Health Monitor®

Clinician Update

COPD Management

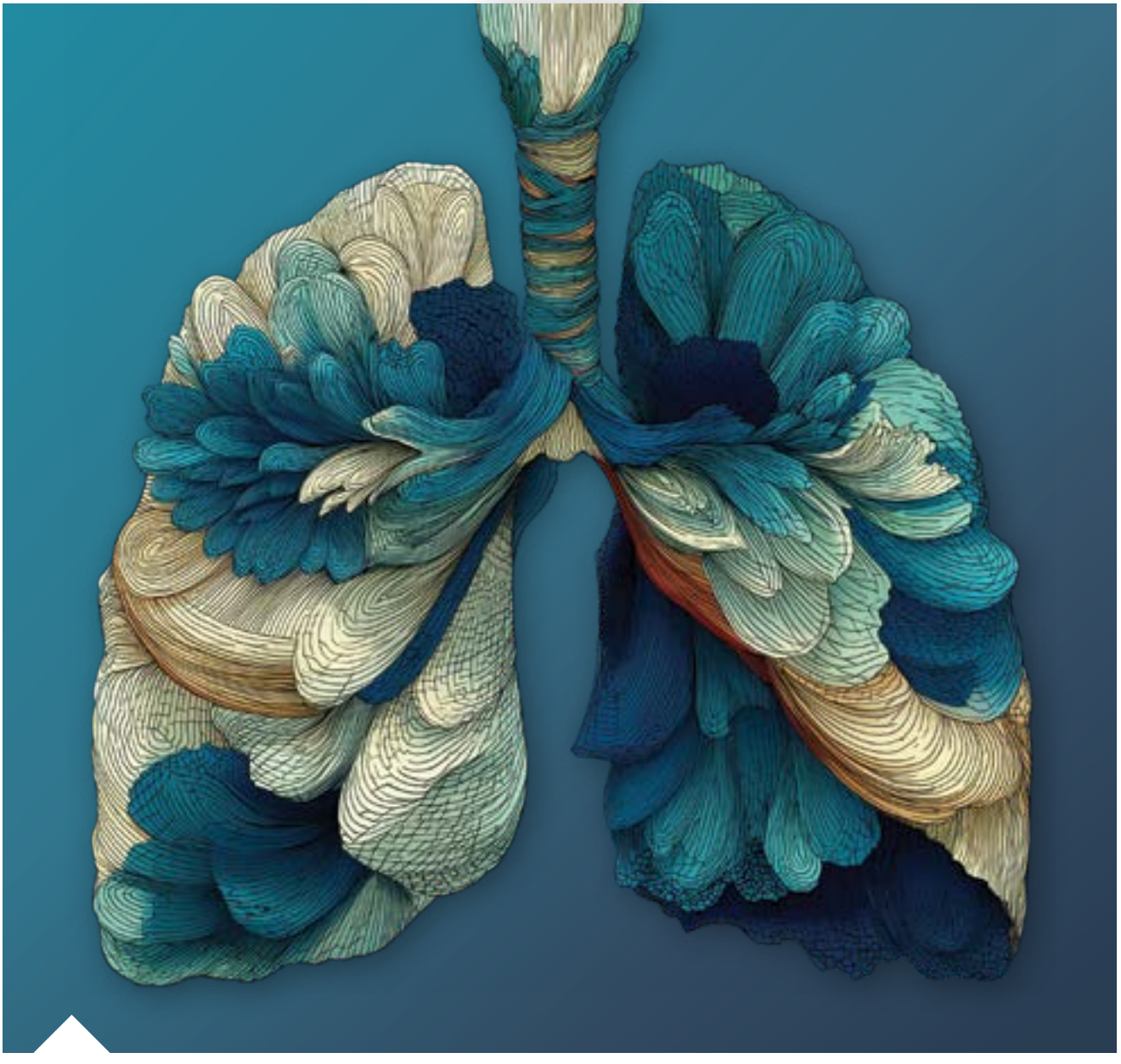

Illustration by Andrew Glazer

GOLD Report 2025 update:

THE CASE FOR *EARLY* INTERVENTION

The latest guidelines encompass a growing body of evidence that clinical outcomes improve when healthcare professionals intervene proactively—before a patient succumbs to hospitalizations, worsening lung function and poor quality of life. Here, experts share strategies for managing COPD with targeted therapies.

The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report marks another step forward in refining chronic obstructive pulmonary disease (COPD) care—not just in terms of what treatments should be recommended, but also how they should be employed in clinical practice. With a renewed focus on exacerbation prevention and precision-based prescribing, the GOLD Report emphasizes that delaying escalation can result in missed opportunities for disease modification.[1] The most notable updates:[1,2]

- **Encourage pre-bronchodilator spirometry** to simplify diagnosis in most patients.
- **Reinforce triple therapy**—inhaled corticosteroid (ICS), long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA)—as the most effective inhaled regimen for exacerbation reduction.
- **Introduce add-on biologic therapy** for patients with chronic bronchitis and high eosinophils who remain uncontrolled on triple therapy.
- **Recommend a dual phosphodiesterase 3 and 4 (PDE3/4) inhibitor** for persistent dyspnea despite dual bronchodilators in patients with chronic bronchitis.
- **Highlight cardiovascular risk, environmental exposures and climate impacts** as integral to COPD management.

These changes reflect a growing body of evidence showing that clinical outcomes improve when healthcare professionals intervene proactively—before repeated hospitalizations, rapid decline in lung function and deteriorating quality of life (QoL) mark a patient's disease trajectory.[3] Below, experts discuss strategies for managing COPD with first-line and add-on treatments.

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Illustration by Andrew Glazer

Initiate triple therapy earlier.

Historically, triple therapy was reserved for GOLD "E-group" patients—those with at least two moderate-to-severe exacerbations or one hospitalization during the previous year.[1] However, real-world clinical experience and modeling studies now suggest that earlier initiation may offer broader benefits, including slowing lung-function decline, improving QoL and reducing symptom burden in patients not adequately controlled with dual therapy.[4]

David Mannino, MD, FCCP, FERS, professor of medicine, Division of Pulmonary, Critical Care and Sleep Medicine at the University of Kentucky College of Medicine and medical director/co-founder of the COPD Foundation, says it makes sense to turn to triple therapy "for people who have had hospitalized COPD exacerbations and are very symptomatic." He adds, "I would guess that most of those people—probably north of 80% or 90%—should be on triple therapy in some way, shape or form."

Dimitrios Kantas, MD, a pulmonologist/intensivist-somnologist and research collaborator at the Mayo Clinic in Rochester, MN, agrees. "Usually, we start with double therapy," Dr. Kantas says. "If they're still symptomatic and they have comorbidities, you start triple therapy earlier."

Choose the right candidates.

Biomarkers are increasingly central to COPD treatment decisions, especially regarding ICS responsiveness.[5] Eosinophil counts, in particular, help distinguish patients with an allergic inflammatory phenotype—those most likely to benefit from ICS-based regimens. The GOLD Report reaffirms that patients with eosinophil levels above 300 cells/μL may be most likely to benefit from earlier initiation of triple therapy and biologic add-on treatment.

"Over the past five to six years, it's become apparent that eosinophils—which are a type of white blood cell—indicate an allergic typology in the patient," Dr. Mannino says. "When that does happen, it's far more likely that those patients are going to be responsive to inhaled steroids." Still, Dr. Kantas highlights the importance of not relying on biomarkers in isolation. He explains that while eosinophils are useful, he focuses primarily on clinical signs—especially changes in sputum, dyspnea and cough—and uses lab values like FEV1/FVC and CRP to support decision-making. "My experience is that most clinicians go straight to the biomarkers and miss the larger picture. I think that's a problem today," he adds.

The role of biologics and other novel therapeutics.

The 2025 GOLD Report introduces several important additions to the COPD treatment landscape—each representing a novel therapeutic class aimed at improving care for patients who remain symptomatic despite standard therapy.[1,2] Dupilumab, a first-in-class, fully human monoclonal antibody (mAb) that blocks IL-4 and IL-13 signaling pathways associated with type 2 inflammation, has been approved for COPD.[6] The GOLD report recommends its use as an add-on to triple therapy in patients with chronic bronchitis, a blood eosinophil count ≥300 cells/μL and a history of two or more moderate exacerbations (or at least one severe exacerbation) in the past year despite therapy with ICS, LABA and LAMA.[1] Clinical trials showed that it improves lung function and QoL in this population.[6,7] Given the targeted mechanism, guidelines say appropriate patient selection and documentation of prior treatment failure are essential before initiating.

Dr. Mannino points out that newer biologics, such as dupilumab, and now, mepolizumab—which was approved for COPD in May 2025—should be considered in patients with allergic typology. He explains that eosinophil counts tend to be lower for people without this allergic type of COPD. "It's an indicator that these allergic-type patients might be more responsive to this type of therapy that targets allergic-type inflammation," he says.

Ensifentrine, in contrast, is not a biologic but a first-in-class inhaled dual PDE3/4 inhibitor with both bronchodilator and anti-inflammatory properties. GOLD recommends ensifentrine as another add-on to dual (LABA/LAMA) therapy in patients who continue to experience persistent dyspnea. It's important to note, however, that although phase 3 trials confirmed improvements in lung function and breathlessness, effects on quality of life were inconsistent and exacerbation data remain limited—especially in patients already on triple therapy.[8]

"Some of the patients have done well on it," Dr. Mannino says about ensifentrine. "It doesn't have a whole lot of side effects, which is one of the problems with many of the other medications we have." He notes, however, that due to the cost, he has just a small number of patients currently using it.

Teach proper inhaler technique.

Regardless of the regimen, improper inhaler technique can dramatically reduce therapeutic benefit. This may be especially true in elderly patients or individuals with cognitive or physical impairments. "Inhaler technique is the most important factor," says Dr. Kantas. "Every time they come into the office, they get trained on the inhaler."

Dr. Mannino echoes this concern, highlighting the unmet need for more user-friendly inhalation devices for patients with COPD. "No medical device we have to treat COPD is as easy to use as a cigarette or a vaping pen," he says. "Unfortunately, all

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> "If [patients] are still symptomatic and they still have comorbidities—you start triple therapy earlier."
>
> *—Dimitrios Kantas, MD*

of our respiratory devices are complex and come with a 30-page instruction booklet."

Both Dr. Kantas and Dr. Mannino recommend caregiver education, video tutorials– which are available on YouTube and the COPD Foundation website– and coordination with pharmacists and other clinical support staff to improve technique and adherence.

Manage comorbidities.

Effective COPD care goes beyond symptom control–it requires a broader view of the patient's overall health. The 2025 GOLD Report reinforces the need to recognize and manage common comorbidities, such as cardiovascular disease, depression and diabetes.[1,2] "COPD doesn't travel alone," says Dr. Mannino. "It tends to travel with things like heart disease, hypertension, diabetes and osteoporosis–all of which can impact COPD patients."

Dr. Kantas notes that comorbid conditions are often a major driver of disease burden, noting that about half of his patients present with coronary heart disease and nearly three out of four have depression. He emphasizes the importance of coordinated care and a multidisciplinary treatment approach. "You need to work with cardiologists, psychiatrists and endocrinologists," he says.

The 2025 GOLD Report now includes a new section on cardiovascular risk, acknowledging increased events like myocardial infarction during and after exacerbations. Identifying these risks early–and treating them appropriately–is critical to improving long-term outcomes and reducing mortality.

Address barriers to treatment.

While early triple therapy has growing clinical support, access to newer inhalers and add-on therapies can be challenging for patients who are uninsured. "You have to demonstrate that they haven't done well on conventional therapies," Dr. Mannino says. Dr. Kantas also points out that there are medical deserts not far outside of many major cities, where some patients may not have access to primary care, let alone a pulmonologist. "Treatment in the U.S. is expensive, and there are many people–maybe 15% to 20%–who don't have insurance."

Drs. Mannino and Kantas emphasize that while patients must advocate for their care, clinicians should educate patients on resources, including patient assistance programs. Several manufacturers have launched programs capping out-of-pocket costs for inhalers at $35 per month for eligible patients. HCPs can also direct patients to sites for savings card enrollment, such as *GoodRx.com*, *ScriptSave.com* and *WellRx.com*. The American Lung Association's Better Breathers Club and Lung Health Navigators (*lung.org*) and the COPD Foundation's COPD 360social (*copdfoundation.org*) offer educational resources, peer support and disease management guidance.

–by Zoe Owrutsky

> "It makes sense to turn to triple therapy for people who have had hospitalized COPD exacerbations and are very symptomatic."
>
> *–David Mannino, MD*

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PRACTICE PEARLS

Educating treatment-naïve patients about COPD

Millions with COPD will join the ranks of those who are unaware they have the disease, even as it progresses.

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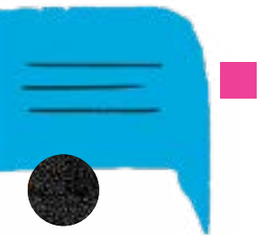

Of the 16 million Americans currently diagnosed with chronic obstructive pulmonary disease (COPD),[1] an estimated one-third are considered treatment-naïve.[2] The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report defines patients with treatment-naïve COPD as those who have not been diagnosed and those who have been diagnosed but have not been treated with an inhaled corticosteroid (ICS), a long-acting antimuscarinic antagonist (LAMA) and/or a long-acting beta-agonist (LABA) in the last 12 months.[2] Most experts also consider treatment-naïve patients to be those who are not on any long-term maintenance therapy. "Early intervention is the best strategy we have," says Diego J. Maselli Caceres, MD, FCCP, professor of medicine, Division of Pulmonary Diseases and Critical Care at Long School of Medicine, UT Health San Antonio. "Screening and diagnosis can lead to treatment, which may prevent further lung damage."

Equally concerning are the low rates of adherence, with less than half of patients following their regimen as prescribed.[2] Studies suggest, however, that educating treatment-naïve COPD patients about disease symptoms and therapies can result in reduced hospitalizations, better quality of life (QoL) and improved self-management.[5] Here are some expert strategies to consider.

Investigate signs of potential COPD.

Asymptomatic patients account for as many as 40% of those with COPD, and clinicians can only evaluate symptoms that their patients report.[5] "Smokers often dismiss key COPD symptoms, such as a nagging cough, fatigue and breathlessness, as part of their smoking habit and delay getting care," Dr. Maselli says. "Lung function decline and damage can be significantly under way by the time they are seen by a provider."

And while smoking remains the primary cause of COPD, data show one-third of patients diagnosed with COPD have never smoked.[4] The GOLD Report also recognizes that COPD can originate from multiple causes, including genetics, occupational and environmental exposures as well as aging, which provides new opportunities for early detection and treatment.[2] "Smoking and other risk factors should be the physician's first line of inquiry, even with patients who are asymptomatic," Dr. Maselli says.

Experts also suggest the use of questionnaires during clinical visits as a valuable tool for patients to self-report COPD symptoms. The modified Medical Research Council (mMRC) Dyspnea Scale, for example, measures breathlessness, a key COPD symptom, based on level of activity[2] (see sidebar on p. 9). Since COPD can mimic other chronic lung conditions, spirometry tests, which Dr. Maselli says are underutilized by clinicians, remain the gold standard for diagnosing and assessment.[2] "If you have a patient with respiratory symptoms and risks for COPD—order the spirometry," Dr. Maselli urges. "Spirometry not only helps HCPs better understand disease severity, but it also gives patients an objective diagnostic metric to help manage their condition."

Optimize initial interventions.

When it comes to treatment-naïve COPD patients, the GOLD Report's recommendations include the use of inhaled dual bronchodilators—a combination of LAMA and LABA—as the first-line intervention for those with moderate symptoms. For those with the mildest symptoms, guidelines say a long-acting bronchodilator is the preferred choice except in patients with very occasional breathlessness.[2]

Since toxicity risks are dose-related, the guidelines do not recommend the use of short-acting bronchodilators on a regular basis, but patients on long-acting bronchodilators may also be prescribed short-acting "rescue" bronchodilators for immediate symptom relief.[2]

Patients whose only therapy has been short-acting bronchodilators are also considered treatment-naïve, says David M. Mannino, MD, FCCP, FERS, professor of medicine, Division of Pulmonary, Critical Care and Sleep Medicine at the University of Kentucky College of Medicine, and medical director/co-founder of the COPD Foundation. "Traditionally, we initially treated COPD with short-acting agents," Mannino says. "But there's been more movement toward combination therapies."

Manage inhaler therapy.

Successful treatment outcomes in COPD depend as much on the inhaler device as on the drug.[2] A variety of inhaler devices are available for delivering treatments to COPD patients, each with benefits and challenges.[2]

"Using an inhaler isn't like taking a pill or an injection," Dr. Mannino says. "Often multiple steps are involved, along with an extensive list of directions. If a person can't use the device correctly, they run the risk of not getting the therapy they need to treat the disease." Experts say that treatment pathways and device selection should be decisions made jointly by clinicians and patients. The GOLD guidelines also provide a set of principles for the shared decision-making process, including device pros and cons as well as a patient's physical and cognitive status.[2]

Educate for adherence.

Research has shown adherence to medication regimens in COPD patients to be less than 50%.[3] Higher education levels and having regular healthcare providers are associated with increased rates of adherence, while the use of multiple medications or having complex treatment regimens is associated with poorer adherence.[3] Less is known about treatment-naïve COPD patients; however, a recent study of those using a prescribed inhaled medication found that patients who understood the serious nature of the disease were more likely to adhere to inhalation therapy.[6]

Other studies have shown that many critical errors by patients are device-specific, with medication persistence after 6 months less likely for patients in treatment with multidose inhalers.[6] "Some devices require one puff a day, others two—some a quick and fast breath, others a slow and steady breath," notes Dr. Mannino. "And you only have so long to get it right for full effectiveness." Experts recommend physicians and nurse practitioners take the time to educate and train patients about the correct use of an inhaler. "Some patients need hands-on help," Dr. Mannino adds. The GOLD guidelines not only recommend this intervention, but also a reassessment of the patient's inhaler technique at every visit and when evaluating treatment response.[2]

Create action plans.

Experts say that drawing up written action plans with newly diagnosed patients will help them manage their COPD and build trust in their clinicians. Having a plan enables treatment-naïve patients to recognize a change in symptoms such as increased breathlessness, cough, sputum or chest tightness and take timely action. Research shows that COPD patients have difficulty recognizing the onset of an exacerbation or flare-up of symptoms for up to 2 weeks, and they delay their decision to seek advice from an HCP, which can lead to hospitalization.[7] "These plans give patients a self-management menu," Dr. Mannino says. "For mild exacerbations, patients taking an extra puff of the bronchodilator may be sufficient, but for moderate exacerbations such as a change in sputum color or cough frequency, patients may need to contact their providers."

Because up to half of COPD exacerbations have a bacterial cause, experts say most of these patients can be managed with antibiotics and stepped-up bronchodilator and corticosteroid

The modified mMRC Dyspnea Scale[2]

The mMRC scale is a self-assessment tool used to measure the level of impairment caused by breathlessness—a key symptom of COPD in many patients, although often unrecognized—during daily activities. Patients are asked to pick one, with the graded scale rated from 0-4.

Grade 0	I only get breathless with strenuous exercise.
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill.
Grade 2	I walk slower than people of my age on level ground because of breathlessness, or I stop for breath when walking at my own pace on level ground.
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
Grade 4	I am too breathless to leave the house, or I am breathless when dressing/undressing.

therapies after an office visit. However, Dr. Mannino says a trip to the ER and hospitalization may be necessary if symptoms become more severe, including shortness of breath, fever, low oxygen levels and swelling of legs and ankles, which can all be signs of heart failure or blood clots. He says the plan should include recommendations for lifestyle changes such as smoking cessation, regular physical activity, a nutritious diet, preventive vaccinations, frequent hand-washing and avoiding sick people to reduce risk of infection.

Stress importance of longer-acting therapy.

Adjustments may be needed after reviewing a patient's response to treatment initiation, depending on documented benefits and exacerbation risks. For example, for those with mild symptoms who experience one exacerbation that doesn't lead to hospitalization for over a year, a long-acting bronchodilator remains an appropriate treatment.[2] However, stepped-up treatment strategies, including double or triple therapy, are recommended for treatment-naïve patients with moderate symptoms who experience up to two exacerbations treated on an outpatient basis—or one leading to hospitalization.[2] "Research shows that one exacerbation is the best predictor of future exacerbations," Dr. Mannino says. "One exacerbation may move clinicians toward a longer-acting maintenance therapy. An acute respiratory tract infection alone could drive that change."

Adopt a holistic perspective.

Studies reveal about half of newly diagnosed treatment-naïve COPD patients with symptoms of respiratory tract infection, including those on short-acting therapies, experienced relapsed or persistent symptoms over a 12-week follow-up.[8] "If you just use lung function as a means of progression, the patient can only get worse," Dr. Mannino says. He and other researchers are now taking a more "holistic" view of COPD progression by developing broader benchmarks around symptomatology, exacerbations and quality of life. "We now recognize that even as lung function continues to decline over time, people with COPD can get better if we reduce or eliminate their exacerbations and decrease their symptoms," says Dr. Mannino. "This can add years not only to their lives by reducing exacerbations, but also add 'life to their years' by decreasing symptoms and improving quality of life." ●

–by Linda Keslar

> "Patients whose only therapy has been short-acting bronchodilators are generally considered treatment-naïve."
>
> *–David Mannino, MD*

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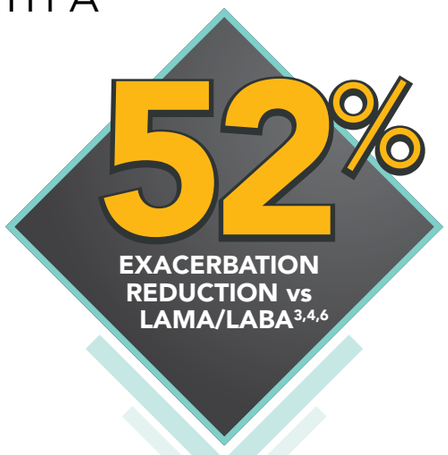
For the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

KRONOS—STUDY 2:

In a 24-week study in which the majority of patients did not have a history of exacerbations within the last year,[4*]

BREZTRI WAS THE ONLY TRIPLE THERAPY[†] TO PREVENT MODERATE OR SEVERE EXACERBATIONS WITH A



Rate ratio: 0.48
unadjusted *P*<0.0001[3,4]

P value is considered unadjusted due to nonsignificant results higher in the testing hierarchy.[4]

18% reduction vs ICS/LABA
(rate ratio=0.82; *P*=0.2792)[3,4]

Annual rate estimate: BREZTRI: 0.46; LAMA/LABA: 0.95; ICS/LABA: 0.56.[4]

*Study 2: Patients (N=1902) were not required to have a history of moderate or severe exacerbations in the year prior to screening.[4]
[†]Fixed-dose combination: ICS/LAMA/LABA.[4]

IMPORTANT SAFETY INFORMATION (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation
- Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap
- Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can 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 during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI
- Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy
- Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur
- If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy
- Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy

For the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

ETHOS STUDY 1*—ANALYSIS

WHAT DOES IT TAKE TO **PREVENT 1 EXACERBATION** WITH **BREZTRI**?

Event-based number needed to treat (NNT)[5,7]

FOR EVERY 7 PATIENTS TREATED OVER A YEAR,

BREZTRI COULD PREVENT 1
ADDITIONAL MODERATE OR SEVERE EXACERBATION vs ICS/LABA[5,7]

For every **3 patients** treated over a year, **BREZTRI** could prevent **1 additional** moderate or severe exacerbation vs LAMA/LABA.

The event-based NNT to prevent 1 moderate or severe exacerbation per year was 3 (95% CI: 3 to 5) for BREZTRI vs LAMA/LABA and 7 (95% CI: 4 to 18) for BREZTRI vs ICS/LABA.[7]

The NNT values reported for ETHOS for the annual rate of COPD exacerbations represent the number of patients needed to treat for 1 year to prevent 1 COPD exacerbation. The NNT is calculated by taking the reciprocal of the absolute risk reduction.[7]

Most common adverse reactions (≥2%) associated with the use of BREZTRI in both studies included upper respiratory tract infection, pneumonia, dysphonia, muscle spasms, back pain, oral candidiasis, influenza, urinary tract infection, cough, sinusitis, and diarrhea.[3]

*Study 1: Patients (N=8588) with ≥1 moderate or severe exacerbation(s) in the year prior to screening. Inclusive of a US patient population.[5]

IMPORTANT SAFETY INFORMATION (cont'd)

- Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate 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
- Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content
- Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur

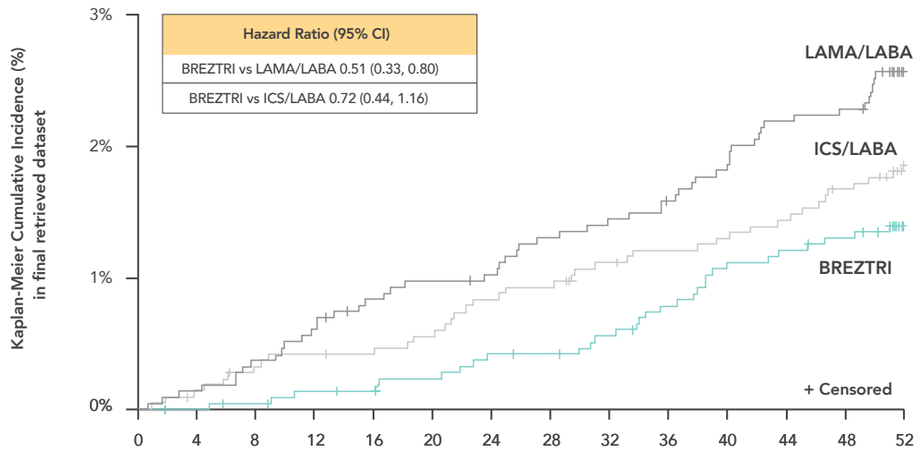
Please see additional Important Safety Information throughout and Brief Summary of Prescribing Information on adjacent pages.

BREZTRI AEROSPHERE®
(budesonide, glycopyrrolate, and formoterol fumarate) Inhalation Aerosol

For the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

ETHOS SECONDARY ENDPOINT:

TIME TO ALL-CAUSE MORTALITY (OVER 52 WEEKS)[8]



Number of Patients at Risk:														
BREZTRI	2137	2136	2134	2131	2130	2127	2123	2122	2118	2112	2106	2103	2100	2075
LAMA/LABA	2120	2117	2112	2106	2100	2097	2095	2089	2086	2082	2077	2069	2067	2045
ICS/LABA	2131	2127	2122	2120	2118	2116	2110	2108	2102	2099	2097	2094	2088	2075

Figure adapted from Martinez FJ, et al. *Am J Respir Crit Care Med*. 2021;203(5):553-564.

Due to nonsignificant results on endpoints higher in the testing hierarchy, these results are observational in nature, and any comparisons between treatment arms should be interpreted with caution.

No drug has been proven to reduce all-cause mortality in patients with COPD.

The analysis of time to death from any cause over 52 weeks was performed in the ITT population with the use of a treatment policy estimand, which included all observed data from the patients regardless of whether they continued to receive their assigned treatment. The effect of ICS withdrawal on these data is unknown.

STUDY DESIGN: **KRONOS**[4,9]

Study 2 design: 24-week, Phase 3, randomized 2:2:1:1, double-blind, multicenter, parallel-group trial of 1902 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=640), GLY/FORM MDI 18/9.6 mcg (n=627), BUD/FORM MDI 320/9.6 mcg (n=316), and open-label BUD/FORM DPI 400/12 mcg (n=319), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies with no requirement for a moderate or severe exacerbation(s) in the previous year. Primary endpoints were FEV_1 AUC_{0-4} for BREZTRI vs BUD/FORM MDI and change from baseline in morning predose trough FEV_1 for BREZTRI vs GLY/FORM MDI at Week 24. Secondary endpoints included the rate of moderate or severe COPD exacerbations.[4] Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics and severe exacerbations as those resulting in hospitalization or death.[9]

STUDY DESIGN: **ETHOS**[5]

Study 1 design: 52-week, Phase 3, randomized 1:1:1:1, double-blind, multicenter, parallel-group trial of 8588 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=2157), BUD/GLY/FORM MDI 160/18/9.6 mcg (n=2137), GLY/FORM MDI 18/9.6 mcg (n=2143), and BUD/FORM MDI 320/9.6 mcg (n=2151), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies, and had a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the annual rate of moderate or severe COPD exacerbations, and secondary endpoints included the annual rate of severe COPD exacerbations and time to death (all cause). Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics and severe exacerbations as those resulting in hospitalization or death.

References: 1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2025 report. Accessed April 29, 2025. https://goldcopd.org/2025-gold-report/ **2.** Data on file, REF-97802, AZPLP. **3.** BREZTRI AEROSPHERE® (budesonide, glycopyrrolate, and formoterol fumarate) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022. **4.** Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial [article and supplementary appendix]. *Lancet Respir Med*. 2018;6(10):747-758. **5.** Rabe KF, Martinez FJ, Ferguson GT, et al; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48. **6.** Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) [package insert]. GSK group of companies, 2023. **7.** Rabe KF, Martinez FJ, Ferguson GT, et al. COPD exacerbation benefits relative to pneumonia risk with budesonide/glycopyrronium/formoterol metered dose inhaler: analyses from ETHOS [abstract]. *Eur Respir J.* 2020;56(suppl 64):5230. **8.** Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease: a randomized, double-blind, multicenter, parallel-group study. *Am J Respir Crit Care Med*. 2021;203(5):553-564. **9.** Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med*. 2018;6(suppl):1-22. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30327-8/abstract

Abbreviations:
AUC_{0-4}=area under the curve from 0-4 hours; BID=twice daily, BUD=budesonide; CI=confidence interval; COPD=chronic obstructive pulmonary disease; DPI=dry powder inhaler; FEV_1=forced expiratory volume in 1 second, FORM=formoterol fumarate; GLY=glycopyrrolate, ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist; MDI=metered dose inhaler.

IMPORTANT SAFETY INFORMATION (cont'd)

- Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines
- Be alert to hypokalemia or hyperglycemia
- Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.1%) and muscle spasms (3.3%)
- BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system
- BREZTRI should be administered with caution to patients being treated with:
  - Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
  - Adrenergic drugs (may potentiate effects of formoterol fumarate)
  - Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
  - Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
  - Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI
- Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

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

You are encouraged to report the negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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AstraZeneca

BREZTRI AEROSPHERE®
(budesonide, glycopyrrolate, and formoterol fumarate) Inhalation Aerosol

BREZTRI AEROSPHERE®
(budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

INDICATIONS AND USAGE
BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

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

CONTRAINDICATIONS
BREZTRI AEROSPHERE is contraindicated in patients who have demonstrated hypersensitivity to budesonide, glycopyrrolate, formoterol, or any of the excipients *[see Warnings and Precautions (5.11) and Description (11) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS
Serious Asthma-Related Events – Hospitalizations, Intubations, Death
The safety and efficacy of BREZTRI AEROSPHERE in patients with asthma have not been established. BREZTRI AEROSPHERE 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 a LABA is 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 do not suggest an increased risk of death with use of LABA in patients with COPD.

Deterioration of Disease and Acute Episodes
BREZTRI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BREZTRI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BREZTRI AEROSPHERE in this setting is not appropriate.

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

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

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of BREZTRI AEROSPHERE should not be increased beyond the recommended dose.

Avoid Excessive Use of BREZTRI AEROSPHERE and Avoid Use with other Long-Acting Beta$_2$-Agonists
As with other inhaled drugs containing beta$_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Patients using BREZTRI AEROSPHERE should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Oropharyngeal Candidiasis
BREZTRI AEROSPHERE contains budesonide, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products containing budesonide. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREZTRI AEROSPHERE continues. In some cases, therapy with BREZTRI AEROSPHERE may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of BREZTRI AEROSPHERE to help reduce the risk of oropharyngeal candidiasis.

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

In a 52-week trial of subjects with COPD (n = 8,529), the incidence of confirmed pneumonia was 4.2% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 2144), 3.5% for budesonide, glycopyrrolate and formoterol fumarate [BGF MDI 160 mcg/18 mcg/9.6 mcg] (n = 2124), 2.3% for GFF MDI 18 mcg/9.6 mcg (n = 2125) and 4.5% for BFF MDI 320 mcg/9.6 mcg (n = 2136).

Fatal cases of pneumonia occurred in 2 subjects receiving BGF MDI 160 mcg/18 mcg/9.6 mcg, 3 subjects receiving GFF MDI 18 mcg/9.6 mcg, and no subjects receiving BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg.

In a 24-week trial of subjects with COPD (n = 1,896), the incidence of confirmed pneumonia was 1.9% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 639), 1.6% for glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg] (n = 625) and 1.9% for budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg] (n = 320). There were no fatal cases of pneumonia in the study.

Immunosuppression and Risk of Infections
Patients who are using drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the Prescribing Information for VZIG and IG). If chicken pox 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; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients from Systemic Corticosteroid Therapy
HPA Suppression/Adrenal Insufficiency
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 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 per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREZTRI AEROSPHERE may provide control of 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 healthcare practitioner 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 BREZTRI AEROSPHERE. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREZTRI AEROSPHERE. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), 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.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids
Transfer of patients from systemic corticosteroid therapy to BREZTRI AEROSPHERE may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

Hypercorticism and Adrenal Suppression
Inhaled budesonide is absorbed into the circulation and can be systemically active. Effects of budesonide on the HPA axis are not observed with the therapeutic doses of budesonide in BREZTRI AEROSPHERE. 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) and Drug Interactions (7.1) in the full Prescribing Information]*.

Because of the possibility of significant systemic absorption of ICS, patients treated with BREZTRI AEROSPHERE 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 initiated as needed.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of BREZTRI AEROSPHERE with long-term ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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

Hypersensitivity Reactions including Anaphylaxis
Immediate hypersensitivity reactions have been reported after administration of budesonide, glycopyrrolate or formoterol fumarate, the components of BREZTRI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips, and face), urticaria, or skin rash, BREZTRI AEROSPHERE should be stopped at once and alternative treatment should be considered *[see Contraindications (4) in the full Prescribing Information]*.

Cardiovascular Effects
Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

If such effects occur, BREZTRI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, BREZTRI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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 (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREZTRI AEROSPHERE and periodically thereafter. If significant reductions in BMD are seen and BREZTRI AEROSPHERE is still considered medically important for that patient's COPD therapy, use of therapy to treat or prevent osteoporosis should be strongly considered.

In a subset of COPD patients in a 24-week trial with a 28-week safety extension that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg and GFF MDI 18/9.6 mcg, the effects on BMD endpoints were evaluated. BMD evaluations were performed at baseline and 52-weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean percent changes in BMD from baseline was -0.1% for BREZTRI AEROSPHERE 320/18/9.6 mcg and 0.4% for GFF MDI 18/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

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

In a 52-week trial that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg, GFF MDI 18/9.6 mcg, and BFF MDI 320/9.6 mcg in subjects with COPD, the incidence of cataracts ranged from 0.7% to 1.0% across groups.

Worsening of Urinary Retention
BREZTRI AEROSPHERE, like all therapies containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

Hypokalemia and Hyperglycemia
Beta-adrenergic agonists 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$_2$-agonist therapies may produce transient hyperglycemia in some patients.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Oropharyngeal candidiasis infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression and risk of infections *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10) in the full Prescribing Information]*
- Hypersensitivity reactions including anaphylaxis *[see Contraindications (4) and Warnings and Precautions (5.11) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma and cataracts *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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

The safety of BREZTRI AEROSPHERE is based on the safety data from one 52-week exacerbation trial (Trial 1) and one 24-week lung function trial with a 28-week safety extension study, resulting in up to 52 weeks of treatment (Trial 2). In Trials 1 and 2, a total of 2783 subjects have received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trials 1 and 2, subjects received one of the following treatments: BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg], or budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg]. Each treatment was administered twice daily.

In Trial 1, a 52-week, randomized, double-blind clinical trial, a total of 2144 subjects with COPD received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 64.7 years, 84.9% Caucasian, 59.7% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trial 2, a 24-week, randomized, double-blind clinical trial, with a 28-week long-term safety extension resulting in up to 52 weeks of treatment, a total of 639 subjects received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 65.2 years, 50.1% Caucasian, 71.2% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

The incidence of adverse reactions from the 52-week trial (Trial 1) is presented in Table 1 for subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, GFF MDI 18 mcg/9.6 mcg, or BFF MDI 320 mcg/9.6 mcg.

Table 1: Adverse reactions occurring at an incidence of ≥ 2% of subjects and more common in BREZTRI AEROSPHERE compared to GFF MDI and/or BFF MDI (Trial 1)

Adverse Reaction	BREZTRI AEROSPHERE[1] 320 mcg/18 mcg/9.6 mcg N=2144 (%)	GFF MDI[1] 18 mcg/9.6 mcg N=2125 (%)	BFF MDI[1] 320 mcg/9.6 mcg N=2136 (%)
Upper Respiratory Tract Infection	123 (5.7)	102 (4.8)	115 (5.4)
Pneumonia	98 (4.6)	61 (2.9)	107 (5.0)
Back pain	67 (3.1)	55 (2.6)	64 (3.0)
Oral candidiasis	65 (3.0)	24 (1.1)	57 (2.7)
Influenza	63 (2.9)	42 (2.0)	61 (2.9)
Muscle spasms	60 (2.8)	19 (0.9)	53 (2.5)
Urinary tract infection	58 (2.7)	60 (2.8)	41 (1.9)
Cough	58 (2.7)	50 (2.4)	51 (2.4)
Sinusitis	56 (2.6)	47 (2.2)	55 (2.6)
Diarrhea	44 (2.1)	37 (1.7)	38 (1.8)

[1] BREZTRI AEROSPHERE = budesonide/glycopyrrolate/formoterol fumarate 320 mcg/18 mcg/9.6 mcg; GFF MDI = glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; BFF MDI = budesonide/formoterol fumarate 320 mcg/9.6 mcg; all treatments were administered twice daily.

In 24-week data from Trial 2, adverse reactions that occurred in subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n=639) at an incidence of ≥ 2% included dysphonia (3.1%) and muscle spasms (3.3%).

Additional Adverse Reactions
Other adverse reactions that have been associated with one or more of the individual components of BREZTRI AEROSPHERE include: hyperglycemia, anxiety, insomnia, headache, palpitations, nausea, hypersensitivity, depression, agitation, restlessness, nervousness, tremor, dizziness, angina pectoris, tachycardia, cardiac arrhythmias (e.g., atrial fibrillation, supraventricular tachycardia, and extrasystoles), throat irritation, bronchospasm, dry mouth, bruising, urinary retention, chest pain, sign or symptoms of systemic glucocorticoid steroid effects (e.g., hypofunctional adrenal gland), and abnormal behavior.

DRUG INTERACTIONS
No formal drug interaction studies have been performed with BREZTRI AEROSPHERE.

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

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

Xanthine Derivatives, Steroids, or Diuretics
Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of beta$_2$-adrenergic agonists such as formoterol, a component of BREZTRI AEROSPHERE.

Non-Potassium Sparing Diuretics
The hypokalemia and/or ECG changes that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta$_2$-agonists, especially when the recommended dose of the beta$_2$-agonist is exceeded.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs
BREZTRI AEROSPHERE, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-adrenergic Receptor Blocking Agents
Beta-adrenergic receptor antagonists (beta-blockers) and BREZTRI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta$_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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

OVERDOSAGE
No cases of overdose have been reported with BREZTRI AEROSPHERE. BREZTRI AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BREZTRI AEROSPHERE. Treatment of overdosage consists of discontinuation of BREZTRI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Budesonide
If used at excessive doses for prolonged periods, systemic corticosteroid effects, such as hypercorticism may occur *[see Warnings and Precautions (5.8) in the full Prescribing Information]*.

Glycopyrrolate
High doses of glycopyrrolate, a component of BREZTRI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation, or difficulties in voiding.

Formoterol Fumarate
An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest, and even death may be associated with overdosage of formoterol fumarate.

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PATIENT ENGAGEMENT

The high risk of vaping—*easier to inhale*, harder to kick

The convenience of vaping devices often leads to more frequent use and increased nicotine consumption compared to traditional cigarettes—potentially making them harder to quit. Here's what experts say about the dangers of vaping and ways to help your patients kick the habit.

While cigarettes remain the most commonly used tobacco product among adults, the number of people using electronic cigarettes or vapes has increased in recent years.[1] Quitting any kind of cigarette is difficult, but vaping devices deliver nicotine more easily and more discreetly, making them effortless to use more often in more places–and even tougher to quit. Yet another obstacle for those trying to quit smoking combustible cigarettes is the mistaken belief that e-cigarettes are a "safer" or "healthier" alternative. One study found that COPD patients who switched to e-cigarettes did so because they thought it would help with exacerbations.[2]

"There are conversations about these products being safer than combustible cigarettes, but it's a risk reduction, not a risk removal," says pulmonologist Panagis Galiatsatos, MD, associate professor of medicine in the Division of Pulmonary & Critical Care Medicine at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine, Baltimore, MD. "For patients who want to stop vaping, you should approach vaping cessation like you would with a traditional cigarette but be aware that these products tend to be introduced at a higher frequency than traditional cigarettes because we've made it harder for people to smoke," says Dr. Galiatsatos. "I'd advise physicians to be mindful that coming off a vape is likely harder than coming off a traditional cigarette."

The dangers of e-cigarettes

Toxic chemicals in the aerosol

Patients need to know that smokeless vapor can still deliver a lot of damage, especially to patients with COPD. Like regular cigarettes, vaping can lead to reduced lung function, shortness of breath, cough, sleep disorders, brain health concerns and heart problems.[3] A recent review of popular disposable e-cigarette vapes also found high levels of metals in the vapors.[4] The CDC reported 2,807 instances of lung damage in 2020 associated with e-cigarette and vaping products.[5] "There are still noxious chemicals that are going to be inhaled with vaping, and they can create an insidious, abhorrent inflammatory response," says Dr. Galiatsatos.

Dr. Galiatsatos advises clinicians to look for subtle symptoms in patients with COPD who are vaping as a way to cut back on smoking regular cigarettes. "What I usually tell healthcare professionals to ask is: 'Does the patient have an infection or a respiratory bug that lingers far beyond what you would have expected?' 'Are their pulmonary symptoms a little bit more refractory to control?' and 'Is there a cough that comes on that kind of lingers longer than they expected it to?'"

Mary Martinasek, PhD, a respiratory therapist, director, Center for Teaching and Learning, and professor of public health at the University of Tampa in Tampa, FL, says, "Vapes begin to degrade the airways of their protective capabilities. Whether you're a young adult who's only smoked e-cigarettes or an older cigarette smoker who's transitioned to vapes, there are chemicals and carcinogens in the vapor that increase the potential for cancers and negative health effects down the road," she says. "It can show up as internal effects, such as blood flow restrictions," she explains. "Even younger patients and athletes say that they can't exercise as long and that they feel worn out."

Faster delivery, varying nicotine levels

When trying to get patients to quit smoking, healthcare professionals need to keep in mind that they are dealing with a nicotine addiction and nicotine-related behavior, Dr. Galiatsatos says. "If they're taking in nicotine levels two or three times more than a traditional cigarette, and our nicotine-replacement therapy (NRT) options cap at 21 mg, doctors need to know that it's going to take a lot longer to get them off these products," says Dr. Galiatsatos. "It's a challenging product to step down from because the physician and patient may not know how much nicotine they are taking in, despite what it says on the packaging," says Martinasek.

Fewer barriers to use

Users tend to vape more frequently throughout the day due to the convenient and discreet mode of delivery. While there are often "no smoking" signs all over the country indoors, vaping hasn't yet been restricted in the same way as regular cigarettes, which can make it more challenging to quit. "Be mindful that these patients are going to struggle a lot more with environmental triggers and, in many cases, patients who vape often do it at higher levels than the traditional combustible cigarette," says Dr. Galiatsatos.

Unregulated ingredients

As of July 2025, the FDA has authorized the sale of 39 tobacco e-cigarette products and devices.[6] And though the FDA says the approved products have undergone scientific review, experts counter that people who vape don't understand exactly what they're inhaling. "The difference between tobacco cigarettes and vaping is that there's so much variability in electronic cigarette devices," says Dr. Galiatsatos. "With electronic cigarettes, there are five generations, and I haven't met a single physician who knows how to identify them all," he adds. "The chemicals in them aren't as well-regulated and some of them are very malleable, so patients may add more nicotine. And e-cigarettes may have synthetic nicotine, which still drives a nicotine addiction."

The lack of regulation, Martinasek notes, makes it impossible to know what's in a vape unless it is tested in a lab, which is difficult to have done. "The majority of vapes come from China, and we've had reports of sedatives being discovered," she says.

The cessation strategies that work

Identify the "why" that's driving the habit

"Strategies around smoking cessation include learning about triggers and when the cravings hit," Dr. Galiatsatos says. "Patients must learn how to 'un-smoke,' or how to replace the cigarette with something safer. I find that patients are very resistant [to cessation] because the cigarette means something to them." He says clinicians need to help the patient understand cessation as a quality of life improvement and that getting off all smoking products can help with COPD symptoms.

Refer patients to cessation experts

Like regular cigarettes, stress is a major factor in why people smoke. The American Lung Association also estimates that at least 35% of smokers also have some kind of mental health con-

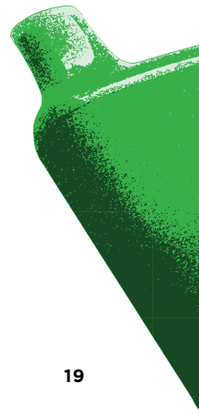

Illustration by Getty Images / smartboy10

dition.[7] Because of this, physicians should recommend mental health support for vape cessation to patients who are trying to quit.

"I've had patients who struggle with depression, and the freebase nicotine [in vapes] eases that symptom," says Dr. Galiatsatos. Research has found cognitive behavioral therapy (CBT) to be helpful with smoking cessation and addictions in patients with depression; studies show it can be particularly effective when used in combination with NRT.[8]

Martinasek also suggests referring patients to a respiratory therapist (RT). She says RTs are trained in smoking cessation, and many are also tobacco treatment specialists so they can work with patients to address their triggers, cravings and nicotine addictions.

Recommend nicotine replacement therapies

FDA-approved nicotine NRTs are an important tool to help patients reduce their cravings. Scientific studies show that using NRTs (such as patches, gum, lozenges, sprays or inhalers) can increase the chances of successfully quitting smoking by as much as 50%-70%.[9] They deliver controlled doses of nicotine, which gradually decreases nicotine intake and reduces withdrawal symptoms.

Talk to your patients about which NRT delivery system works best for them. Combining different forms of NRT can be even more effective, as it addresses both baseline cravings and breakthrough urges. Dr. Galiatsatos also notes that tailoring NRT dosage to match vape-use intensity might require trial and error.

Discuss habit changes

In addition to emotional triggers, smokers often use cigarettes and vapes out of sheer habit. Consider sharing these smoking cessation tips with your patients:

- **Choose a quit date.** Setting a specific quit date helps them mentally prepare, makes their intention concrete and allows them to plan for challenges.
- **Replace a cigarette with a cinnamon stick.** The American Cancer Society recommends using cinnamon sticks, which mimic the hand-to-mouth action and oral stimulation of smoking, to help reduce cravings.[10] If cinnamon sticks aren't appealing, choose a similarly shaped oral substitute to help manage cravings.
- **Take a different route away from where they purchase smoking products.** Altering their routine can help avoid triggers and cues associated with smoking (such as passing the usual convenience store that sells vape juice or e-juice).
- **Drink cold water.** Drinking cold water can help curb cravings, provide oral stimulation and keep patients hydrated as a bonus.

Help them build a support system

Encourage patients to tell friends and family they're quitting. This can give them a built-in support system to offer encouragement and provide accountability. Friends and family can also help patients stay motivated and celebrate their progress, making relapse less likely. In addition, patients can find support digitally at:

- The American Lung Association's program "Freedom From Smoking," which offers online resources including peer support groups (*lung.org/quit-smoking*).
- *Smokefree.gov*, a CDC program where patients sign up for texts that provide motivation, reminders, tips and encouragement, as well as lists of activities that may keep them occupied when cravings hit.

–by Diana Kelly Levey

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PATIENT: CAROL, 72, DEVELOPED COPD THROUGH SECONDHAND SMOKE. SHE ALSO HAD A HISTORY OF BREAST CANCER AND OTHER COMORBIDITIES.

"Carol was wheezing more and felt her therapy wasn't working as well as before"

PHYSICIAN:

David Mannino, MD, FCCP, FERS

Professor of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of Kentucky College of Medicine, Lexington, KY; Medical Director/Co-Founder, COPD Foundation

Illustration by Juhee Kim

Treatment history:
Carol was referred to me three years ago for COPD. She was a never-smoker but was married to a heavy smoker for 42 years. Her husband had died of lung cancer six years earlier. She had retired from her job as a manager in a dental office. In addition to COPD, Carol had mild hypertension, which was controlled with diet and a diuretic taken daily. She was also diagnosed with breast cancer 15 years ago, which was treated with surgery and radiation. At that time, her pulmonary function test results showed an FEV1 of 51% and an FVC of 60%, with an FEV1/FVC ratio of 0.85. After 4 puffs of albuterol, her FEV1 improved to 60% and FVC to 70% with FEV1/FVC of 0.62. She was prescribed fluticasone/salmeterol in a dry powder inhaler (DPI) to be used twice daily. She also took albuterol in a metered dose inhaler 4 to 5 times daily.

At her most recent visit, Carol told me she didn't feel as though her medication was working as well as it had previously. She had to visit the emergency room the month before I saw her, and she was treated with a course of antibiotics and steroids. She reported being short of breath on minimal exertion and felt like she was wheezing more. Her physical examination was normal except for decreased breath sounds and wheezing.

We did a COPD Assessment Test (CAT), which had a score of 22. Pulmonary function testing showed an FEV1 of 38% and FVC of 59% with an FEV1/FVC of 0.55. After a bronchodilator, her FEV1 improved to 45% and FVC to 63% with an FEV1/FVC of 0.66. Her peak inspiratory flow (PIF) was measured at 40 L/min. Because of her worsening symptoms, she has not been able to exercise as much as she had previously. Considerations for Carol's management included her worsening symptoms, elevated CAT score, low PIF and decreased exercise capability.

Initiating treatment:
Carol's medication was changed to triple therapy with ICS/LAMA/LABA in a metered dose inhaler (MDI) that she would use with a spacer. She was also prescribed albuterol, which would be administered with a nebulizer. In addition, she was referred to pulmonary rehabilitation–her first time in pulmonary rehab. Her worsening symptoms, recent exacerbation and decreased lung function led to my decision to increase her therapy. Because of her low PIF, I decided to use an MDI as opposed to a DPI, because the MDI can be used with a spacer. I instructed Carol to use the medication twice daily. In addition, she had a nebulizer that could be used for short-acting relief.

At her six-week follow-up visit, Carol said that she felt like her medication was getting into her lungs better with the spacer. She also reported doing well in pulmonary rehabilitation and said she felt as if it helped improve her exercise capacity.

Considerations:
Triple therapy is an important treatment consideration in COPD patients who are having ongoing symptoms and exacerbations on their current therapy. Adding a spacer also can improve medication delivery to the lungs, especially for those who find it difficult to coordinate the inhaler actuation with inhalation. It's important to note that not all triple therapies are the same. Patients who have low PIF will do better with an MDI rather than a DPI, as they use the former with a spacer. Pulmonary rehabilitation is also an essential intervention for most patients, because it addresses many important components of optimizing health in people with COPD, such as exercise, diet and vaccinations.

> "Triple therapy is an important treatment consideration in COPD patients who are having ongoing symptoms and exacerbations on their current therapy."

Q

A

Expert insight on COPD management

Reducing secondhand smoke

Q: What do you suggest to patients who have quit smoking but still live with a smoker?

A: While the ideal scenario is for patients to completely avoid exposure to any smoke, situations like cohabitation with a smoker can make this more challenging. However, several steps can minimize an individual's exposure to secondhand smoke.

Designating a separate smoking area, ideally outdoors and as far from the living space as possible, is one of the most effective strategies. This creates a clear boundary and reduces the likelihood of smoke drifting indoors. Additionally, using HEPA filters in the home can significantly decrease airborne smoke particles and improve air quality. Regularly cleaning carpets, upholstery, curtains, and other fabrics that can trap smoke particles also helps reduce residual exposure.

–Diego Marin, DO, *Pulmonologist and Intensivist, West Palm Beach VA Healthcare System; Clinical Affiliate Assistant Professor of Pulmonary Medicine, Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL*

Assuaging exercise fears

Q: How do you counsel patients who are afraid to engage in physical activity because they think it's unsafe?

A: To say I'm a strong advocate for staying physically active would be an understatement, especially given the overwhelming medical evidence supporting its benefits. As a pulmonologist, I frequently refer patients to pulmonary rehabilitation, which we know can significantly reduce the frequency and severity of pulmonary exacerbations while improving overall quality of life.

I also prioritize maintaining an active lifestyle myself and encourage my patients to do the same. I'm sure many of my patients have heard me say, "Frailty is death," a phrase that highlights the critical importance of preserving skeletal muscle and strength for long-term health. Maintaining muscle mass is essential not just for lifespan but also for extending health span—the period of life during which we remain healthy and functional.

In addition to focusing on health benefits, I incorporate principles of longevity into patient care. I often ask patients to imagine what they would like their lives to look like at 70, 80, 90 and beyond. Do they want to be able to travel, hike, or simply play with grandchildren? Once they have that mental picture, we can work backward to create a plan that identifies the physical abilities they need to maintain to achieve those future goals.

–Diego Marin, DO

AI-generated using Midjourney

Keys to self-management

Q: Along with taking their medication as prescribed, what else can help patients manage their COPD?

A: This has been an interesting issue for physicians managing COPD patients. The American College of Chest Physicians emphasizes the importance of patient education, action plan development and case management in enabling patients to manage their disease effectively. The key components of self-management include:

- **Education.** Providing patients with comprehensive information about the disease, signs of progression, signs of exacerbation, proper inhaler technique and proper immunizations.
- **Action plans.** Developing individualized action plans that help patients identify worsening symptoms and what to do and when to seek medical help promptly.
- **Behavioral interventions.** Lifestyle changes such as smoking cessation, healthier nutritional habits, regular physical activity and exercise and, if indicated, pulmonary rehabilitation.
- **Psychosocial support.** Addressing anxiety and depression, which can significantly affect disease management and quality of life. This support may come from family, mental health providers or support groups.
- **Regular monitoring and feedback.** Continuous assessment and feedback from healthcare professionals to ensure that self-management strategies are effective and to make the necessary adjustments when needed.

–Michael Ghobrial, MD, *Pulmonary Physician, Medical Director of Pulmonary Rehabilitation and Respiratory Therapy, Cleveland Clinic, OH*

Overcoming inhaler challenges

Q: What do you recommend to patients who are having difficulty using their inhalers?

A: Proper inhaler technique is one of the cornerstones of treatment for patients with COPD. Struggling to correctly use the prescribed inhaler is the reason many patients report persistence of symptoms and failure of therapy. It's crucial for clinicians to choose the most appropriate inhaler for each patient and to educate patients on how to use their inhalers. There is a plethora of inhalers, and patients' needs differ considerably. Moreover, a single patient may end up needing to use 2-3 different inhalers at one point and should be instructed on the proper use of each of them. Data from a randomized controlled trial in Switzerland in 2018 showed that incorrect inhaler use ranged from 0% to 53% depending on the type of inhaler. In a recent report published in CHEST, approximately two-thirds of hospitalized adults with COPD had improper inhaler technique as the main contributor to suboptimal treatment with inhalers.

If a patient is struggling to use their inhaler, I recommend discussing options like using a spacer device or switching to a different type (like a dry powder). For patients who have difficulties using different types of inhalers, nebulized breathing treatments provide the best way to deliver the medications to them more efficiently, especially for young children or those with severe difficulty inhaling medication properly.

–Michael Ghobrial, MD

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EXAM TOOL

Assessing severity of COPD symptoms

Updates in the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report reflect the latest evidence-based strategies for proactively managing COPD at all levels of disease severity. One feature to note: a treatment algorithm that highlights escalating therapy after a moderate-to-severe exacerbation or hospitalization to help prevent future episodes. Other things to weigh include a change in how patients feel or their level of activity. When assessing worsening symptoms—which may require more aggressive therapy—consider the following criteria.

DYSPNEA *(based on mMRC Dyspnea Scale)*

Ask patients which of the following best describes them:

Mild
- ☐ I only get breathless with strenuous exercise.

Moderate
- ☐ I get short of breath when hurrying on level ground or walking up a slight hill.

Moderate-to-severe
- ☐ I walk slower than people of my same age because of breathlessness.
- ☐ I have to stop for breath when walking at my own pace on level ground.
- ☐ I can't do my usual exercise routine, or I don't do it as often, because I get breathless.

Severe
- ☐ I stop for breath after walking a few yards, or a few minutes, on level ground.
- ☐ I get breathless walking to or back from the mailbox.

Most severe
- ☐ I am too breathless to leave the house.
- ☐ I am breathless when dressing or undressing.

OTHER SIGNS *(based on COPD Assessment Test)*

Ask patients to rate the following based on a scale of 0 (not a problem) to 5 (a major problem):

Cough
0 1 2 3 4 5

Mucus in chest
0 1 2 3 4 5

Chest tightness
0 1 2 3 4 5

Limited in doing activities at home
0 1 2 3 4 5

Not confident leaving home because of lung problems
0 1 2 3 4 5

Poor sleep
0 1 2 3 4 5

Little or no energy for everyday activities
0 1 2 3 4 5

Source: *goldcopd.org*.