difference in ventilator-free days (21 days in each group), median length ICU and hospital stay, ICU mortality rates, and 28- and 90-day mortality. Also, there was no difference in new-onset ARDS, severe atelectasis, sedation use, and delirium (*JAMA.* 2018; 320[18]:1872). This study suggests that in non-ARDS patients, MV should be individualized according to each patient's clinical situation, the nature of the disease, and its effect on lung mechanics, especially in patients who cannot tolerate low tidal volumes.

Margaret A. Disselkamp, MD
Steering Committee Member

Mohammed A. Megri, MD
Steering Committee
Fellow-in-Training

Interstitial and Diffuse Lung Disease

Idiopathic pneumonias that are not all that idiopathic

Despite being defined as an individual entity for research purposes in 2015 (Fisher, et al. *Eur Respir J.* 2015;46:976), interstitial pneumonias with autoimmune features (IPAF) remain a heterogeneous group of interstitial lung diseases that puzzle the clinician. Since the introduction of the IPAF definition, there have been attempts to validate the diagnostic criteria and study their prognostic implications. Some of these studies showed differential prognosis in patients who met the IPAF criteria (Oldham, et al. *Eur Respir J.* 2016;47:1767).

Although the implications of the presence of autoimmune antibodies in idiopathic interstitial pneumonias (IIPs) is not fully understood, the treatment often entails immunosuppression, especially in those with non-UIP patterns of disease and/or clinical features of autoimmune disease. The stakes are high when IIPs are associated with antibodies correlated with rapidly progressive disease, such as MDA-5 antibody or anti-synthetase antibodies. Pulmonologists often lack the

Dr. Wynn

clinical expertise to detect occult autoimmune disorders, though the role of the rheumatologist in facilitating the diagnosis and treatment of IPAF is not well delineated. Most health-care systems are not equipped with collaborative ILD-rheumatology clinics or even easy access to a rheumatologist. There is a need for real-world pragmatic studies to establish the optimal way to evaluate patients with ILD for autoimmune features and identify patients who would benefit most from an early referral to rheumatology to aid with diagnosis, treatment, and sometimes monitoring for extrapulmonary manifestations of auto-immune disorders.

Avanthika Thanushi Wynn, MD
Steering Committee
Fellow-in-Training

Home-Based Mechanical Ventilation and Neuromuscular Disease

Improving access to sleep medicine care for patients with NMD

Sleep-disordered breathing (SDB) occurs in up to 5% of children, with adverse implications for growth and development. Children with neuromuscular disease are at significantly higher risk than unaffected children (Chiang, et al. *Children.* 2018;5:e78). Respiratory dysfunction that may present as SDB before daytime impairment in gas exchange is evident. Diagnosing and treating SDB (to include OSA, CSA, and hypoventilation syndromes) early can significantly improve morbidity and mortality.

Unfortunately, diagnostic sleep medicine resources are limited. Children may wait up to a year or more for definitive testing with in-laboratory, attended polysomnography (PSG). Among children with neuromuscular disease, fewer than 10% may undergo a sleep clinic evaluation, and, of those who do, they may have only one visit over a 3-year period of care (Rose, et al. *Pediatr Pulmonol.* 2018;53:1378). Home sleep testing (HST) has been evaluated as an alternative to PSG given lower cost, availability, and advantage of the child sleeping in his/her own bed. Although HST is indicated in adults with a high pretest probability for moderate to severe OSA, it is not indicated in children, given the potential to underestimate disease severity or to miss the diagnosis entirely (Kirk, et al. *J Clin Sleep Med.* 2017;13[10]:1199). HST lacks electroencephalogram (EEG) and capnography. Technical recording mishaps are more common in children, but in-lab PSG has the advantage of on-site troubleshooting by a technologist. A recently published study by Fishman and colleagues attempted to compare gold standard in-lab PSG to HST with capnography (Fishman, et al. *J Clin Sleep Med*. 2018;14(12):2013). Despite a well-designed study with a carefully selected population, HST failed to reliably diagnose SDB. HST underestimated disease severity and, in some cases, missed the diagnosis of SDB entirely. The addition of end tidal CO_2 monitoring failed to improve diagnostic accuracy, and HST and PSG-$ETCO_2$ values were poorly correlated.

Dr. Collen

Although children with neuromuscular disease face long wait times for sleep evaluations, HST is clearly not the solution for now. It remains to be seen if innovations in HST with extended monitoring (and transcutaneous CO_2) become viable. In the meantime, finding ways to improve access to sleep medicine care for children with neuromuscular disease is a must.

Jacob Collen, MD, FCCP
Steering Committee Member

Crack pneumonia cases faster.

Get fast, comprehensive results with the BioFire® FilmArray® Pneumonia Panel.

When patients present with severe respiratory symptoms, an accurate diagnosis can set the stage for clinical success. The BioFire Pneumonia Panel utilizes a syndromic approach—simultaneously testing for different infectious agents that can cause similar symptoms. The BioFire Pneumonia Panel tests for bacterial and viral infections, as well as antimicrobial resistance genes, directly from lower-respiratory specimens. You get the helpful answers you need all in about one hour—ultimately aiding in diagnosis and subsequent treatment.

Learn more at **biofiredx.com**

The BioFire Pneumonia Panel

Bacteria (semi-quantitative)
Acinetobacter calcoaceticus baumannii complex
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae group
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacteria (qualitative)
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Viruses (qualitative)
Adenovirus
Coronavirus
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza B
Parainfluenza virus
Respiratory Syncytial virus

Resistance Markers
Carbapenemase
- IMP
- KPC
- NDM
- Oxa48-like
- VIM

ESBL
- CTX-M

MRSA
- *mec*A/C and MREJ

BIOFIRE®
A BIOMÉRIEUX COMPANY

Syndromic Testing: The Right Test, The First Time.

BFDX-MKT-0257-01