COPD is characterized by chronic respiratory symptoms (eg, dyspnea, cough, sputum production) caused by pathologic changes in the airway or alveoli; these changes result in chronic and progressive airway obstruction.\textsuperscript{1} Patients often report chronic cough (with or without sputum) and shortness of breath that restrict their ability to perform daily activities, along with acute exacerbations during which symptoms increase in severity.\textsuperscript{1} Exposure to tobacco smoke is the leading risk factor for COPD in high-income countries such as the United States, although exposure to burning biomass (eg, wood, animal waste, crop residue, coal) is also a key risk factor that contributes to a greater proportion of the total COPD burden in low- to middle-income countries.\textsuperscript{1,2} Patient factors, such as abnormal development and aging of the lungs, also likely contribute to the development of COPD.\textsuperscript{1} Mutation in the SERPINA1 gene, which leads to α-1 antitrypsin deficiency, is the most significant (albeit uncommon) genetic risk factor for COPD; other genetic variants with a low individual effect size are associated with altered lung function and risk for COPD.\textsuperscript{1}

Comorbidities are common in patients with COPD and can affect COPD-related outcomes.\textsuperscript{3} Many comorbidities have shared risk factors (eg, cigarette smoking increases risk for both COPD and lung
The economic costs of COPD are likely higher than published numbers, because only about half of patients with symptoms of COPD receive a diagnosis.

Michael Hess, MPH, RRT, RPFT

(CONTINUED ON PAGE 10)
consider when managing patients with COPD. Cardiovascular disease is particularly prevalent among patients with COPD, although metabolic syndrome, osteoporosis, and skeletal muscle dysfunction are also important comorbidities; they may develop from the decreased mobility associated with COPD. Depression and anxiety are also common in patients with COPD and may result from limitations in daily activity caused by poor lung function.

The direct and indirect economic costs of COPD are likely higher than published numbers, because only about half of patients with symptoms of COPD receive a diagnosis, and the disease imposes a constant social burden for patients, explained Mike Hess, MPH, RRT, RPFT, senior director of public outreach and education at the COPD Foundation in Kalamazoo, Michigan. Additionally, the withdrawal from social activities and the psychological burden related to their smoking habit’s contribution to their COPD can also add to their depression, which may, in turn, worsen other comorbidities.

“Breathing literally affects every moment of your day, waking or not,” Hess said. “If you’re getting out of breath going to check your mail or going to use your restroom, you probably won’t do a lot of the things that engage you in your community. You may become withdrawn from your family, you may leave the workforce earlier, or you may have absenteeism. You’re not going to be involved in church or spiritual events.”

According to Hess, patients with low SES are hit with a “double whammy,” because they (1) are particularly prone to start smoking and to live in an environment with poor air quality indoors and outdoors, and (2) encounter barriers to accessing care once they receive a diagnosis. He added that exposures to poor air quality often extend back to the patient’s youth, with exposure to burning biomass in the house being a key factor in many rural areas of the United States. Addressing these factors is complex, said Hess, but screening for COPD at an earlier age, before lung damage has occurred and symptoms restrict activities of daily living, is likely to have the greatest immediate effect on improving patient outcomes.

GUIDELINE-BASED DISEASE MANAGEMENT IN COPD

According to the GOLD guidelines, smoking cessation is the cornerstone of COPD management and has the strongest ability to affect the natural history of the disease.1 Nicotine replacement products are more effective than placebo in terms of increasing long-term rates of smoking cessation, and pharmacologic agents such as varenicline, bupropion, and nortriptyline may be considered in conjunction with a behavioral intervention program.1 Intensive counseling from physicians and other health care professionals is more effective than self-initiated strategies for increasing cessation rates, and using a combination of pharmacologic therapy and behavioral counseling further increases cessation rates.1

Pharmacologic therapy is recommended for patients with stable COPD to decrease symptoms and exacerbations and to improve exercise capacity and health status.1 Bronchodilation with combinations of drugs that have different mechanisms of action and durations of effect may improve bronchodilation and reduce risk for adverse effects compared with escalating the dose of a single bronchodilator.2 The most commonly used bronchodilators in COPD are β2-agonists, which activate β2-adrenergic receptors to relax airway smooth muscle, and antimuscarinic drugs, which reduce bronchoconstriction by interfering with the binding of acetylcholine to M3 muscarinic receptors in airway smooth muscle.1 Long-acting versions of β2-agonists (LABAs) and antimuscarinic agents (LAMAs) are generally used for management of stable disease, with short-acting versions used on an as-needed basis but generally not recommended for regular use.1 The results of a Cochrane review that included 10 trials involving 10,894 patients with COPD (most with moderate or severe disease) showed that treatment with a combination of the LAMA tiotropium and a LABA led to a greater improvement in mean health-related quality of life, as measured by the St George’s Respiratory Questionnaire, compared with tiotropium alone (mean difference, −1.34; 95% CI, −1.87 to −0.80; P < .0001) or a LABA alone (mean difference, −1.25; 95% CI, −2.14 to −0.37; P = .01).6 Addition of a LABA to tiotropium also yielded a small, but significant, mean increase in prebronchodilator FEV1 (mean difference, 0.06; 95% CI, 0.05−0.07; P < .0001).7 Multiple LABA-LAMAs combinations are available in a single device and are dosed every 12 to 24 hours.1

Inhaled corticosteroids (ICS) alone have limited effectiveness in reducing long-term decreases in FEV1 and rates of mortality in patients with COPD; however, the results of a Cochrane review showed that adding an ICS to LABA therapy was associated with lower exacerbation rates (rate ratio, 0.76; 95% CI, 0.68-0.84; P < .0001), less use of rescue medication, and better improvement in health-related quality of life, symptoms, and FEV1 compared with LABA monotherapy.1 Triple therapy with an ICS, a LABA, and a LAMA in a single inhaler device may be more effective for reducing moderate to severe exacerbations than is ICS-LABA or LABA-LAMA single-inhaler dual therapy in patients with symptomatic COPD and frequent exacerbations. Investigators of the IMPACT trial (NCT02164513) randomly assigned 10,355 patients 40 years or older with symptomatic COPD (FEV1 < 50% of the predicted value and ≥1 moderate or severe exacerbation within the past year, or an FEV1 of 50% to 80% of predicted value with ≥2 moderate or 1 severe exacerbation in the past year) to either the triple therapy or one of the 2 dual therapies.8 In this study, the patients who received ICS-LABA-LAMA triple therapy (ie, fluticasone furoate, umclidinium, and vilanterol) had a lower rate of moderate or severe exacerbations during the 52-week treatment period than did those who received dual therapy with ICS-LABA (0.91 vs 1.07, respectively; rate ratio, 0.85; 95% CI, 0.80−0.90; P < .001) or with LABA-LAMA (0.91 vs 1.21, respectively; rate ratio, 0.75; 95% CI, 0.70−0.81; P < .001).8 However, while triple therapy was associated with a lower annual exacerbation rate than were the
other treatments regardless of patient eosinophil count, the treatment difference was smaller in those with blood eosinophil counts of less than 150 cells/μL (triple therapy, 0.85 [95% CI, 0.80-0.91]; ICS-LABA, 1.06 [95% CI, 0.99-1.14]; and LABA-LAMA, 0.91 [95% CI, 0.88-1.07]) and greater in those with blood eosinophil counts greater than 150 cells/μL (triple therapy, 0.95 [95% CI, 0.90-1.01]; ICS-LABA, 1.08 [95% CI, 1.02-1.14]; and LABA-LAMA, 1.39 [95% CI, 1.29-1.51]). The results of a post hoc analysis of 3 randomized trials (NCT00206167, NCT00206154, and NCT00419744) also showed that addition of the ICS budesonide to the LABA formoterol led to a significant reduction in exacerbations when eosinophil counts were 100 cells/μL or more, and the mean exacerbation rate ratio was less than 0.5 when eosinophil counts were greater than 340 cells/μL. The GOLD guidelines state that this cutoff of 100 cells/μL can be used to estimate likelihood of benefit from ICS therapy, but assessment of exacerbation risk should also be considered when deciding whether to include ICS in the therapeutic regimen.

Although the adverse effect profiles were similar among triple therapy and both dual therapy combinations in the IMPACT trial, a higher incidence of pneumonia was observed in groups that received ICS than in the group that received LABA-LAMA, and the triple therapy group had a significantly higher risk for clinician-diagnosed pneumonia compared with the LABA-LAMA group (HR, 1.53; 95% CI, 1.22-1.92; P < .001), although the pneumonia risk was similar between the ICS-containing groups. In the SUMMIT trial (NCT01313676), the rate of pneumonia was not increased with fluticasone furoate (either alone or in combination with the LABA vilanterol) in patients with moderate COPD, but the risk for cardiovascular disease was increased. The GOLD guidelines recommend considering the individual's risk for pneumonia when deciding whether to add ICS to long-acting bronchodilator therapy and recommend against its use in patients with a history of multiple pneumonia events or mycobacterial infections.

### STAKEHOLDER INSIGHTS

Reynold Panettieri Jr, MD, vice chancellor for translational medicine and science director at the Rutgers Institute for Translational Medicine and Science in New Brunswick, New Jersey; professor of medicine at Robert Wood Johnson Medical School in New Brunswick, New Jersey; and emeritus professor of medicine at the University of Pennsylvania in Philadelphia; prefers to prescribe LABA-LAMA combination therapy in a single inhaler rather than monotherapy for most of his patients with COPD, unless they have a specific contraindication for a LAMA (eg, urinary retention) or a LABA (eg, narrow-angle glaucoma, narrow complex tachycardia). However, Hess noted that single-device LABA-LAMA therapy may not be feasible due to lack of insurance coverage or availability at the patient's pharmacy.

Risk for pneumonia is a common concern when deciding whether to include an ICS in the therapeutic regimen, although the risk appears to be higher in patients with severe or very severe airflow limitation than in those with moderate airflow limitation, said Courtney Crim, MD, clinical associate professor of medicine at the University of North Carolina at Chapel Hill School of Medicine in Raleigh, North Carolina, and COPD360 medical director at the COPD Foundation, in Miami, Florida. Therefore, the benefits of ICS-LABA therapy for improving lung function and decreasing risk for exacerbations must be weighed against the potential risks for development of pneumonia, thrush, and low bone mineral density, all of which are associated with chronic ICS use; additionally, the likelihood of response to ICS based on blood eosinophil count should also be considered. According to the panelists, adding ICS to LABA-LAMA therapy is often considered for patients who have persistent symptoms or an exacerbation on their current therapy. Clinicians should evaluate the effect of symptoms and exacerbations on the patient's life and engage in shared decision-making with the patient when considering whether to add ICS to LABA-LAMA therapy. When deciding whether to de-escalate treatment, Panettieri said that he may consider removing an ICS from the LABA-LAMA regimen if the patient has not had an exacerbation for several years, although he rarely de-escalates LABA-LAMA therapy, because he has found that dual therapy maximizes exercise tolerance.

Crim discussed generally taking an aggressive approach to reduce the patient's symptoms as quickly as possible when starting treatment. Clinical tools such as the COPD Assessment Test can be used to track therapeutic response; however, he noted that the patient can usually judge whether a medication is improving their COPD symptoms without a formalized assessment. He added that clinicians should also keep in mind that disease progression can occur even if a patient is not having exacerbations.

Panettieri emphasized that while patient-reported outcomes (PROs) are typically measured as secondary outcomes in drug trials, PROs are the top concern in his clinical practice, because patients are unlikely to continue their medication if it does not improve their symptoms. Providers should educate patients on how to self-monitor their symptoms and progression by using a smartphone application (such as the one provided by the COPD Foundation), recording factors that trigger or improve symptoms in a journal, and following their action plan—which may include having a standing prescription for antibiotics or systemic corticosteroids to be used at the first sign of an exacerbation. Peer education from other patients and support groups can also be valuable, particularly because many patients tend to be most motivated to learn from other patients who are on a similar medical journey. Pulmonary rehabilitation can also improve patient morale if patients are able to perform activities of daily living without symptoms after completing the rehabilitation program. Ultimately, defining the patient's view of successful outcomes is important for the clinician to consider when developing a management strategy, said Panettieri.
PATIENT PERSPECTIVES AND ADHERENCE CONCERNS IN COPD

Administering triple therapy via a single inhaler is believed to improve persistence and adherence (and, thereby, clinical outcomes) and is generally preferred by patients. Although triple therapy has shown efficacy in clinical trials, this regimen initially necessitated the use of multiple inhalers, which has been associated with poorer persistence and adherence compared with use of single inhalers. Results from the INTREPID study (NCT03467425), which included 3092 patients with COPD who received triple therapy in a typical clinical setting, showed that a greater proportion of patients who received triple therapy with a single inhaler had a clinically meaningful response (defined as a decrease in COPD Assessment Test score of at least 2 units from baseline) after 24 weeks compared with patients who received triple therapy with multiple inhalers (OR, 1.31; 95% CI, 1.13-1.51; P < .001; intention-to-treat analysis). The mean change in FEV1 from baseline to 24 weeks was larger with single-inhaler therapy than with multiple-inhaler therapy in the population assessed for FEV1 (single-inhaler, 77 mL [95% CI, 57-98 mL], n = 691; multiple-inhaler, 28 mL [95% CI, 6-49 mL], n = 675), and the proportion of patients with 1 or more critical errors in inhalation technique was similar between groups in the population assessed for critical errors (6% with single-inhaler therapy [n = 691] vs 3% with multiple-inhaler therapy [n = 267]; OR, 1.99; 95% CI, 0.87-4.53; P = .103). However, the authors noted that measurement of adherence was not feasible due to the minimal intervention design of the trial, which was intended to reflect usual patient care and behaviors (ie, only the screening and randomization visit and the visit after 24 weeks of treatment were mandatory).

STAKEHOLDER INSIGHTS

Educating patients on inhaler techniques and appropriate use of long-acting and short-acting inhalers is important for maximizing adherence to therapy, said Hess. He added that he reviews inhaler technique and when to use short-acting medications at every visit (every 3-6 months) to prevent “technique decay,” in which patients who have performed the inhaler technique properly at the start of treatment have a breakdown in technique after several months. Hess also noted that the type of device may play a role in achieving good inhaler technique. Combination inhalers are generally preferred over multiple separate inhalers unless the co-pay for a combination inhaler is unaffordable, and multiple inhalers could be especially problematic if they involve use of 2 different techniques.

Patients often have preferences regarding dosing frequency, and clinicians should use shared decision-making accordingly when selecting a medication. For example, Panettieri said that in his experience, older patients often prefer twice-daily dosing based on the perception that it is more effective for improving symptoms.

Each type of device (eg, metered dose inhaler, dry powder inhaler, soft mist, nebulizer) has benefits and drawbacks, and the primary goal is to choose the device that accommodates the patient’s individual characteristics and goals for therapy. The formulary of the patient’s health plan is often a key factor in selecting a device, but patients may be able to obtain approval for the desired device if they were unable to use the previous one effectively, said Hess. Additionally, Crim noted that the results of the INTREPID study support his real-world observations that simplifying the delivery of medication through a single inhaler improves the likelihood of a clinical response.

In addition to optimizing pharmacologic treatment, improving the uptake of nonpharmacologic strategies is necessary to optimize patient outcomes; such strategies include pulmonary rehabilitation, tobacco cessation, and diet and exercise interventions, as well as promoting patient-provider and provider-payer communication. Exacerbations, particularly those that require visits to a health care provider, are the largest drivers of cost, so optimizing medications to reduce exacerbations is instrumental to reducing costs, Crim explained.

Panettieri advocated for more rapid formulary inclusion of novel therapies that have shown greater efficacy compared with currently available options. He noted that the frequent changes in payer formularies based on rebating can be difficult for providers and nurses to navigate. For example, formulary changes may mean that a patient who has been stable on a previously approved medication must go through the preauthorization process to continue taking the medication. He added that pharmacy benefit managers may be primarily focused on medication costs without recognizing the potential overall cost savings (eg, through reduced health care utilization) with a more expensive medication. Patients also need to know how to use the inhaler device correctly, and device coverage changes by the payer may be problematic if the patient is unable to use the new device correctly, said Hess. He added that improving communication between the clinician and payer on the practicality of a device for a patient is important to help the patient access a therapy that is likely to be effective.

CLOSING REMARKS

The understanding of COPD and related comorbidities has improved considerably over the past 2 to 3 decades, and early identification of individuals who are at increased risk of COPD is important for improving outcomes moving forward, said Crim. Early recognition also requires increased awareness of COPD among the general population as well as among providers in the clinical setting, so that patients can report symptoms earlier and clinicians can identify risk factors and collaborate to improve treatment and transitions of care, Hess added. Panettieri remarked that it is important for providers to recognize that manage-
ment of COPD involves treatment of the individual as opposed to the disease. Providers should strive to understand how COPD is affecting the individual and their family and utilize shared decision-making when developing a treatment plan.

REFERENCES


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