VOL 85, SUPPLEMENT 1 | FEBRUARY 2018 | www.ccjm.org

Cleveland Clinic Journal of Medicine

COPD in Primary Care: Key Considerations for Optimized Management

This supplement was sponsored by AstraZeneca.

Introduction

Barbara P. Yawn, MD, MSc, FAAFP

More than 13 million people in the United States have been diagnosed with chronic obstructive pulmonary disease (COPD),[1] a complex, heterogeneous respiratory condition characterized by persistent, and usually progressive, airflow limitation.[2,3] The prevalence of COPD is rising: It has been declared the third leading cause of death in the United States,[4] and the World Health Organization has predicted that it will become the third leading cause of death worldwide by 2030.[5] This increase is driven by an aging population, and tobacco smoking, which is the primary risk factor for COPD in high-income countries.[6]

Symptoms of COPD, as well as the severity of these symptoms, can vary, but patients typically present with dyspnea, chronic cough, and sputum production.[2] These symptoms are often underreported by patients with COPD,[2] but have a significant impact on patients' day-to-day lives, adversely affecting their quality of life and their ability to engage in physical activity, further contributing to disease progression.[7,8]

Comorbidities are common in patients with COPD, and can pose significant challenges to the diagnosis and management of the condition. Some of these comorbidities, such as lung cancer and ischemic heart disease, share a common etiologic pathway with COPD—smoking; while others, such as anxiety and depression, appear to be unrelated to COPD pathogenesis, although they may share a systemic inflammatory basis, and are highly prevalent in patients with COPD.[9]

Primary care physicians are the key point of contact for most patients with COPD,[10] and play a critical role in diagnosis, drug and device selection, and long-term disease management of COPD and associated comorbidities. A number of pharmacologic and nonpharmacologic treatment options are available to manage COPD symptoms, which can confer considerable benefits to patients. Selection of pharmacologic treatment should be based on an individual patient's symptom burden and their exacerbation history, and it is important that physicians are aware of when therapy should be escalated, and indeed stopped if no longer required.[2]

Proper device selection is an important part of choosing treatments for patients with COPD. A variety of inhaler devices are available for COPD medications, and it is important that devices are matched to patients' needs and preferences based on device characteristics and individual patient capabilities.

The aim of this supplement is to provide readers with an introduction to 4 key topics critical to the effective management of COPD in primary care, highlighting best practices to optimize patient care and outcomes. In the first article, Dr. Marchetti and Dr. Kaplan review physical activity in COPD, discussing its inter-relationship with dyspnea and hyperinflation, and its importance in modifying disease progression.

The second article examines anxiety and depression in COPD. Prof. Yohannes, Dr. Kaplan, and Dr. Hanania review the prevalence, mechanisms, and impact of the 2 often overlooked and undertreated psychologic comorbidities in patients with COPD. The authors provide guidance on how anxiety and depression can be detected and managed in patients with COPD in a primary care setting.

The third article is authored by Dr. Dhand, Dr. Cavanaugh, and Dr. Skolnik, and reviews the device options available for COPD pharmacologic therapy. It summarizes the key features of each respective inhaler device, discusses considerations for patient-device matching, and emphasizes the importance of training in correct device use.

Finally, Dr. Victor Kim and I assess different COPD treatment options in the supplement's fourth article. We review the latest updates in recommendations from both the Global

Barbara P. Yawn, MD, MSc, FAAFP, Department of Family and Community Health, University of Minnesota, Blaine, Minnesota

DISCLOSURES

Dr. Yawn reports receipt of personal payments for COPD-related advisory boards for AstraZeneca, Boehringer Ingelheim GmbH, and GlaxoSmithKline, and COPD-related research grant funding from Boehringer Ingelheim GmbH. She has served as a content developer and peer reviewer for Medscape and UpToDate, and has received grant support from the National Heart, Lung, and Blood Institute and the Patient-Centered Outcomes Research Institute for COPD-related research.

Funding for this article was provided by AstraZeneca LP (Wilmington, DE, USA). Medical writing support was provided by Hannah Burke, BSc, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip, of Core (London, UK), which were funded by AstraZeneca LP (Wilmington, DE, USA), in accordance with Good Publication Practice guidelines (Battisti WP et al. *Ann Intern Med*. 2015;163:461–464. doi: 10.7326/M15-0288).

This article is being co-published in *The Journal of Family Practice* and *Cleveland Clinic Journal of Medicine.*
doi: 10.3949/ccjm.85.s1.01

Initiative for Chronic Obstructive Lung Disease (GOLD) and the COPD Foundation, discuss the importance of personalized treatment goals for patients, and review how to address current unmet needs in patient management.

REFERENCES

1. Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance—United States, 1999-2011. *Chest*. 2013;144(1):284-305.
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med*. 2017;195(5):557-582.
3. Barrecheguren M, Miravitlles M. COPD heterogeneity: implications for management. *Multidiscip Respir Med*. 2016;11:14.
4. National Center for Health Statistics (US). Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD; National Center for Health Statistics: 2016.
5. World Health Organization. World Health Statistics 2008. http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf?ua=1. Accessed August 2017.
6. Waatevik M, Skorge TD, Omenaas E, Bakke PS, Gulsvik A, Johannessen A. Increased prevalence of chronic obstructive pulmonary disease in a general population. *Respir Med*. 2013;107(7):1037-1045.
7. O'Donnell DE, Gebke KB. Activity restriction in mild COPD: a challenging clinical problem. *Int J Chron Obstruct Pulmon Dis*. 2014;9:577-588.
8. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. *Respir Res*. 2017;18(1):67.
9. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:95-109.
10. Foster JA, Yawn BP, Maziar A, Jenkins T, Rennard SI, Casebeer L. Enhancing COPD management in primary care settings. *MedGenMed*. 2007;9(3):24.

Dyspnea and Hyperinflation in Chronic Obstructive Pulmonary Disease: Impact on Physical Activity

Nathaniel Marchetti, DO; and Alan Kaplan, MD

Introduction

Dyspnea, the sensation of difficult or labored breathing, is the most common symptom in chronic obstructive pulmonary disease (COPD) and the primary symptom that limits physical activity in more advanced disease.[1] According to the American Thoracic Society, dyspnea may be measured according to 3 domains[2]:

- what breathing feels like for the patient
- how distressed the patient feels when breathing
- how dyspnea affects functional ability, employment, health-related quality of life, or health status.

Several studies have shown that patients find dyspnea and other COPD symptoms most cumbersome in the early morning and at night-time.[3,4] However, symptoms can often be underreported by patients.[5] The impact of COPD symptoms manifests in various aspects of patients' day-to-day lives, perhaps none more significantly than in the context of physical activity. Inability to engage in sustained physical activity is a common feature of COPD, and even in cases of mild COPD, activity restriction can be evident.[6] An estimated 29% to 44% of patients with COPD report persistent and troublesome activity-related dyspnea, which may occur early in the disease course.[6,7] While a number of factors are thought to contribute to the reduced physical activity observed in COPD patients, dyspnea has been identified as a primary contributor.[8] Patients with COPD may enter a downward spiral of dyspnea-induced inactivity, resulting in muscular and aerobic deconditioning (**FIGURE 1**),[9,10] which, in turn, results in an increased unwillingness to attempt activity in the future.[11]

As disease severity increases, breathlessness becomes more disabling at lower activity levels. These changes further impact the quality of life of patients, and can lead to anxiety and depression.[11]

Physical inactivity is often considered to be a major contributor to the progression of COPD,[6] and is linked to hospitalizations and increased all-cause mortality.[12] There is therefore a need to recognize symptoms early and treat them accordingly.

CASE STUDY:

KD, a 64-year-old woman, presented to her primary care physician's office for a routine visit. Upon assessment, KD revealed that she used to enjoy going on walks with her neighbor, but she cannot walk up the hills in her neighborhood anymore without feeling "incredibly breathless." She has become increasingly concerned that she is "having trouble getting a full breath." KD informed her doctor that these symptoms had worsened since her last visit, and so she had stopped going on neighborhood walks. She was diagnosed with COPD 4 years ago, and is currently using a long-acting muscarinic antagonist (LAMA) bronchodilator. KD has a 40 pack-year smoking history, and has previously been advised to stop smoking, but has relapsed several times. She has a medical

Nathaniel Marchetti, DO, Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

Alan Kaplan, MD, Family Physician Airways Group of Canada, Ontario, Canada

DISCLOSURES

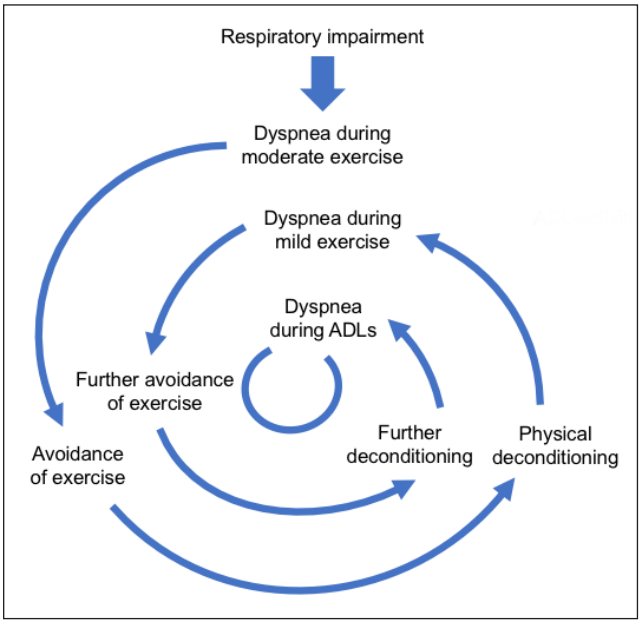
Dr. Marchetti has no conflicts of interest.

Dr. Kaplan has been a speaker or an advisory board member for AstraZeneca; Becton, Dickinson and Company; Boehringer Ingelheim, GmbH; GlaxoSmithKline; Johnson & Johnson; Mylan Laboratories Inc.; Paladin Labs Inc.; Pfizer Inc.; Purdue Pharma L.P.; Novartis Pharmaceuticals Corporation; and Trudell Medical International.

Funding for this article was provided by AstraZeneca LP (Wilmington, DE, USA). Medical writing support was provided by Hannah Burke, BSc, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip, of Core (London, UK), which were funded by AstraZeneca LP (Wilmington, DE, USA), in accordance with Good Publication Practice guidelines (Battisti WP et al. *Ann Intern Med*. 2015;163:461–464. doi: 10.7326/M15-0288).

This article is being co-published in *The Journal of Family Practice* and *Cleveland Clinic Journal of Medicine.*
doi: 10.3949/ccjm.85.s1.02

FIGURE 1 **The dyspnea spiral**[10]



Abbreviation: ADLs, activities of daily living.

This figure was published in *Principles and Practice of Pulmonary Rehabilitation*, Haas F, Salazar-Schicci J, Axen K. Desensitization to dyspnoea in chronic obstructive pulmonary disease, 241-251, Copyright Elsevier 1993.

history of hypertension and depression, and a notable family history of emphysema, breast cancer, and diabetes.

The relationship between lung hyperinflation and dyspnea in COPD

In COPD, pathologic changes give rise to physiologic abnormalities such as mucus hypersecretion and ciliary dysfunction, gas exchange abnormalities, pulmonary hypertension, and airflow limitation and lung hyperinflation.[13] Lung hyperinflation, an increase in resting functional residual volume above a normal level, represents a mechanical link between the characteristic expiratory airflow impairment, dyspnea, and physical activity limitation in COPD.[1]

The lungs of patients with COPD can be hyperinflated both at rest (static hyperinflation) and/or during exercise (dynamic hyperinflation).[14] Static hyperinflation is caused by a decrease in elasticity of the lung due to emphysema, resulting in decreased lung recoil pressure and a higher resting lung volume.[15] In dynamic hyperinflation (**FIGURE 2**),[15,16] the lungs operate at progressively higher volumes of air with each breath, approaching total lung capacity (TLC); this is made worse during exertion as the respiratory rate increases, allowing less time for exhalation.[17] As a result, the volume of air taken in on each breath becomes more limited by higher end-expiratory lung volumes, and the "work" of breathing is increased.[17]

Although patients can compensate for several of the negative consequences of hyperinflation (eg, altering the chest wall due to overdistended lungs), such compensatory mechanisms are unable to cope with large increases in ventilation, such as those that occur during exercise.[1] Air trapping, together with ineffectiveness of respiratory muscle function, leads to increased ventilation requirements and dynamic pulmonary hyperinflation, resulting in dyspnea.[1]

Patients with COPD describe a sensation of "air hunger," reporting "unsatisfied" or "unrewarded" inhalation, "shallow breathing," and a feeling that they "cannot get a deep breath,"[18] whereas, in fact, they are limited in their ability to fully exhale. Verbal descriptors (eg, "air hunger" or "chest tightness") are important tools in understanding a patient's experience with dyspnea, and a patient's choice of descriptor may be related to dyspnea severity, and the level of distress that dyspnea causes a given patient.[19] Air hunger in turn encourages faster breathing, leading to further shortness of breath and more dynamic hyperinflation.[1,20]

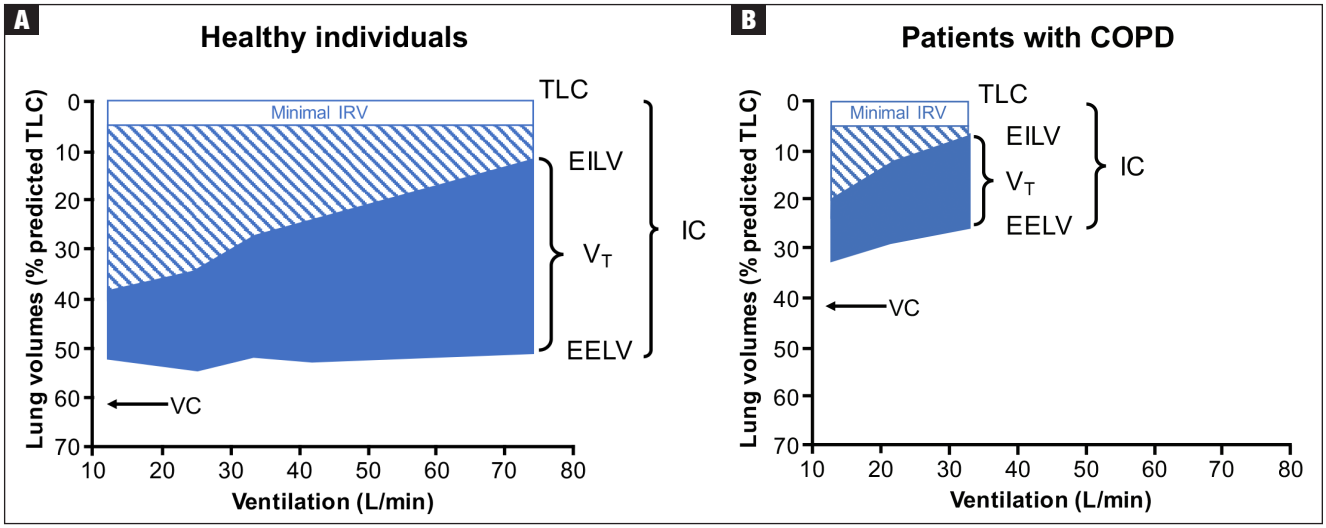
To deflate the lungs of patients with COPD, physiologic, pharmacologic, and possibly surgical interventions are required:

- Controlled breathing techniques (eg, purse-lipped breathing) that encourage slow and deep breathing can correct abnormal chest wall motion, decrease the work of breathing, increase breathing efficiency, and improve the distribution of ventilation to empty the lungs.[21]
- Bronchodilators can help to achieve lung deflation by improving ventilatory mechanics, as shown by increases in inspiratory capacity and vital capacity.[22]
- Lung volume reduction surgery can also be considered to treat severe hyperinflation in emphysematous patients[5]; bronchoscopic interventions that lower lung volumes are also in development.[23]

The impact of lung hyperinflation and dyspnea on physical activity in COPD

Dynamic hyperinflation can develop early in COPD, when patients generally experience dyspnea only during more intense exertion.[11,22] However, as COPD progresses and airflow limitation increases, patients begin to experience shortness of breath with minimal effort and, eventually, during activities of daily living (ADLs), or even at rest.[5,11] It is important that dyspnea, as well as airway obstruction, is considered as a variable that affects mortality in patients with COPD. Categorizing patients with COPD based on dyspnea severity has been shown to be a more effective predictor of mortality than using classifications based on

FIGURE 2 Changes in operational lung volumes shown as ventilation increases in (A) healthy individuals and (B) patients with COPD[16]



Abbreviations: COPD, chronic obstructive pulmonary disease; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; TLC, total lung capacity; VC, vital capacity; V_T, tidal volume.

percentage of predicted forced expiratory volume in 1 second (FEV_1) (**FIGURE 3**).[24] Similarly, inspiratory capacity (IC), a surrogate measure of hyperinflation, shows better correlation with exercise endurance time than FEV_1.[26] Resting IC, measured as the IC/TLC ratio (which is approximately 60% in healthy individuals[27]) has also been identified as an independent risk factor for mortality in patients with COPD[28]; in their study, Casanova et al examined the predictive capacity of various IC/TLC ratios, ranging from 15% to 40%, and found that an IC/TLC threshold of 25% provided the best power to predict mortality in patients with COPD.[28]

Dyspnea and hyperinflation are closely interrelated with physical activity limitation,[16,29,30] and so can be viewed as significant contributors to patient disability. During an acute exacerbation, patients with COPD will experience worsening airway obstruction, dynamic hyperinflation, and dyspnea.[31] Patients with a greater number of comorbid conditions may also have greater shortness of breath.[32] In addition, patients with COPD and hyperinflation perform less physical activity than individuals without hyperinflation, regardless of COPD severity, as assessed using the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging (stage I, mild; stage II, moderate; stage III, severe; stage IV, very severe) and BODE (**B**ody-mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise) index.[33] These patients also exhibit increases in dyspnea perception during commonly performed ADLs, which may limit physical activity and worsen lung hyperinflation.[33] More limited physical activity also contributes to higher dyspnea scores during ADLs.[8]

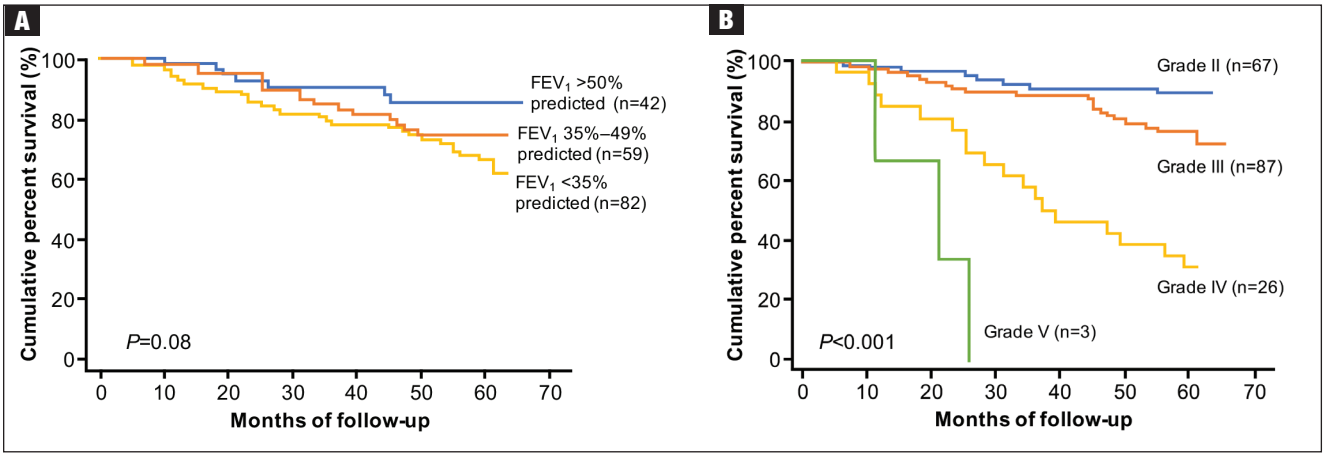
Furthermore, the ability to perform typical ADLs may be significantly altered or eliminated altogether in patients with COPD.[11] Leisure activities are often the first to be dropped by patients, as they generally require greater effort than simpler tasks, and are not critical to daily life.[11] Eventually, these activities become progressively more difficult, and most patients with moderate or severe COPD can struggle to complete even the most basic daily activities.[11]

In addition to the morbidity burden and impact on ADLs, lower levels of physical activity in patients with COPD have also been shown to increase the risk of mortality and exacerbations, and elevate the risk of comorbidities such as heart disease and metabolic disease.[34] In light of these observations, improving exercise capacity should be a key goal in COPD management.

Assessment and measurement of dyspnea and hyperinflation

Reducing hyperinflation and dyspnea is essential for improving physical activity endurance and overall physical activity in patients with COPD; therefore, measuring the degree of impairment is important.[22] Clinicians should be aware that some patients may have relief of dyspnea due to improvements in hyperinflation, despite relatively mild changes in FEV_1.[35] Lung

FIGURE 3 **Five-year survival according to (A) percentage of predicted FEV_1 and (B) dyspnea level[24]**



(A) Grades determined by 1995 American Thoracic Society staging guideline, which is categorized according to percentage of predicted FEV_1. (B) Grades determined by an adapted version of the Medical Research Council grading system (distinct from the modified Medical Research Council scale, which is used widely and cited in the GOLD report,[5] in which dyspnea is classified from Grade 0 to Grade 4), developed by Fletcher et al[25]: Grade I, I get breathless at times other than when doing strenuous exercise; Grade II, I am short of breath when hurrying on the level or walking up a slight hill; Grade III, I have to walk slower than most people on the level and I have to stop after a mile or so (or after 1/4 hour) on the level at my own pace; Grade IV, I have to stop for breath after walking about 100 yards (or after a few minutes) on the level; Grade V, I am too breathless to leave the house, or breathless after undressing.

volume measures, including total lung capacity, residual volume and functional residual capacity, are valuable tools in the assessment of lung hyperinflation in COPD, and therefore constitute a key component of pulmonary function testing.[36] However, expanded pulmonary function testing may be required for patients with severe dyspnea that does not correspond to spirometric findings, or cases in which diagnosis is uncertain.[37]

Lung volumes are evaluated primarily by body plethysmography, during which a patient sits inside an airtight "body box" equipped to measure pressure and volume changes.[14,38] Helium dilution and nitrogen washing can also be used to measure functional residual capacity in patients with COPD,[14] but body plethysmography is considered to be a more accurate method of lung volume evaluation in patients with severe airflow obstruction.[14,38] Radiographic techniques can also be used, but due to a lack of standardization, they are not typically utilized in clinical practice.[14] Measurement of IC may complement other lung volume measures as part of assessment of hyperinflation.[16] This can be measured using either spirometry or body plethysmography.[39,40]

In addition to evaluating hyperinflation, ADLs, physical activity, exercise capacity, and dyspnea should all be assessed in patients with COPD in primary care. It is known that patients may self-limit ADLs to avoid symptoms of COPD; in doing so, worsening symptoms may be underappreciated, and subsequently underreported, by the patient. Thus, it is essential that physicians ask patients with COPD, as well as individuals at risk of COPD, questions about changes in their physical activity or ability to perform common tasks. There are a number of methods to measure functional performance, but for a simple assessment of ADLs, clinicians can ask the patient or caregiver questions related to basic daily tasks.[11] In early COPD, patients who experience mild dyspnea during exercise should be able to perform most productive activities. Patients with stable COPD and moderate dyspnea during exercise should be able to carry out most of the higher functioning ADLs, whereas patients with severe COPD may struggle to complete basic ADLs without assistance.[11] It should be noted, however, that patients may experience dyspnea with fairly routine activities, and even reduce physical activity at relatively early stages of airflow limitation.[41,42]

There is a clear distinction between symptom assessment tools that *should* be used, and which of these *can* be used practically in primary care. Although family physicians rarely perform spirometry or measure lung volumes in the clinic, it is important to highlight that spirometry assessment *is* conducted by some primary care practitioners, and should be utilized more readily in primary care to provide reinforcement of diagnoses. Similarly, the St. George's Respiratory Questionnaire and the Chronic Respiratory Questionnaire, which are widely used in the scientific literature to assess symptoms,

TABLE 1 Summary of commonly used dyspnea measures in primary care[5,44,45]

Dyspnea measure	Key features	Strengths	Limitations
COPD Assessment Test (CAT)	Evaluates 8 items on a 6-point scale, corresponding to health status impairment in COPD Higher scores represent worse health	Short, simple questionnaire Covers wide range of symptoms Well-validated and reliable Correlates closely with SGRQ Readily available	Does not categorize patients into symptom severity groups for scores in the range of 10–40
Medical Research Council (MRC) Dyspnea Scale	Evaluates everyday situations/ activity levels on a 5-point scale Higher scores represent greater disability	Short, simple questionnaire Well-validated and reliable Relates well to other measures of health status Able to predict future mortality risk Readily available	Less effective at detecting change in response after an intervention than alternative measures Considers dyspnea alone, so does not account for the broader impact of COPD
COPD Control Questionnaire (CCQ)	Evaluates 10 items on a 6-point scale based on the previous week's symptoms, measuring COPD-related health status Higher scores represent worse health	Short, simple questionnaire Well-validated and reliable Measures functional and mental capacities as well as symptoms Readily available	Does not categorize patients into symptom severity groups
Chronic Respiratory Questionnaire (CRQ)	Evaluates 20 items on a 7-point scale across 4 domains: dyspnea, fatigue, emotional function, mastery Higher scores represent better health-related quality of life	Well-validated and reliable Responds well to changes over time	License required to use questionnaire Longer than alternative dyspnea measures Does not categorize patients into symptom severity groups

Abbreviations: COPD, chronic obstructive pulmonary disease; SGRQ, St. George's Respiratory Questionnaire.

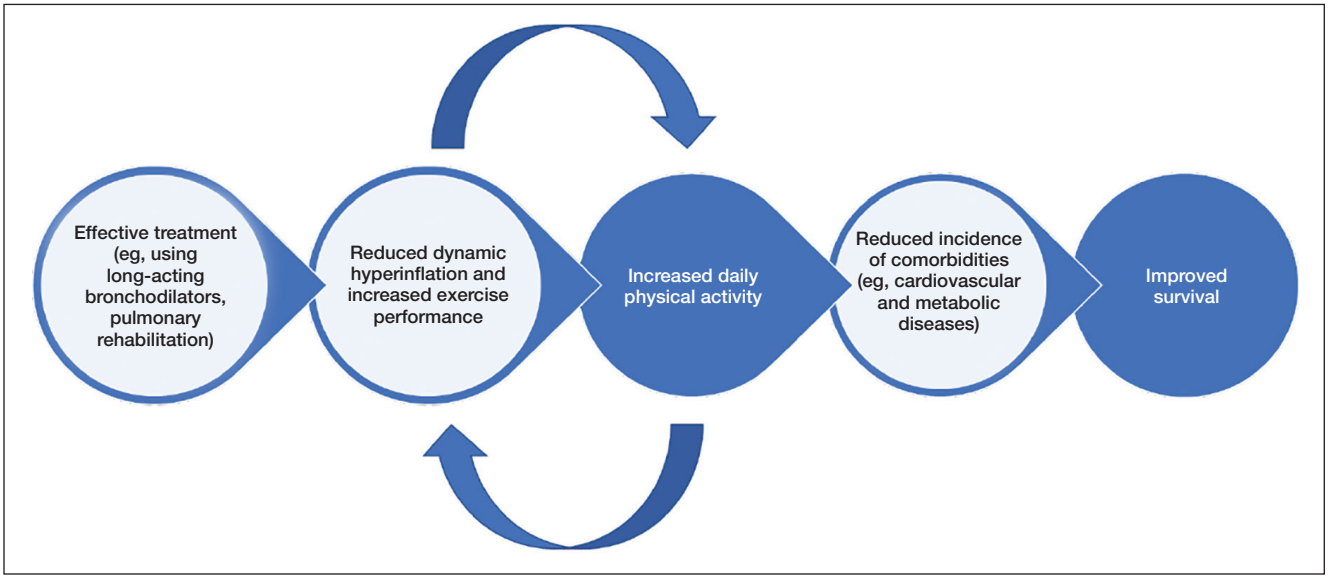
are generally considered to be too time-consuming for use in routine clinical practice[5]; the Transition Dyspnea Index is similarly lengthy.[43] However, shorter measures, such as the COPD Assessment Test (CAT) and the COPD Control Questionnaire are suitable,[5] with the CAT score representing the best available tool for primary care physicians to evaluate COPD symptoms (**TABLE 1**). The International Primary Care Respiratory Group Research Subcommittee was set up to provide guidance on the best measures of quality of life in COPD.[44] The committee scored the CAT, COPD Control Questionnaire, and Chronic Respiratory Questionnaire highly for a primary care population.[44] An additional tool often useful in clinical practice is the Medical Research Council (MRC) Dyspnea Scale,[5] but it is important to note that this measure does not provide information on any symptoms other than dyspnea.

Other tests may be useful in assessing the impact of an intervention, be it pharmacologic or nonpharmacologic, on dyspnea severity. For example, increases in the 6-minute-walk distance (6MWD) have been shown to correlate with improvements in dyspnea.[46] The 6MWD has also been shown to be an important predictor of hospitalization and mortality in patients with COPD.[47] However, it is important to note that improvements in 6MWD show only a very weak correlation with patient-reported outcomes,[48] and may be a less sensitive measure for patients with less disability than those with more profound functional limitation.[49] Moreover, 6MWD can be affected by a patient's psychologic motivation,[6,50] as well as other comorbidities observed in patients with COPD, such as osteoporosis, heart failure, and peripheral vascular disease.[46,51] Although not used for COPD diagnosis or evaluation of dyspnea or physical activity limitation, a chest X-ray can also be a useful tool for excluding alternative diagnoses, as well as for detecting significant comorbidities in patients with COPD, such as concomitant respiratory, cardiac, and skeletal diseases.[5]

Management of dyspnea and hyperinflation in primary care

Physicians can utilize a variety of pharmacologic and

FIGURE 4 The crucial role of daily activity in patients with COPD[34]



nonpharmacologic strategies to reduce hyperinflation and dyspnea and improve physical activity in patients with COPD (**FIGURE 4**).[34]

Pulmonary rehabilitation is a tailored intervention that encompasses exercise training, education, and self-management support for people with chronic respiratory disease, based on detailed assessment of their exercise capacity and symptoms.[52] Pulmonary rehabilitation is as important as medication in COPD management, providing a cost-effective intervention with minimal adverse effects.[53] Moreover, pulmonary rehabilitation has been shown to benefit patients with mild to severe dyspnea (as classified according to the Medical Research Council dyspnea scale), demonstrating the value of successful execution of these programs in patients with COPD, irrespective of disease severity.[54] Although the most significant improvements in patient quality of life are observed when a multimodality approach is used, exercise and proper pulmonary rehabilitation programs have been shown to improve quality of life more than medication alone.[5,55] Notably, there are few supporting data for the use of supplemental oxygen in patients experiencing dyspnea without hypoxemia. Oxygen supplementation is only of minimal benefit to relieving the sensation of dyspnea.[56,57]

The relationship between the impact of pulmonary rehabilitation in patients with COPD and frailty scores has also been evaluated. Frailty scores are calculated based on an individual's level of physical activity, and other key criteria that are indicative of their ability to self-manage their medical condition.[58] These scores are particularly relevant in the context of COPD, given the high prevalence of the condition in older people.[58] Although frailty is a strong independent predictor of noncompletion of pulmonary rehabilitation, completion of a pulmonary rehabilitation program in patients who are frail has been shown to reverse their frailty in the short term.[58] It is therefore important that physicians guide and encourage these patients for the duration of a pulmonary rehabilitation program, from initiation through to completion, to ensure that those who are likely to derive the greatest benefit from pulmonary rehabilitation are supported to do so.

In addition to pulmonary rehabilitation, other nonpharmacologic interventions have emerged in recent years that may help to relieve dyspnea in patients with COPD. Airway clearance devices, such as acapella (Smiths Medical; Minneapolis, MN), Flutter (Allergan; Dublin, Ireland), Lung Flute (Medical Acoustics; Buffalo, NY), Quake (Thayer Medical; Tucson, AZ), and Aerobika (Monaghan Medical; Plattsburgh, NY) promote the clearance of sputum through the application of positive expiratory pressure, possibly allowing medicines to penetrate the lungs more effectively, and improving diffuse airflow obstruction.[59-61] Incorporating an airway clearance device into a bronchodilator therapy regimen has been shown to improve dyspnea scores, both before and after exercise, compared with bronchodilator therapy combined with a nonfunctional control device in patients with severe COPD.[59] In addition, noninvasive forms of ventilation, such as continuous positive airway pressure and bi-level positive airway pressure (BiPAP), have been shown to effectively reduce dyspnea in patients with COPD.[62,63] In a 24-month study in patients with severe COPD, resting dyspnea improved significantly in patients using the BiPAP Auto-Trak (Philips Respironics, Best,

The Netherlands) in conjunction with their regular bronchodilator therapy, compared with those receiving long-term oxygen therapy in addition to their typical therapeutic regimen.[63] Further studies are required to establish the impact of these devices in the management of dyspnea and other symptoms of COPD.

These nonpharmacologic interventions can be supplemented with pharmacologic treatments to help patients achieve their treatment goals of improved dyspnea and increased exercise performance. Bronchodilators, which form the basis of various COPD treatment options, include[5]:

- short-acting muscarinic antagonists (SAMAs), such as ipratropium
- short-acting β_2-agonists (SABAs), such as albuterol, levalbuterol, and terbutaline
- SAMA/SABA combinations
- LAMAs, such as aclidinium, glycopyrrolate, tiotropium, and umeclidinium
- long-acting β_2-agonists (LABAs), such as arformoterol, indacaterol, formoterol, olodaterol, salmeterol, and vilanterol
- LAMA/LABA combinations (umeclidinium/vilanterol, tiotropium/olodaterol, glycopyrrolate/formoterol, glycopyrrolate/indacaterol)

Inhaled corticosteroids can also be used in a fixed-dose combination with a LABA, which can be combined with a LAMA, in select patients[5]; however, these combination products may have minimal value in treating dyspnea unless asthma is concomitantly present.[5,64] Further discussion of the different treatment options available for patients with COPD can be found in the final article of this supplement.

In addition to improving quality of life, long-acting bronchodilators, such as LAMAs, LABAs, and LAMA/LABA combinations, increase expiratory flow, reduce dynamic hyperinflation, and improve exercise capacity of patients.[65-67] As disease severity worsens, physicians may opt for long-acting bronchodilator options that have twice-daily dosing, which may confer a benefit in improving night-time symptom control.[68]

As well as active pharmacologic and nonpharmacologic interventions, physicians should always encourage smoking cessation in patients with COPD, as this has the greatest capacity to influence the natural course of the disease.[5] It is essential that health care providers continually deliver smoking cessation messages to patients with COPD; patients can also be supported to stop smoking by using nicotine replacement therapy, pharmacologic interventions, attending smoking cessation programs, and counseling.[5]

Lung volume reduction surgery may also be considered as a strategy for the management of dyspnea in severe, refractory COPD.[69] Similarly, nonsurgical bronchoscopic interventions are being developed that look to achieve similar results to lung volume reduction surgery, including endobronchial one-way valves, lung volume reduction coils, airway bypasses, adhesives, and vapor therapy.[23]

CASE STUDY:

The primary care physician assessed KD's dyspnea using the CAT and ordered a chest X-ray to identify any significant comorbidities, such as concomitant respiratory, skeletal, or cardiac diseases. As KD's CAT score was 17, and her symptoms were uncontrolled on LAMA monotherapy, her physician prescribed a long-acting LAMA/LABA combination, along with pulmonary rehabilitation. The physician also counseled KD on the importance of smoking cessation, and referred her to a local smoking cessation program.

Conclusions

Dyspnea, the most common symptom of COPD and the primary consequence of the condition's characteristic lung hyperinflation, is a heavy burden on the lives of patients. The impact of dyspnea is perhaps most apparent in the context of physical activity, with activity limitation observed frequently in patients with COPD, regardless of disease stage. This can affect patients' quality of life significantly, and has long-term consequences on disease progression. Improving dyspnea and increasing exercise endurance should therefore be a key goal for COPD management, which should encompass both nonpharmacologic interventions, such as pulmonary rehabilitation, and pharmacologic interventions, such as use of bronchodilator therapy.

REFERENCES

1. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006;3(2):180-184.
2. Parshall MB, Schwartzstein RM, Adams L, et al; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435-452.
3. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*. 2011;37(2):264-272.
4. Agusti A, Hedner J, Marin J, Barbé F, Cazzola M, Rennard S. Night-time symptoms: a forgotten dimension of COPD. *Eur Respir Rev*. 2011;20(121):183-194.
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2017. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Accessed November 27, 2017.
6. O'Donnell DE, Gebke KB. Activity restriction in mild COPD: a challenging clinical problem. *Int J Chron Obstruct Pulmon Dis*. 2014;9:577-588.
7. Elbehairy AF, Ciavaglia CE, Webb KA, et al; Canadian Respiratory Research Network. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med*. 2015;191(12):1384-1394.
8. Barriga S, Rodrigues F, Bárbara C. Factors that influence physical activity in the daily life of male patients with chronic obstructive pulmonary disease. *Rev Port Pneumol*. 2014;20(3):131-137.
9. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(9):972-977.
10. Haas F, Salazar-Schicci J, Axen K. Desensitization to dyspnoea in chronic obstructive

pulmonary disease. In: Casaburi R, Petty TL, eds. *Principles and Practice of Pulmonary Rehabilitation*. Philadelphia, PA: W.B. Saunders; 1993:241-251.
11. Belfer MH, Reardon JZ. Improving exercise tolerance and quality of life in patients with chronic obstructive pulmonary disease. *J Am Osteopath Assoc*. 2009;109(5):268-278.
12. Troosters T, van der Molen T, Polkey M, et al. Improving physical activity in COPD: towards a new paradigm. *Respir Res*. 2013;14:115.
13. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946.
14. Gagnon P, Guenette JA, Langer D, et al. Pathogenesis of hyperinflation in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;9:187-201.
15. Ferguson GT. Why does the lung hyperinflate? *Proc Am Thorac Soc*. 2006;3(2):176-179.
16. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164(5): 770-777.
17. Dubé BP, Guerder A, Morelot-Panzini C, Laveneziana P. The clinical relevance of the emphysema-hyperinflated phenotype in COPD. *COPD Res Pract*. 2016;2:1.
18. Scano G, Stendardi L, Grazzini M. Understanding dyspnoea by its language. *Eur Respir J*. 2005;25(2):380-385.
19. Chowienczyk S, Javadzadeh S, Booth S, Farquhar M. Association of descriptors of breathlessness with diagnosis and self-reported severity of breathlessness in patients with advanced chronic obstructive pulmonary disease or cancer. *J Pain Symptom Manage*. 2016;52(2):259-264.
20. Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD. *Prim Care Respir J*. 2013;22(1):101-111.
21. Gosselink R. Controlled breathing and dyspnea in patients with chronic obstructive pulmonary disease (COPD). *J Rehabil Res Dev*. 2003;40(5 Suppl 2):25-33.
22. O'Donnell DE, Webb KA, Neder JA. Lung hyperinflation in COPD: applying physiology to clinical practice. *COPD Res Pract*. 2015;1:4.
23. Browning RF, Parrish S, Sarkar S, et al. Bronchoscopic interventions for severe COPD. *J Thorac Dis*. 2014;6(Suppl 4):S407-S415.
24. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest*. 2002;121(5):1434-1440.
25. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J*. 1959;2(5147):257-266.
26. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1999;160(2):542-549.
27. Light RW. Mechanics of respiration. In: George RB, ed. Chest Medicine: Essentials of Pulmonary and Critical Care Medicine. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:24-38.
28. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(6):591-597.
29. O'Donnell DE, Guenette JA, Maltais F, Webb KA. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. *Chest*. 2012;141(3):753-762.
30. O'Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors. *COPD*. 2007;4(3):225-236.
31. Holland AE. Physiotherapy management of acute exacerbations of chronic obstructive pulmonary disease. *J Physiother*. 2014;60(4):181-188.
32. Barr RG, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med*. 2010;362(3):217-227.
33. Garcia-Rio F, Lores V, Mediano O, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *Am J Respir Crit Care Med*. 2009;180(6):506-512.
34. Di Marco F, Santus P, Sotgiu G, Blasi F, Centanni S. Does improving exercise capacity and daily activity represent the holistic perspective of a new COPD approach? *COPD*. 2015;12(5):575-581.
35. Newton MF, O'Donnell DE, Forkert L. Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. *Chest*. 2002;121(4):1042-1050.
36. Bailey KL. The importance of the assessment of pulmonary function in COPD. *Med Clin North Am*. 2012;96(4):745-752.
37. Burkhardt R, Pankow W. The diagnosis of chronic obstructive pulmonary disease. *Dtsch Arztebl Int*. 2014;111(49):834-845, quiz 846.
38. O'Donnell CR, Bankier AA, Stiebellehner L, Reilly JJ, Brown R, Loring SH. Comparison of plethysmographic and helium dilution lung volumes: which is best for COPD? *Chest*. 2010;137(5):1108-1115.
39. Criée CP, Sorichter S, Smith HJ, et al; Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography—its principles and clinical use. *Respir Med*. 2011;105(7):959-971.
40. Lutfi MF. The physiological basis and clinical significance of lung volume measurements. *Multidiscip Respir Med*. 2017;12:3.
41. Lahaije AJ, van Helvoort HA, Dekhuijzen PN, Vercoulen JH, Heijdra YF. Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV1. *Respir Med*. 2013;107(6):834-840.
42. Troosters T, Sciurba F, Battaglia S, et al. Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respir Med*. 2010;104(7):1005-1011.
43. Calverley PMA, Georgopoulos D. Symptoms and signs of COPD. In: Siafakas NM, ed. Management of Chronic Obstructive Pulmonary Disease: European Respiratory Society Journals; 2006.
44. Cave AJ, Atkinson L, Tsiligianni IG, Kaplan AG. Assessment of COPD wellness tools for use in primary care: an IPCRG initiative. *Int J Chron Obstruct Pulmon Dis*. 2012;7:447-456.
45. Cazzola M, Hanania NA, MacNee W, Rüdell K, Hackford C, Tamimi N. A review of the most common patient-reported outcomes in COPD—revisiting current knowledge and estimating future challenges. *Int J Chron Obstruct Pulmon Dis*. 2015;10:725-738.
46. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
47. Polkey MI, Spruit MA, Edwards LD, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med*. 2013;187(4):382-386.
48. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schünemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur Respir J*. 2008;32(3):637-643.
49. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil*. 2010;91(2):221-225.
50. Grant A, Moore L. Pulmonary rehabilitation. In: Blackler L, Jones C, Mooney C, eds. Managing Chronic Obstructive Pulmonary Disease. West Sussex, England: John Wiley & Sons; 2007.
51. Crisafulli E, Gorgone P, Vagaggini B, et al. Efficacy of standard rehabilitation in COPD outpatients with comorbidities. *Eur Respir J*. 2010;36(5):1042-1048.
52. Spruit MA, Singh SJ, Garvey C, et al; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64.
53. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest*. 2007;131(5 Suppl):4S-42S.
54. Evans RA, Singh SJ, Collier R, Williams JE, Morgan MD. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. *Respir Med*. 2009;103(7):1070-1075.
55. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;(2):CD003793.
56. Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B; Long-term Oxygen Treatment Trial Research Group. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. *Chest*. 2010;138(1):179-187.
57. Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database Syst Rev*. 2016;11:CD006429.
58. Maddocks M, Kon SS, Canavan JL, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax*. 2016;71(11):988-995.
59. Wolkove N, Kamel H, Rotaple M, Baltzan MA Jr. Use of a mucus clearance device enhances the bronchodilator response in patients with stable COPD. *Chest*. 2002;121(3):702-707.
60. Chatburn RL. High-frequency assisted airway clearance. *Respir Care*. 2007;52(9):1224-1235; discussion 1235-1227.
61. Clini E. Positive expiratory pressure techniques in respiratory patients: old evidence and new insights. *Breathe*. 2009;6(2):153-159.
62. Petrof BJ, Legaré M, Goldberg P, Milic-Emili J, Gottfried SB. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990;141(2):281-289.
63. Clini E, Sturani C, Rossi A, et al; Rehabilitation and Chronic Care Study Group; Italian Association of Hospital Pulmonologists (AIPO). The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J*. 2002;20(3):529-538.
64. Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. *Thorax*. 1998;53(6):477-482.
65. Berton DC, Reis M, Siqueira AC, et al. Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD. *Respir Med*. 2010;104(9):1288-1296.
66. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J*. 2004;23(6):832-840.
67. O'Donnell DE, Sciurba F, Celli B, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest*. 2006;130(3):647-656.
68. Blasi F, Canonica GW, Miravitlles M. Is aclidinium alone or combined with a LABA a rational choice for symptomatic COPD patients [published correction appears in *Respir Res*. 2017;18(1):35]. *Respir Res*. 2017;18(1):19.
69. Shah AA, D'Amico TA. Lung volume reduction surgery for the management of refractory dyspnea in chronic obstructive pulmonary disease. *Curr Opin Support Palliat Care*. 2009;3(2):107-111.

Anxiety and Depression in Chronic Obstructive Pulmonary Disease: Recognition and Management

Abebaw Mengistu Yohannes, PhD; Alan Kaplan, MD; and Nicola A. Hanania, MD, MS

Introduction

Anxiety and depression are common in patients with chronic obstructive pulmonary disease (COPD), occurring more frequently than in the general population[1-4] or patients with other chronic diseases such as hypertension, diabetes, cancer, or musculoskeletal disorders.[5,6] Their presence is associated with worse outcomes of COPD, and increased morbidity, mortality, disability, and health care expenditure.[6-8] In spite of this, both anxiety and depression are frequently overlooked and undertreated in patients with COPD,[9] and symptoms of anxiety and depression can overlap significantly, as well as overlap with COPD symptoms.[7,10]

Comorbid depressive disorders that may occur in patients with COPD include major depressive disorder, dysthymias (chronic depressive symptoms of mild severity), and minor depression.[11] Depressive disorders are characterized by feelings of sadness, emptiness, and/or irritability, along with cognitive and somatic symptoms, which have a detrimental effect on the patient's ability to function.[11] Anxiety disorders include generalized anxiety disorder (GAD), phobias, and panic disorders.[11] The main features of anxiety disorders, such as excessive fear and anxiety, may be accompanied by behavioral disturbances related to these symptoms, such as panic attacks and avoidance.[11,12]

The reported prevalence of depression in COPD varies widely between studies, owing to differences in sampling methods and degrees of illness severity used in assessment of depression[6]; rates have been reported to range from 10% to 42% in patients with stable COPD,[6,13] and from 10% to 86% in patients with acute COPD exacerbation.[14] Individuals with severe COPD are twice as likely to develop depression than patients with mild COPD.[10]

Prevalence rates for clinical anxiety in COPD range from 13% to 46% in outpatients and 10% to 55% among inpatients. GAD, panic disorders, and specific phobias are reported most frequently.[15] Patients with COPD are 85% more likely to develop anxiety disorders compared with matched controls without COPD,[4] and panic disorder is reported with a prevalence that is up to 10-fold higher than in the general population.[16]

Global prevalence rates of anxiety and depression are 1.8- and 1.4-fold higher in women than men, respectively[17]; the same gender difference is observed in patients with COPD.[6] The higher prevalence rates of anxiety and depression in women are thought to be a result of sex differences in brain structure, function, and stress responses, as well as differences in exposure to reproductive hormones, social

Abebaw Mengistu Yohannes, PhD, Azusa Pacific University, Department of Physical Therapy, Azusa, California

Alan Kaplan, MD, Family Physician Airways Group of Canada, University of Toronto, Toronto, Ontario, Canada

Nicola A. Hanania, MD, MS, Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas

DISCLOSURES

Dr. Yohannes has no conflicts to disclose.

Dr. Kaplan has served as a consultant or speaker for AstraZeneca; Boehringer Ingelheim, GmbH; GlaxoSmithKline; Grifols; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Novo Nordisk Inc.; Paladin Labs Inc.; Pfizer Inc.; Purdue Pharma L.P.; and Trudell Medical International.

Dr. Hanania received honoraria for serving as a consultant or advisory board member for AstraZeneca; Boehringer Ingelheim, GmbH; F. Hoffmann-La Roche Ltd; GlaxoSmithKline; Mylan Laboratories Inc.; Novartis Pharmaceuticals Corporation; Teva Pharmaceutical Industries Ltd.; and Sanofi-Regeneron. His institution has received research grant support from AstraZeneca; Boehringer Ingelheim, GmbH; Cheisi USA, Inc.; F. Hoffmann-La Roche Ltd; and GlaxoSmithKline.

Funding for this article was provided by AstraZeneca LP (Wilmington, DE, USA). Medical writing support was provided by Hannah Burke, BSc, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip, of Core (London, UK), which were funded by AstraZeneca LP (Wilmington, DE, USA), in accordance with Good Publication Practice guidelines (Battisti WP et al. *Ann Intern Med*. 2015;163:461–464. doi: 10.7326/M15-0288).

This article is being co-published in *The Journal of Family Practice* and *Cleveland Clinic Journal of Medicine.*
doi: 10.3949/ccjm.85.s1.03

constraints, and experiences between women and men.[18] However, psychologic comorbidity is an issue for both men and women with COPD, so it is important that clinicians are vigilant in recognizing anxiety and depression in both sexes, and are careful not to underestimate the burden in the male patient population.

It is also important to note that depression and anxiety often occur simultaneously in patients with COPD, with prevalence estimates of 26% to 43%.[9,19,20] COPD patients with both depression and anxiety are at a heightened risk of suicidal ideation, increased physical disability, and chronic depressive symptoms versus those with either disorder alone.[10,15] It is therefore important that comorbid anxiety and depression is not overlooked in patients with COPD.

Ensuring that anxiety and depression are recognized and treated effectively in patients with COPD is essential for optimizing outcomes. Primary care practitioners are well placed to diagnose anxiety and depression, and to ensure these conditions are suitably managed alongside treatments of COPD.

Potential mechanisms of anxiety and depression in COPD

Growing evidence suggests that the relationship between mood disorders—particularly depression—and COPD is bidirectional, meaning that mood disorders adversely impact prognosis in COPD, whereas COPD increases the risk of developing depression.[21] For example, in a study of 60 stable patients with COPD, elevated dyspnea and reduced exercise capacity were the predominant mechanisms leading to anxiety and depression symptoms associated with the condition.[22] In addition, the risk of new-onset depression was increased in COPD patients with moderate-to-severe dyspnea in a 3-year follow-up study.[23] Conversely, depression has been shown to be a significant risk factor for disabling dyspnea (modified Medical Research Council score ≥2) in patients with COPD.[24]

COPD can lead to feelings of hopelessness, social isolation, reduced physical functioning, and sedentary lifestyle, all of which are associated with an increased level of depressive symptoms.[25] Similarly, inadequate social support increases the risk of anxiety in patients with COPD.[26] Therefore, ensuring that patients with COPD have high-quality support is very important for reducing anxiety and depressive symptoms.[27]

The exact mechanisms for the association between mood disorders and COPD remain unclear.[7,10] Research to date indicates that the relationship between depression and impaired pulmonary function may be partly mediated by chronic inflammation[7,10]; systemic inflammation has been associated with other comorbidities of COPD (eg, muscle wasting and osteoporosis),[28] and emerging data appear to show that proinflammatory cytokines partly mediate the association between depressive symptoms and pulmonary function.[29] Smoking and hypoxemia may also influence the prevalence of depression in COPD, but symptom severity and impaired quality of life remain the most important determinants.[6,30]

Clinical studies have demonstrated that a number of patient-related factors, including female gender, younger age, current smoking, greater severity of airflow limitation, and lower socioeconomic status, are associated with a higher prevalence and/or increased risk of depression and/or anxiety in COPD.[3,4,30,31] Frequent episodes of rehospitalization, and comorbidities such as hypertension, arthritis, cancer, and heart disease, have been found to increase the risk of anxiety and depression in patients with COPD.[3,32] Risk of anxiety has been shown to increase with greater dyspnea severity.[4] Pain, a frequently overlooked symptom in COPD, has been shown to be associated with symptoms of both anxiety and depression in patients with COPD.[33] This is driven by worsened quality of life and sleep quality, decreased physical activity, and an increased fear of movement that occur as a result of pain.[34]

The impact of anxiety and depression in COPD

Comorbid anxiety and depression have a significant detrimental impact on morbidity and mortality in patients with COPD. Both disorders have been associated with an increased risk of death in COPD.[13,35-37] Indeed, of 12 comorbidities proposed to be predictors of mortality in a cohort of 187 female outpatients with COPD, anxiety was associated with the highest risk of death.[35,36]

In addition, patients with COPD and anxiety and/or depression have a higher risk of COPD exacerbations,[4,8,23,36,38-40] hospitalization,[41,42] rehospitalization,[14,36,43] longer hospital stays,[37,41,44] and mortality after exacerbations,[14,36,41] compared with patients without these comorbidities. Patients with COPD who have elevated anxiety symptoms also often experience their first hospitalization earlier in the natural course of COPD than those without anxiety.[36]

Psychologic comorbidities are also associated with worse lung function, dyspnea, and respiratory symptom burden in patients with COPD.[37,40] Patients with COPD and anxiety are more likely to experience greater dyspnea at an earlier stage of disease than those without anxiety.[36] Persistent smoking at 6 months after hospitalization for an acute exacerbation of COPD is also more likely to be seen in patients with depression.[37]

Patient-centered outcomes are worse in COPD patients with mood disorders. Both anxiety and depression have been

shown to correlate with significantly reduced health-related quality of life (HRQoL), poorer physical health status, functional limitations, and reduced exercise capacity.[4,23,37,40,45] The presence of either anxiety or depression at baseline has been shown to correlate with reduced HRQoL at 1-year follow-up, but depression appears to be the stronger predictor of low future HRQoL than anxiety.[45]

Additionally, mood disorders—particularly depression—reduce physical activity in patients with COPD.[46,47] Emotional responses to COPD symptoms, such as dyspnea, can further decrease activity and worsen deconditioning, resulting in a downward spiral of reduced inactivity, social isolation, fear, anxiety, and depression.[48]

COPD patients with any comorbidity exhibit lower rates of medication adherence than those without comorbidities.[49-51] Clinical studies have demonstrated that anxiety and depression are significant predictors of poor adherence to COPD interventions, including pulmonary rehabilitation (PR).[51-55] Nonadherence to COPD therapies is associated with poor clinical outcomes, including higher hospitalization rates and increased emergency department visits, and increased costs.[56,57] Health care expenditure, in terms of both specific COPD-related costs and general "all-cause" costs, is significantly higher in COPD patients with anxiety and/or depression than in those without.[8]

Diagnosis of anxiety and depression in patients with COPD

The underdiagnosis and undertreatment of anxiety and depression in this population is common and can adversely affect patient outcomes.[6,7,9,10,58] Hence, it is crucial that anxiety and depression are identified and more effectively managed in clinical practice.[10]

Primary care practitioners are the main point of contact for many patients with COPD,[6,59,60] and so can play a key role in screening for and early identification of anxiety and depression. However, detection of mood disorders by primary care practitioners is challenging for several reasons. These include the lack of a standardized approach in diagnosis, and inadequate knowledge or confidence in assessing psychological status (particularly given the number of strategies available for screening patients for mood disorders),[6] as well as factors associated with time constraints, such as competing agendas, duration of visits, and high patient load.[6,61] Furthermore, system-level barriers, such as lack of electronic medical records and adequate health insurance, as well as any communication gaps between primary care and mental health care, may hinder the detection and management of anxiety and depression.[6] In addition, patients themselves may have a limited understanding of these comorbidities, or may be hesitant to discuss symptoms of anxiety or depression with their primary care practitioner owing to stigma around mental illness.[6]

Patients with COPD should be screened and assessed for anxiety and depression, and the United States Preventive Services Task Force recommends that clinicians screen for depression in all adults.[6,62] There are several validated screening tools suitable for clinical use:

- Anxiety Inventory for Respiratory (AIR) Disease score: a brief, easy-to-use tool for screening and measuring anxiety in COPD.[63,64] It is a self-administered scale, and takes approximately 2 minutes to complete. The AIR scale is responsive to PR.[64]
- COPD Anxiety Questionnaire (CAF): a reliable tool for early identification of COPD-related anxiety.[65]
- Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (PHQ; available at: http://www.phqscreeners.com/select-screener/): the PRIME-MD comprises 26 yes/no questions on the 5 most common psychiatric disorders, including depression and anxiety.[66,67] This is not a diagnostic tool, but a high number of positive responses from a patient in any given module indicates that they require further clinical evaluation.
- PHQ-2 and PHQ-9 (**TABLE 1**; PHQ-9 available at http://www.phqscreeners.com/select-screener/): widely-used self-administered 2- and 9-item versions of the PRIME-MD, specific to depression; similarly, the 3-item PHQ-3 is available for anxiety assessment (**TABLE 2**).[6,67,68] In a study investigating tools used by family physicians in England to assess depression, over 75% used PHQ-9.[69]
- Generalized Anxiety Disorder 7-item (GAD-7) scale: an efficient, self-report scale that scores 7 common anxiety symptoms and can be used for screening and severity assessment of GAD in clinical practice.[70]
- Hospital Anxiety and Depression Scale (HADS) and General Health Questionnaire-version 20 (GHQ-20): both can be used to screen for psychologic distress in patients with COPD.[71]
- The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI): two 21-item self-report questionnaires that are widely used in the United States to evaluate anxiety and depression.[72]

In addition to specific anxiety and depression questionnaires (**TABLES 1** and **2**), more general COPD assessments tools, such as the COPD Assessment Test and the COPD Clinical Questionnaire, also incorporate questions that may be indicative of symptoms of these comorbidities in patients with COPD.[73]

TABLE 1 PHQ-2 and PHQ-9 screening questionnaires for depression[6,67]

PHQ-2	In the past month, have you been bothered a lot by: 1. Little interest or pleasure in doing things? 2. Feeling down, depressed, or hopeless?
PHQ-9	Over the past 2 weeks, how often have you been bothered by any of the following problems (not at all, for several days, for more than half the days, or nearly every day)? 1. Little interest or pleasure in doing things 2. Feeling down, depressed, or hopeless 3. Trouble falling or staying asleep, or sleeping too much 4. Feeling tired or having little energy 5. Poor appetite or overeating 6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down 7. Trouble concentrating on things, such as reading the newspaper or watching television 8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual 9. Thoughts that you would be better off dead or hurting yourself in some way

Reprinted from: *Chest*,134(4 Suppl):43S-56S. Maurer J, Rebbapragada V, Borson S, et al. ACCP Workshop Panel on Anxiety and Depression in COPD. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Copyright 2008, with permission from Elsevier. PHQ-9 questionnaire developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc.

Management of anxiety and depression in COPD

Even though anxiety and depression are among the most common and burdensome comorbid conditions in COPD, less than one-third of patients with these comorbidities receive effective intervention.[6,10] Primary care providers have an excellent opportunity to impact this care gap.

It is important that all health care professionals involved in the care of patients with COPD are vigilant for anxiety and depressive symptoms, as well as the possibility of a major anxiety or depressive disorder. Communication with other multidisciplinary team members is central to ensuring appropriate psychiatric treatment in patients with COPD, particularly sharing key information about medication history, warning signs of depression and anxiety, and any indication of suicide ideation.[74] Referral to palliative care teams can also help to manage these psychological comorbidities in patients with severe COPD at advanced stages.[75]

As in non-COPD patients, comorbid depression and anxiety may be treated with nonpharmacologic and/or pharmacologic interventions (**FIGURE 1**).[76]

Nonpharmacologic interventions

Evidence to date suggests that nonpharmacologic interventions such as behavioral therapy are as effective as antidepressants, and may be preferred by patients with mood disorders.[12]

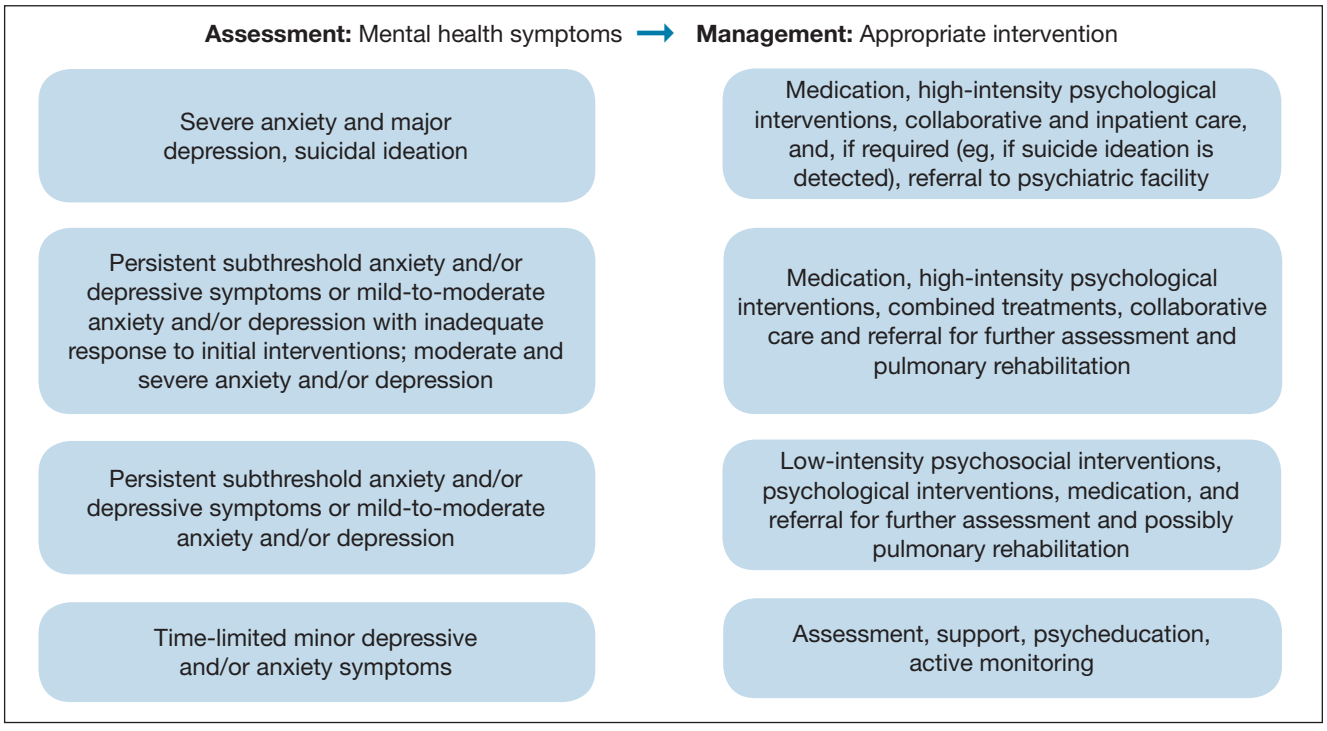
TABLE 2 PHQ-3 screening questionnaire for anxiety[6,67]

PHQ-3	In the past month, have you been bothered a lot by: 1. 'Nerves,' or feeling anxious or 'on edge'? 2. Worrying about a lot of different things? During the past month: 3. Have you had an anxiety attack (ie, suddenly feeling fear or panic)?

Reprinted from: *Chest*,134(4 Suppl):43S-56S. Maurer J, Rebbapragada V, Borson S, et al. ACCP Workshop Panel on Anxiety and Depression in COPD. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Copyright 2008, with permission from Elsevier.

Cognitive behavioral therapy (CBT), which is typically administered by psychologists/psychiatrists, may be effective in treating COPD-related anxiety and depression, especially in conjunction with exercise and education.[12,76,77] Individualized or group CBT is the treatment of choice for addressing thinking patterns that contribute to anxiety and depression to change a patient's behavior and emotional state.[76] PR programs involve several components,

FIGURE 1 **Recommendations for the treatment of psychiatric symptoms in patients with COPD[76]**



including aerobic exercise, lung function training, and psycho-education.[62,76] PR is suitable for most patients with COPD, and provides multiple benefits, including reduced hospitalizations in patients who have had a recent exacerbation, and improved dyspnea, exercise tolerance, and health status in patients with stable disease,[62] as well as clinically and statistically significant improvements in depression and anxiety, irrespective of age.[7,78,79] Exercise-based forms of PR appear to be the most effective for reducing mood symptoms,[12,76] and incorporating psychotherapy may also improve psychologic outcomes.[80] Stress reduction (relaxation) therapy aims to reduce anxiety-related physiologic changes, and includes a variety of techniques (eg, breathing exercises, sequential muscle relaxation, hypnosis, mindfulness meditation), some of which may be included in PR or used alongside other treatments (eg, CBT).[76] Limited data indicate that such therapy may be beneficial for reducing anxiety and depression, as well as respiratory symptoms and dyspnea, in patients with COPD.[12,76]

Self-management techniques improve clinical outcomes in patients with COPD, but data on the management of depression or anxiety are inconclusive.[7,12] A minimal, home-based, nurse-led, psycho-educational intervention was designed to encourage more open-ended, descriptive discussions of thoughts, emotions, behaviors, and bodily sensations in patients with COPD.[81] The intervention, which involved nurses attending a 1-hour face-to-face session in the patients' homes with a 15-minute telephone "booster" session 2 weeks later, helped patients with advanced COPD to self-manage their condition and provide relief from anxiety.[81,82] However, it should be noted that there is currently a lack of high-quality data evaluating psychologic interventions in the COPD population.[83]

In addition, it is important that caregivers are supported in the management of patients with COPD and comorbid anxiety and/or depression; areas in which caregivers can be assisted in their role may include disease education and counseling, where appropriate.[84]

Given that smoking cessation is a key recommendation for patients with COPD,[44,62] practitioners should be aware that patients with comorbid depression and anxiety may experience greater difficulty in smoking cessation, and worsened mood during nicotine withdrawal.[44] Clinicians should therefore carefully monitor current smokers with

COPD and comorbid depression/anxiety (using the tools described previously[63,68,70,71]) when they are attempting to quit smoking.

Pharmacologic interventions

Pharmacologic therapy of anxiety and depression has so far only been investigated in patients with COPD in small studies.[76] However, the available evidence does not indicate that COPD patients with anxiety and depression should be managed any differently from individuals without COPD.[62] As such, pharmacologic interventions are particularly important for patients with acute or severe anxiety or depression.

Antidepressant agents are categorized according to their mechanism of action, and most commonly include selective serotonin-reuptake inhibitors (SSRIs), selective norepinephrine-reuptake inhibitors, bupropion (a norepinephrine- and dopamine-reuptake inhibitor; also approved for smoking cessation[85]), and mirtazapine (a norepinephrine and serotonin modulator), among others.[86] SSRIs are the current first-line drug treatment for depression, and have been shown to significantly improve depression and anxiety in patients with COPD in some, but not all, trials published to date.[76] However, it is important to note that a diagnosis of bipolar disorder must be ruled out before initiating standard antidepressant therapy.[87] In addition to antidepressants, atypical antipsychotics have also been shown to be useful for treating anxiety, either as monotherapy or combination therapy, and possibly as an adjunctive therapy for the management of depression.[88,89]

Primary care practitioners can refer to existing guidelines on the management of anxiety and depression in patients with COPD,[86,90] while taking certain factors into consideration. Any pharmacologic management strategy for the treatment of COPD may increase the risk of drug–drug or drug–disease interactions.[76] For example, it is important to avoid medications that cause respiratory depression (eg, benzodiazepines [unless used with extreme caution], particularly in patients who are already CO_2 retainers) or sedation; chosen drugs should have minimal other adverse effects.[76] Moreover, SSRIs may also be associated with troublesome adverse effects during treatment initiation, such as gastrointestinal upset, headache, tremor, psychomotor activation, and sedation[76]; in addition, dry mouth is an adverse effect associated with both SSRI treatment and several inhaled therapies, so may be particularly problematic in patients with COPD.[91,92] Currently, data are particularly scarce for the management of anxiety in patients with COPD, with inconclusive or contradictory findings reported for SSRIs, azapirones (including buspirone), and tricyclic antidepressants.[76]

In addition to monitoring adherence to COPD therapies, primary care practitioners should carefully monitor patients treated with antidepressants and anxiolytics for adherence. A meta-analysis of 18,245 individuals with chronic diseases showed that depressed patients had a 76% significantly higher risk of nonadherence to medication compared with those without depressive symptoms.[93]

Targeting dyspnea is key to the management of anxiety and depression in COPD, as breathlessness is frequently associated with the onset of both comorbidities.[21,22] Therapeutic approaches to alleviating dyspnea include PR, optimizing respiratory mechanics and muscle function (with bronchodilator therapy), and reducing central neural drive to respiratory muscles with supplemental oxygen or opioid medication.[94]

Although bronchodilator therapy for COPD has not been shown to have significant direct effects on depression or anxiety,[95] it can be assumed that the beneficial effects on dyspnea are likely to alleviate associated emotional and mood symptoms.

Further research into effective screening, diagnosis, and management of comorbid anxiety and depressive disorders in COPD is warranted, including evaluation of a broad range of nonpharmacologic and drug-based interventions, alone and in combination.[76]

Conclusions

Anxiety and depression are common, yet frequently overlooked, comorbidities in COPD. The impact of these psychologic comorbidities is significant; their consequences are evident in morbidity and mortality data, as well as in patient-reported outcomes. As key points of contact for patients with COPD, it is essential that primary care practitioners are vigilant in monitoring for anxiety and depression in their patients with COPD, making the most of the available tools that can support them in doing so, and maintain an ongoing line of communication with other members of the multidisciplinary team. Treatment of anxiety and depression in COPD should adopt a holistic approach that incorporates both nonpharmacologic and pharmacologic interventions. However, the impact of effective screening, diagnosis, and management of anxiety and depression on COPD burden in patients requires further investigation. ●

REFERENCES

1. Chaudhary SC, Nanda S, Tripathi A, et al. Prevalence of psychiatric comorbidities in chronic obstructive pulmonary disease patients. *Lung India*. 2016;33(2):174-178.
2. Zhang MW, Ho RC, Cheung MW, Fu E, Mak A. Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. *Gen Hosp Psychiatry*. 2011;33(3):217-223.
3. Tsai TY, Livneh H, Lu MC, Tsai PY, Chen PC, Sung FC. Increased risk and related

factors of depression among patients with COPD: a population-based cohort study. *BMC Public Health*. 2013;13:976.
4. Eisner MD, Blanc PD, Yelin EH, et al. Influence of anxiety on health outcomes in COPD. *Thorax*. 2010;65(3):229-234.
5. Marsh S, Guck TP. Anxiety and depression: easing the burden in COPD patients. *J Fam Pract*. 2016;65(4):246-256.
6. Maurer J, Rebbapragada V, Borson S, et al; ACCP Workshop Panel on Anxiety and Depression in COPD. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest*. 2008;134(4 Suppl):43S-56S.
7. Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression—important psychological comorbidities of COPD. *J Thorac Dis*. 2014;6(11): 1615-1631.
8. Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of depression/anxiety in chronic obstructive pulmonary disease patients within a managed care population. *COPD*. 2011;8(4):293-299.
9. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*. 2005;127(4):1205-1211.
10. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. *Eur Respir Rev*. 2014;23(133):345-349.
11. American Psychiatric Association. Depressive Disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
12. Panagioti M, Scott C, Blakemore A, Coventry PA. Overview of the prevalence, impact, and management of depression and anxiety in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;9:1289-1306.
13. Laforest L, Roche N, Devouassoux G, et al. Frequency of comorbidities in chronic obstructive pulmonary disease, and impact on all-cause mortality: a population-based cohort study. *Respir Med*. 2016;117:33-39.
14. Lecheler L, Richter M, Franzen DP, et al. The frequent and underrecognised co-occurrence of acute exacerbated COPD and depression warrants screening: a systematic review. *Eur Respir Rev*. 2017;26(144):pii: 170026.
15. Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. *Respir Care*. 2013;58(5):858-866.
16. Livermore N, Sharpe L, McKenzie D. Panic attacks and panic disorder in chronic obstructive pulmonary disease: a cognitive behavioral perspective. *Respir Med*. 2010;104(9):1246-1253.
17. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva, Switzerland; World Health Organization: 2017.
18. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. 2014;35(3):320-330.
19. Biswas D, Mukherjee S, Chakroborty R, et al. Occurrence of anxiety and depression among stable COPD patients and its impact on functional capability. *J Clin Diagn Res*. 2017;11(2):OC24-OC27.
20. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. *Int J Geriatr Psychiatry*. 2000;15(12):1090-1096.
21. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. *Chest*. 2013;144(3):766-777.
22. Tetikkurt C, Ozdemir I, Tetikkurt S, Yilmaz N, Ertan T, Bayar N. Anxiety and depression in COPD patients and correlation with sputum and BAL cytology. *Multidiscip Respir Med*. 2011;6(4):226-231.
23. Yohannes AM, Müllerová H, Hanania NA, et al. Long-term course of depression trajectories in patients with COPD: a 3-year follow-up analysis of the evaluation of COPD longitudinally to identify predictive surrogate endpoints cohort. *Chest*. 2016;149(4):916-926.
24. Sundh J, Ekström M. Persistent disabling breathlessness in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2805-2812.
25. Kirkil G, Deveci F, Deveci SE, Atmaca M. Anxiety and depression symptoms in patients with chronic obstructive pulmonary disease. *Bulletin Clin Psychopharmacol*. 2015;25(2):151-161.
26. Fuller-Thomson E, Lacombe-Duncan A. Understanding the association between chronic obstructive pulmonary disease and current anxiety: a population-based study. *COPD*. 2016;13(5):622-631.
27. Yohannes AM. Is it quality or quantity of social support needed for patients with chronic medical illness? *J Psychosom Res*. 2013;74(2):87-88.
28. Fabbri LM, Luppi F, Beghe B, Rabe KF. The multiple components of COPD. In: Hanania NA, Sharafkhaneh A, eds. *COPD: a guide to diagnosis and clinical management*. Humana Press; 2010.
29. Lu Y, Feng L, Feng L, Nyunt MS, Yap KB, Ng TP. Systemic inflammation, depression and obstructive pulmonary function: a population-based study. *Respir Res*. 2013;14:53.
30. Hanania NA, Müllerova H, Locantore NW, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med*. 2011;183(5):604-611.
31. Zhang Q, Liao J, Liao X, et al. Disease knowledge level is a noteworthy risk factor of anxiety and depression in patients with chronic obstructive pulmonary disease: a cross-sectional study. *BMC Pulm Med*. 2014;14:92.
32. Jose AK, Chelangara DP, Shaji KS. Factors associated with anxiety and depression in chronic obstructive pulmonary disease. *Int J Res Med Sci*. 2016;4(4):1074-1079.
33. van Dam van Isselt EF, Groenewegen-Sipkema KH, Spruit-van Eijk M, et al. Pain in patients with COPD: a systematic review and meta-analysis. *BMJ Open*. 2014;4(9):e005898.
34. Lee AL, Harrison SL, Goldstein RS, Brooks D. Pain and its clinical associations in individuals with COPD: a systematic review. *Chest*. 2015;147(5):1246-1258.
35. Divo M, Cote C, de Torres JP, et al; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155-161.
36. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10:95-109.
37. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Arch Intern Med*. 2007;167(1):60-67.
38. Montserrat-Capdevila J, Godoy P, Marsal JR, et al. Overview of the impact of depression and anxiety in chronic obstructive pulmonary disease. *Lung*. 2017;195(1): 77-85.
39. Laurin C, Moullec G, Bacon SL, Lavoie KL. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*. 2012;185(9):918-923.
40. Martinez Rivera C, Costan Galicia J, Alcázar Navarrete B, et al. Factors associated with depression in COPD: a multicenter study. *Lung*. 2016;194(3):335-343.
41. Pooler A, Beech R. Examining the relationship between anxiety and depression and exacerbations of COPD which result in hospital admission: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2014;9:315-330.
42. Dahlén I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. *Chest*. 2002;122(5):1633-1637.
43. Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J*. 2005;26(3):414-419.
44. Mikkelsen RL, Middelboe T, Pisinger C, Stage KB. Anxiety and depression in patients with chronic obstructive pulmonary disease (COPD). A review. *Nord J Psychiatry*. 2004;58(1):65-70.
45. Blakemore A, Dickens C, Guthrie E, et al. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2014;9:501-512.
46. Dueñas-Espín I, Demeyer H, Gimeno-Santos E, et al. Depression symptoms reduce physical activity in COPD patients: a prospective multicenter study. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1287-1295.
47. Lee SH, Kim KU, Lee H, Kim YS, Lee MK, Park HK. Factors associated with low-level physical activity in elderly patients with chronic obstructive pulmonary disease [published online ahead of print June 7, 2017]. *Korean J Intern Med*. 2017;doi: 10.3904/kjim.2016.090.
48. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. *Eur Respir J*. 2008;31(3):667-677.
49. George J, Kong DC, Thoman R, Stewart K. Factors associated with medication nonadherence in patients with COPD. *Chest*. 2005;128(5):3198-3204.
50. Morrison D, Agur K, Mercer S, Eiras A, González-Montalvo JI, Gruffydd-Jones K. Managing multimorbidity in primary care in patients with chronic respiratory conditions. *NPJ Prim Care Respir Med*. 2016;26:16043.
51. Khdour MR, Hawwa AF, Kidney JC, Smyth BM, McElnay JC. Potential risk factors for medication non-adherence in patients with chronic obstructive pulmonary disease (COPD). *Eur J Clin Pharmacol*. 2012;68(10):1365-1373.
52. Busch AM, Scott-Sheldon LA, Pierce J, et al. Depressed mood predicts pulmonary rehabilitation completion among women, but not men. *Respir Med*. 2014;108(7):1007-1013.
53. Heerema-Poelman A, Stuive I, Wempe JB. Adherence to a maintenance exercise program 1 year after pulmonary rehabilitation: what are the predictors of dropout? *J Cardiopulm Rehabil Prev*. 2013;33(6):419-426.
54. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101-2107.
55. Fan VS, Giardino ND, Blough DK, Kaplan RM, Ramsey SD; Nett Research Group. Costs of pulmonary rehabilitation and predictors of adherence in the National Emphysema Treatment Trial. *COPD*. 2008;5(2):105-116.
56. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax*. 2008;63(9):831-838.
57. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Mölken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med*. 2014;108(1):103-113.
58. Dury R. COPD and emotional distress: not always noticed and therefore untreated. *Br J Community Nurs*. 2016;21(3):138-141.
59. Price D, Crockett A, Arne M, et al. Spirometry in primary care case-identification, diagnosis and management of COPD. *Prim Care Respir J*. 2009;18(3):216-223.
60. van Boven JF, Ryan D, Eakin MN, Canonica GW, Barot A, Foster JM; Respiratory Effectiveness Group. Enhancing respiratory medication adherence: the role of health care professionals and cost-effectiveness considerations. *J Allergy Clin Immunol Pract*. 2016;4(5):835-846.

61. Wittchen HU, Mühlig S, Beesdo K. Mental disorders in primary care. *Dialogues Clin Neurosci*. 2003;5(2):115-128.
62. Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Accessed June 2017.
63. Willgoss TG, Goldbart J, Fatoye F, Yohannes AM. The development and validation of the anxiety inventory for respiratory disease. *Chest*. 2013;144(5):1587-1596.
64. Yohannes AM, Dryden S, Hanania NA. The responsiveness of the anxiety inventory for respiratory disease scale following pulmonary rehabilitation. *Chest*. 2016;150(1):188-195.
65. Kühl K, Kuhn C, Kenn K, Rief W. [The COPD-Anxiety-Questionnaire (CAF): a new instrument to assess illness specific anxiety in COPD patients]. *Psychother Psychosom Med Psychol*. 2011;61(1):e1-e9. German.
66. Tamburrino MB, Lynch DJ, Nagel RW, Smith MK. Primary care evaluation of mental disorders (PRIME-MD) screening for minor depressive disorder in primary care. *Prim Care Companion J Clin Psychiatry*. 2009;11(6):339-343.
67. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282(18):1737-1744.
68. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med*. 2010;8(4):348-353.
69. Yohannes AM, Hann M, Sibbald B. The management of depressive symptoms in patients with COPD: a postal survey of general practitioners. *Prim Health Care Res Dev*. 2011;12(3):237-244.
70. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.
71. Bratås O, Grønning K, Forbord T. Psychometric properties of the Hospital Anxiety and Depression Scale and The General Health Questionnaire-20 in COPD inpatients. *Scand J Caring Sci*. 2014;28(2):413-420.
72. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther*. 1995;33(3):335-343.
73. Sundh J, Ställberg B, Lisspers K, Kämpe M, Janson C, Montgomery S. Comparison of the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ) in a clinical population. *COPD*. 2016;13(1):57-65.
74. Cantor L, Jacobson R. COPD: How to manage comorbid depression and anxiety. *Curr Psychiatry*. 2003;2(11):45-54.
75. Yohannes AM. Palliative care provision for patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. 2007;5:17.
76. Tselebis A, Pachi A, Ilias I, et al. Strategies to improve anxiety and depression in patients with COPD: a mental health perspective. *Neuropsychiatr Dis Treat*. 2016;12:297-328.
77. Doyle C, Bhar S, Fearn M, et al. The impact of telephone-delivered cognitive behaviour therapy and befriending on mood disorders in people with chronic obstructive pulmonary disease: a randomized controlled trial. *Br J Health Psychol*. 2017;22(3):542-556.
78. Alsaraireh FA, Aloush SA. Does pulmonary rehabilitation alleviate depression in older patients with chronic obstructive pulmonary disease. *Saudi Med J*. 2017;38(5):491-496.
79. Bennett D, Bowen B, McCarthy P, Subramaniam A, O'Connor M, Henry MT. Outcomes of pulmonary rehabilitation for COPD in older patients: a comparative study. *COPD*. 2017;14(2):170-175.
80. Smith SM, Sonego S, Ketcheson L, Larson JL. A review of the effectiveness of psychological interventions used for anxiety and depression in chronic obstructive pulmonary disease. *BMJ Open Respir Res*. 2014;1(1):e000042.
81. Bove DG, Overgaard D, Lomborg K, Lindhardt BØ, Midtgaard J. Efficacy of a minimal home-based psychoeducative intervention versus usual care for managing anxiety and dyspnoea in patients with severe chronic obstructive pulmonary disease: a randomised controlled trial protocol. *BMJ Open*. 2015;5(7):e008031.
82. Bove DG, Lomborg K, Jensen AK, Overgaard D, Lindhardt BØ, Midtgaard J. Efficacy of a minimal home-based psychoeducative intervention in patients with advanced COPD: a randomised controlled trial. *Respir Med*. 2016;121:109-116.
83. Usmani ZA, Carson KV, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;3: CD010673. doi:10.002/14651858.CD010673.pub2.
84. Cafarella P, Effing T, Frith P. An evaluation of the needs of carers of people with COPD. *EurResp J*. 2012;40(Suppl 56).
85. Zyban [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zyban/pdf/ZYBAN-PI-MG.PDF. Accessed June 2017.
86. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder. *Am J Psychiatry*. 2010;167(10):1.
87. Pary R, Matuschka PR, Lewis S, Lippmann S. Managing bipolar depression. *Psychiatry (Edgmont)*. 2006;3(2):30-41.
88. Blier P. Atypical antipsychotics for mood and anxiety disorders: safe and effective adjuncts? *J Psychiatry Neurosci*. 2005;30(4):232-233.
89. Vulink NC, Figee M, Denys D. Review of atypical antipsychotics in anxiety. *Eur Neuropsychopharmacol*. 2011;21(6):429-449.
90. Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician*. 2015;91(9):617-624.
91. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database Syst Rev*. 2014;(3):CD010844. doi:10.1002/14651858.CD010844.pub2.
92. Scully C. Drug effects on salivary glands: dry mouth. *Oral Dis*. 2003;9(4):165-176.
93. Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J Gen Intern Med*. 2011;26(10):1175-1182.
94. O'Donnell DE, Webb KA, Harle I, Neder JA. Pharmacological management of breathlessness in COPD: recent advances and hopes for the future. *Expert Rev Respir Med*. 2016;10(7):823-834.
95. Hyun MK, Lee NR, Jang EJ, Yim JJ, Lee CH. Effect of inhaled drugs on anxiety and depression in patients with chronic obstructive pulmonary disease: a prospective observational study. *Int J Chron Obstruct Pulmon Dis*. 2016;11:747-754.

Considerations for Optimal Inhaler Device Selection in Chronic Obstructive Pulmonary Disease

Rajiv Dhand, MD; Tricia Cavanaugh, MD; and Neil Skolnik, MD

Introduction

Inhalation is the standard route of administration for drugs used to treat chronic obstructive pulmonary disease (COPD) and asthma.[1] Inhalation is a quick drug delivery method that offers both efficacy and safety.[2,3] Inhaled administration allows targeted delivery of the active drug to the site of action, enabling lower doses and resulting in fewer systemic adverse events than oral therapy.[3] There are 4 main types of devices used to deliver inhaled medication: pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft-mist inhalers (SMIs), and nebulizers. Each type of inhaler device is associated with advantages and limitations that determine their suitability for any given patient with COPD[4,5] (**TABLE 1**).[3,6,7] Understanding those advantages and limitations helps clinicians in choosing the proper device for the individual patient's clinical needs and preferences. However, with the wide range of permutations of drug combinations now possible, inhaler selection remains challenging.[4] For all inhaler devices, adequate training for patients on how to use their device is required to achieve optimal therapeutic benefits.[1]

Rajiv Dhand, MD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Tennessee Medical Center, Knoxville, Tennessee.

Tricia Cavanaugh, MD, Abington Hospital–Jefferson Health, Abington, Pennsylvania

Neil Skolnik, MD, Abington Family Medicine, Jenkintown, Pennsylvania

DISCLOSURES

Dr. Dhand has participated on advisory boards for AstraZeneca, Bayer Healthcare, Cipla Limited, and GlaxoSmithKline, and has received honoraria from AstraZeneca, Cipla Limited, and Sunovion Pharmaceuticals Inc.

Dr. Cavanaugh has no financial interests to declare.

Dr. Skolnik has participated on advisory boards for AstraZeneca; Boehringer Ingelheim GmbH; Eli Lilly and Company; Intarcia Therapeutics, Inc.; Janssen Pharmaceuticals, Inc.; sanofi-aventis U.S. LLC; and Teva Pharmaceutical Industries, Ltd.; as a speaker for AstraZeneca and Boehringer Ingelheim GmbH; and has received research support from AstraZeneca and sanofi-aventis U.S. LLC.

Funding for this article was provided by AstraZeneca LP (Wilmington, DE, USA). Medical writing support was provided by Hannah Burke, BSc, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip, of Core (London, UK), which were funded by AstraZeneca LP (Wilmington, DE, USA), in accordance with Good Publication Practice guidelines (Battisti WP et al. *Ann Intern Med*. 2015;163:461–464. doi: 10.7326/M15-0288).

This article is being co-published in *The Journal of Family Practice* and *Cleveland Clinic Journal of Medicine.*
doi: 10.3949/ccjm.85.s1.04

Device considerations

Examples of the different inhaler devices available for COPD treatments are provided in **FIGURE 1**, and their key characteristics are summarized in **TABLE 2**.[3,7] Traditional pMDIs require actuation of the device at the beginning of a slow, deep inhalation to optimize drug delivery. This technique requires hand–breath coordination, which can be difficult for some patients, particularly those who are elderly or severely short of breath; spacers can be used in combination with pMDIs to help to overcome some technique issues (**FIGURE 1**).[3,8] Breath-actuated (BA) pMDIs may also be used in some countries (though are not currently licensed in the United States); these devices release the dose on inhalation, removing the need for hand–breath coordination.[3]

DPIs are also breath-actuated, with the patient providing the force necessary to deliver the drug on inhalation; drug delivery with DPIs is therefore dependent on patients achieving a high enough peak inspiratory flow (PIF) rate to disperse the drug, in contrast to BA pMDIs, which are activated at a lower PIF rate.[3,8] Generating the inspiratory flow required for effective function of DPIs can be problematic for some patients with COPD.[9] Suboptimal PIF rates have been associated with age (≥60 years), female gender, shorter height, and lower values for forced vital capacity and inspiratory capacity as percentage predicted in stable patients with severe COPD[10]; in addition, patients with COPD can have a temporarily reduced PIF rate after hospitalization for an

TABLE 1 Key characteristics of different device types[3,6,7]

Characteristics	pMDIs	DPIs	SMIs	Nebulizers
Ease of use	Requires coordination between actuation and inhalation (which can be eased when used in conjunction with a spacer, or by using a breath-actuated pMDI)	Varies; they are generally breath-actuated and do not require coordination between actuation and inhalation	Requires assembly and coordination between actuation and inhalation	No specific breathing techniques have to be taught for using nebulizers
Suitable for maintenance or reliever medication	Reliever and maintenance	Reliever and maintenance	Reliever and maintenance	Reliever and maintenance
Treatment time	Short	Short	Short	Longer than pMDIs / DPIs (duration depends on nebulizer device type)
Portability	High	High	High	Depends on type
Multi-dose device	Yes	Some DPIs	Yes	No
Dose counter	Yes	Yes	Yes	No

Abbreviations: DPIs, dry powder inhalers; pMDIs, pressurized metered-dose inhalers; SMIs, soft mist inhalers.

acute exacerbation.[11,12] There is a range of DPIs available in three main categories: single-dose, multi-dose, and power-assisted devices.[7] It is important to protect DPI devices from the effects of humidity, which can increase particle adhesion and therefore reduce efficacy.[13]

The SMI delivers the aerosol as a fine mist with slow velocity lasting >1 second, which is considerably slower than spray delivery with pMDIs.[14] The aim of this design is to make it easier for patients to coordinate actuation with inhalation, but it is important to note that some coordination is still required for SMI devices to function correctly.[14] In addition, the SMI is not dependent on a patient's ability to generate sufficient PIF for effective drug delivery. A limitation of the SMI is the need to assemble the device, as patients with poor manual dexterity may encounter difficulty when attempting to load the drug cartridge.[15]

Nebulizers deliver aerosolized drug in a fine mist. Newer-generation portable vibrating mesh nebulizers can deliver a dose over a period of ~2 minutes, compared with 10 minutes for conventional pneumatic devices.[16] Patients find them effective and easy to use, and the newer generation devices overcome problems with portability and length of treatment, which may be an issue during the daytime for ambulatory patients, along with the requirement for cleaning after each dose.[4,8] However, drug delivery may be somewhat compromised with nebulizers compared with other inhalation devices, as medication can be dispersed into the atmosphere and lost, rather than inhaled.[7] An additional point to consider is medication availability; some medications, particularly fixed-dose combination maintenance therapies, are currently unavailable in a nebulized format.[16]

The most important device-related factors influencing the site of deposition within the lungs are aerosol velocity and particle size of the inhaled drug.[3,7,17] To maximize clinical effectiveness, adequate distribution throughout the lung is required to reach target sites of action for β_2-agonists, anticholinergics, and corticosteroids.[17] Particle size differs between inhaler device types, but all available devices generate drug particles sufficient for deposition throughout the lower airways and lung periphery, ie, within the range of 1–5 microns.[3,18-21] Extra fine particles of <1 micron (or "submicron particles") can be deposited deeper in the pulmonary acinus, but a higher fraction of such particles may be exhaled compared with particles 1–5 microns in size.[3,20,22] In contrast, particles >5 microns deposit in the oropharynx and may be swallowed, potentially leading to systemic adverse effects.[3,20,22]

When more than one drug is required, it may be preferable to deliver them via a single device where possible to facilitate patient compliance with correct technique, and decrease confusion about how to use different inhalers.[23] The inhaler device ideally serves as a platform on which many treatments

are available; the greater the number of devices employed by the patient, the greater the likelihood of making an error with the usage of each device.[24]

Importance of proper inhaler technique

Errors relating to device handling are common in patients with COPD. The results of a meta-analysis by Chrystyn et al reported that overall error rates were high across all devices in patients with COPD and asthma, ranging from 50%–100%[25]; the reported frequencies of patients with at least one error were 86.8% and 60.9% for pMDIs and DPIs, respectively. However, the authors note that heterogeneity between the studies used in the analysis was high, and suggest that future investigations should look to use a more standardized approach in assessment of inhaler device errors.[25] Moreover, further studies to investigate the frequency of errors in SMI devices, and to establish the relationship between critical errors in device handling and device efficacy, are warranted.

Handling errors are directly linked to compromised drug delivery and reduced treatment efficacy.[3] This may lead to more frequent or inappropriate medication use that, in turn, could result in unnecessary dose increases by the physician due to perceived lack of efficacy, and subsequently more adverse effects.[3,26-28] However, these errors can be addressed through proper training and demonstration.[29-32]

Common device-handling errors include[4,26,27,32,33]**:**

- **pMDIs:** not shaking the inhaler (for suspensions), not exhaling fully before actuation, inhaling too forcefully, and not holding their breath for long enough after inhalation.
- **DPIs:** exhaling into the device mouthpiece, not exhaling fully before inhalation, not inhaling deeply or forcefully enough, and not holding their breath after inhalation.
- **SMIs:** not rotating the inhaler with mouth cap facing upwards, rotating the inhaler while looking into the spray nozzle with the cap open (before inhalation), and not maintaining inhalation with drug spray.

Critical inhaler use errors (where an error results in no or an insufficient amount of medicine being delivered to the lungs, thereby leading to suboptimal disease control[25]) are less common; the frequencies of these errors for pMDIs and DPIs are summarized in **TABLE 3**.[26]

Incorrect inhaler use is a common cause of secondary nonadherence (ie, relating to incorrect medication use) among patients with COPD.[4,34] Compromised inhaler technique and medication nonadherence jeopardize health outcomes and add to the economic burden of COPD.[8,12,26]

FIGURE 1 Examples of different inhaler device and spacer types

Abbreviations: COPD, chronic obstructive pulmonary disease; DPIs, dry powder inhalers; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor antagonist; pMDIs, pressurized metered-dose inhalers; SAMA, short-acting muscarinic receptor antagonist; SMI, soft mist inhalers.

Please note that some COPD drugs are available in other devices not shown in this figure. (A) Atrovent, a pMDI SAMA (also available in a nebulized format), (B) Symbicort, a pMDI LABA/ICS, (C) Serevent, a DPI LABA, (D) Anoro, a DPI LAMA/LABA, (E) Spiriva, an SMI LAMA (also available in a DPI device), (F) Vortex, a small volume valve spacer with nonelectrostatic interior, (G) Volumatic, a large volume spacer.

TABLE 2 Characteristics of inhaler devices[3,7]

Device type	Mechanism of action
HFA pMDI	Pressurized suspension of micronized drug particles distributed in propellant; others are ethanolic solutions
	Precise amount (20–100 µL) dispensed with each press of canister
	Shaking not required as with CFC pMDIs
	Pressing canister releases drug
Breath-actuated pMDI	Pressurized canister with flow-triggered system driven by a spring
	Inhalation drives spring to trigger inhalation
	Requires higher PIF than HFA pMDIs, but lower than DPIs
DPI	Dry powder inside capsule (manual loading) or inside device
	Micronized drug particles (1–5 µm) blended with inactive excipient (40 µm) or used alone
	Inhalation deaggregates medication particles and disperses them within airways
	Minimum PIF rate required for deaggregation (varies by DPI device)
	Passive (breath-actuated)
SMI	Propellant-free
	Drug stored inside cartridge (loaded on first use)
	Spring releases dose into micropump; dose released when button is pressed
	"Uniblock" passes dose through minute channels releasing jet streams of drug solution
Breath-enhanced jet nebulizer	Air stream moves through jet causing drug solution to be aerosolized; powered by compressor
	Additional room air taken into nebulizer during inhalation drives aerosolization
	Nebulizer drug solution cools during nebulization
	Vents the expired air outside device
	Tabletop and portable models available
Breath-actuated jet nebulizer	Air stream moves through tube causing drug solution to be aerosolized; powered by compressor
	Patient inhalation drives aerosolization (does not occur unless patient inhales)
	Tabletop and portable models available
Ultrasonic nebulizer	Piezoelectric crystals vibrate causing aerosolization
	Nebulized drug solution gets heated during nebulization
	Portable
Vibrating mesh nebulizer	Piezoelectric crystals vibrate a mesh plate causing aerosolization
	Very fine droplets
	No significant change in temperature of the solution during nebulization
	Lower residual drug remaining in chamber compared with jet nebulizers
	Portable

Abbreviations: CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; PIF, peak inspiratory flow; pMDI, pressurized metered-dose inhaler; SMI, soft-mist inhaler.

A 2005 study estimated that over 20% of the $25 billion spent on inhalers annually in the United States is wasted as a direct consequence of incorrect device handling.[35]

Failing to inhale correctly to achieve the optimal inspiratory flow for the specific device being used—deep and slow for pMDIs, or forceful, quick and deep for DPIs—is a critical handling error for inhaler devices.[26] Significant associations between critical errors and clinical outcomes (hospitalization,

TABLE 3 **Critical errors and their reported frequencies for pressurized metered-dose inhalers and dry powder inhalers[26]**

pMDIs		DPIs			
Critical error	**Frequency (% of users)**	**Critical error**	**Frequency (% of users)**		
			HandiHaler /Aerolizer	**Diskus**	**Turbuhaler**
Failure to remove mouthpiece cap	0.15	Failure of priming			
Actuation against teeth, lips, or tongue	0.7	Failure to open the device	0	0.65	0
Activation after end of inhalation	5	Failure to insert the capsule	9	NA	NA
Stopped inhalation immediately after firing	10	Failure to pierce the capsule	3	NA	NA
Inhalation through nose during and after actuation	2	Failure of loading			
		Incorrect dose loading	NA	7.3	14
		Keep inhaler inclined ≤45° from the vertical axis during loading	NA	NA	23
		Inhaling by nose	2	1	0
		Not sealing lips around mouthpiece during inhalation	5	5	4
		Slow and not forceful inhalation	24	28	22

Abbreviations: DPI, dry powder inhaler; NA, not applicable; pMDI, pressurized metered-dose inhaler.

Reprinted from: *Respiratory Medicine*, 105(6). Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control, 930-938, Copyright 2011, with permission from Elsevier

emergency department visits, antibiotic courses, and corticosteroid courses) have been reported in COPD patients.[26] In a retrospective analysis of COPD inpatients, suboptimal PIF rates with DPIs were associated with worse scores on the COPD Assessment Test, higher COPD and all-cause readmission rates, and shorter time to next COPD exacerbation.[12]

Patient considerations

While various inhaled medications for COPD are available in different device types (**TABLE 4**), it is important to consider a patient's perspective as part of treatment and device selection. For example, the effectiveness of an inhaled drug is dependent on the patient's ability to use their prescribed inhaler correctly, which may be affected by physical issues (eg, poor manual dexterity, tremors, inspiratory flow rate) and cognitive or psychiatric issues (eg, poor memory/learning, depression).[36] It is also important to consider that patient preferences for inhaler devices may differ from the perspective of a physician (**FIGURE 2**).[4,23,37,38]

One of the key factors affecting optimal drug delivery via an inhaler is whether the patient can generate a sufficient or appropriate PIF rate.[3,9,12,39-42] Inhalation flow rates required for optimal drug deposition in the lungs differ between device types: for pMDIs, slow and deep inhalation at a flow rate of <90 L/min is generally recommended, whereas most DPIs require a minimum flow rate of 30 L/min, and a flow rate of >60 L/min to function optimally.[3,39,43,44] DPIs with higher resistance allow for lower inhalation flow rates since the device-generated turbulence results in better drug disaggregation and microdispersion. However, patients with weaker or less efficient respiratory muscles may still struggle to attain an adequate PIF rate.[39,40] For this reason, it may be preferential for patients with a PIF rate of <30 L/min to use a pMDI or SMI device, rather than a DPI.

Poor inhaler technique is frequently reported in patients with COPD or asthma, irrespective of the device used and with considerable variability in handling error rates for each individual device.[25,26,35,45] Although clinical evidence is limited,[25] research to date indicates that some DPIs may require less training than pMDIs.[23,29,45,46] Therefore, DPI devices may

TABLE 4 **Inhaled drugs by device type (with current FDA approval for patients with COPD)**

		Drugs available							
		SAMA	**SABA**	**SAMA/ SABA**	**LAMA**	**LABA**	**LAMA/ LABA**	**ICS/LABA**	**ICS/ LAMA/ LABA**
HFA MDIs		IPR (Atrovent)[a]	ALB (ProAir HFA,[b] Ventolin HFA,[c] Proventil HFA[d]) LLB (Xopenex HFA[e])				GLY/FOR (Bevespi Aero-sphere)[f]	FP/SAL (Advair)[c] BUD/FOR Inhalation Aerosol (Symbicort)[f]	
DPIs	Aerolizer[g]					FOR (Foradil)			
	Diskus[c]					SAL (Serevent)		FP/SAL (Advair)	
	Ellipta[c]				UME (Incruse)		UME/VIL (Anoro)	FF/VIL (Breo)	FF/UME/ VIL (Trelegy)
	HandiHal-er[a]				TIO (Spiriva)				
	Neohaler[g]				GLY (Seebri)	IND (Arcapta)	GLY/IND (Utibron)		
	Pressair[f]				ACL (Tudorza)				
SMIs	Respimat[a]			IPR/ALB (Combi-vent)	TIO (Spiriva)	OLO (Striverdi)	TIO/OLO (Stiolto)		
Nebulizers*	Breath-enhanced jet (eg, PARI LC Plus[h])	IPR (Atrovent)[a]	ALB (Proventil[d], Ventolin[c]) LLB (Xopenex[e])	IPR/ALB (DuoNeb)[i]		ARF (Brovana)[e] FOR (Performo-mist)[i]			
	Breath-actuated jet (eg, AeroEclipse II BAN[j])								
	Ultrasonic (eg, UltraNeb[j])								
	Vibrating mesh† (eg, AKITA APIXNEB[k])								

Abbreviations: ACL, aclidinium; ALB, albuterol; ARF, arformoterol; BAN, breath actuated nebulizer; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDA, US Food and Drug Administration; FF, fluticasone furoate; FOR, formoterol; FP, fluticasone propionate; GLY, glycopyrrolate; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; IND, indacaterol; IPR, ipratropium bromide; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor antagonist; LLB, levalbuterol; MDI, metered-dose inhaler; OLO, olodaterol; SABA, short-acting β_2-agonist; SAL, salmeterol; SAMA, short-acting muscarinic receptor antagonist; SMI, soft-mist inhaler; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

The SAMA and SABA treatments above are indicated for rescue therapy in patients with COPD. The LAMA, LABA, LAMA/LABA and ICS/LABA treatments are indicated for the maintenance treatment of COPD. Ipratropium (Atrovent) and ipratropium/albuterol (Combivent and DuoNeb) may be used as both a maintenance and rescue therapy.

[a]Boehringer Ingelheim; [b]Teva Respiratory; [c]GlaxoSmithKline; [d]Schering; [e]Sunovion; [f]AstraZeneca; [g]Novartis; [h]PARI International; [i]Monaghan Medical Corporation; [j]DeVilbiss Healthcare; [k]Activaero GmbH; [l]Mylan.

*One example of each nebulizer device type provided.

†Not yet approved for therapy in patients with COPD.

be viewed as a more appropriate option for patients who encounter difficulty in coordinating the inhalation and actuation required for effective operation of a pMDI device. Alternatively, use of a spacer with pMDIs appears to reduce handling errors compared with pMDIs alone, but whether a pMDI plus spacer improves technique versus DPIs remains unclear.[25,46,47] Lack of device training appears to be a key reason for inhaler handling errors across device types.[26]

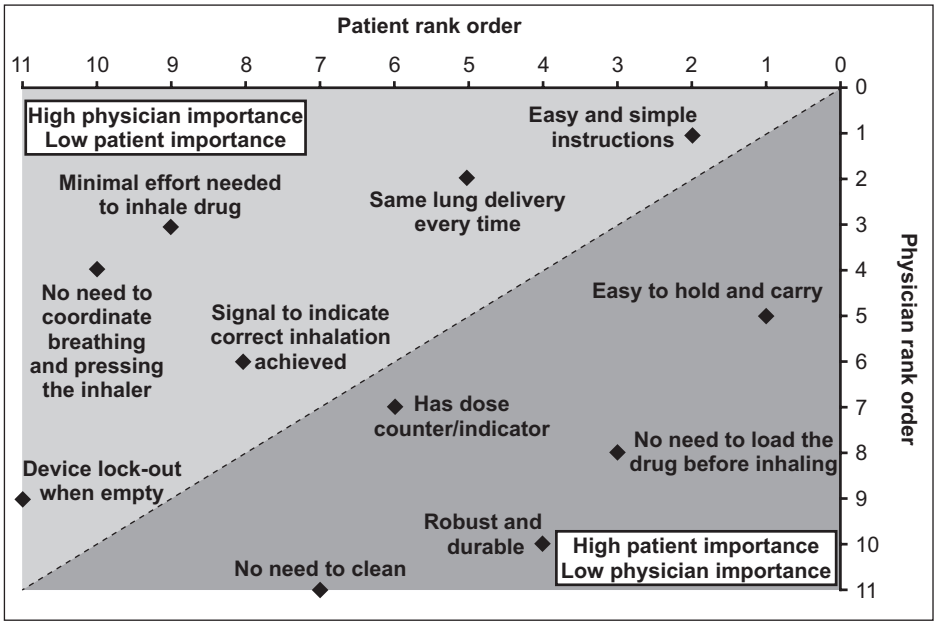
Elderly patients need special consideration when selecting an inhaler and ensuring it is used correctly.[48] Reduced physical ability and cognitive function due to age-related conditions (eg, dementia, depression, neuromuscular and cerebrovascular diseases) are the main reasons for suboptimal inhaler use in older patients, but other factors may also contribute (eg, multiple comorbid conditions, consequent complicated medication regimens).[15] Older age is strongly associated with inhaler misuse,[26] and has also been shown to have a negative correlation with PIF, independent of COPD severity.[41] When compared with younger patients, older patients make more attempts before mastering the inhalation technique for a specific device, and need longer instruction time from trained health care professionals to correct inhaler mishandling.[49,50] In elderly patients with adequate cognitive and manual ability, the most important factors in selecting a device are availability, convenience, ease of use, patient preference, and cost.[8,23]

Device continuity is a key consideration when multiple inhaled medications are needed.[23] Lack of continuity of device type for different clinical needs means that patients may need to master the different techniques for each device.[3] For instance, a patient may have a pMDI rescue medication, one or more DPIs for their maintenance therapy, and a nebulizer for additional bronchodilation, which may lead to confusion and incorrect device usage. Device continuity has been shown to improve disease control compared with using multiple inhalers in patients with asthma.[51]

Economic factors, particularly cost reimbursement in the United States, may influence a patient's ability to access certain treatments and devices.[8] Unfortunately, reasonably-priced, effective medication is not currently available for COPD, unlike other conditions such as diabetes. Medication cost has been shown to have a detrimental effect on adherence in patients with COPD.[34]

A full summary of patient- and physician-related considerations for device selection, along with suggestions for how these can be addressed, is provided in **TABLE 5**.

FIGURE 2 Preferences of patients and physicians regarding different aspects of inhaler device design[38]



Reproduced with permission from: Roche N, Scheuch G, Pritchard JN, et al. Patient focus and regulatory considerations for inhalation device design: Report from the 2015 IPAC-RS/ISAM Workshop. 2017 Feb;30:pp.1–13. The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers.

Inhaler device training for patients and physicians

Comprehensive instruction, including practical demonstration, is important for ensuring patients with COPD use the correct inhaler technique, with regular review and repeated instruction generally needed for continued correct use.[1,23,32,42] Lack of instruction is significantly associated with inhaler misuse in patients with COPD or asthma.[26] Verbal training on inhalation technique increased the number of patients achieving the minimum inhalation flow rate required for a range of different DPIs.[39] Similarly, training helped patients using a pMDI to slow their inhalation rate to <90 L/min, as recommended for this type of device.[39] The 'teach-back' method, where patients are asked to demonstrate correct usage of their inhaler after instruction from a health care professional,[52] has shown to be particularly effective in pharmacist-led patient

TABLE 5 Factors affecting inhaler device selection and solutions

	Selection and usage considerations	Measures to address these
Patient-related factors	• Understanding of need for inhaler device/medication • Age • Coordination • Manual dexterity • PIF rates • Cognitive impairment • Comorbidities • Patient preference	• Provide adequate training for all patients • Older patients may need additional time for training • Consider using BA devices or spacers if coordination/manual dexterity is poor • DPIs usually require good inspiratory flow; consider other devices if PIF is very low • Consider easier-to-use/passive inhalation devices with cognitive impairment (eg, nebulizers) • Where possible, combine multiple medications in one device, or maintain consistency of device types across medications • Take patient preference/finances into account
System/health care professional factors	• Knowledge/training of health care professional • Device availability • Cost (including out-of-pocket cost to patient)	• Provide adequate training to health care professionals as well as patients • Ensure device is available to patient • Evaluate cost vs clinical benefit

Abbreviations: BA, breath-actuated; DPI, dry powder inhaler; PIF, peak inspiratory flow.

device training.[53] Educational interventions that incorporated a physical demonstration significantly improved inhaler technique in patients with COPD and asthma compared with patients receiving written and verbal information alone.[53] Proper device training in primary care settings should also include education about why the inhaler is needed.[3]

Face-to-face instruction from trained caregivers for approximately 5 to 10 minutes improves the use of MDIs and DPIs by patients.[49] However, clinical research indicates that learning correct handling and use may be easier and quicker for some devices than for others.[31,49] For example, patients naïve to the PulmoJet (a DPI device not currently available in the United States) were found to have fewer serious errors after training than those using Diskus or Turbuhaler devices.[24] In another study, it took less time to correct errors in inhaler use with the Diskus compared with the Handi-Haler.[44] Health care professionals themselves may lack training or knowledge on correct use of inhaler devices,[35,36,54] with 1 study finding that up to 67% of nurses, doctors, and respiratory therapists were unable to describe or perform critical steps for using inhalers.[35]

A range of resources is available to aid in training patients and health care professionals in inhaler techniques:

- Tools such as the In-Check DIAL inspiratory flow meter (Clement Clarke International Ltd, Harlow, UK), TurbuHaler Trainer (AstraZeneca, Lund, Sweden), Diskus/Accuhaler Training Device (Vitalograph, Ennis, Ireland), and 2Tone Trainer (Canday Medical Ltd, Newmarket, UK) can be used to evaluate a patient's physical ability to use a specific inhaler.[55]
- The emergence of electronic monitoring devices, such as SmartTrack, SmartTurbo, and SmartMat (all developed by Adherium Ltd, Auckland New Zealand), can provide objective and detailed adherence data to support clinical decision-making.[56]
- It is essential that patients and physicians alike utilize the instructions and video demonstrations available online to understand how to use a device correctly, and avoid errors. These resources can be found on a number of organizations' websites (eg, COPD Foundation, Allergy and Asthma Network, Centers for Disease Control and Prevention, National Jewish Health, Asthma UK, Centre for Pharmacy Postgraduate Education) and on manufacturers' websites for individual inhalers or treatments (eg, https://www.advair.com/how-to-use-advair.html, https://www.incruse.com/how-to-use-incruse.html, https://www.mysymbicort.com/copd/taking-symbicort/how-to-use-the-inhaler.html, https://www.tudorzahcp.com/tudorza-instructions-dosing.html, www.us.respimat.com ("How to Use the RESPIMAT Inhaler"), https://www.utibron.com/how-to-use.html).

Conclusions

A number of inhalation devices are available for the treatment of COPD. However, incorrect usage or a poor match between the patient and the device may lead to confusion, suboptimal treatment, and increased cost to the patient and health care system. Considering both patient- and health care system-related factors can ensure that appropriate inhaler section and usage can be optimized.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd. Accessed July 2017.
2. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *Lancet*. 2011;377(9770):1032-1045.
3. Bonini M, Usmani OS. The importance of inhaler devices in the treatment of COPD. *COPD Res Pract*. 2015;1(1):9.
4. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(3):371-384.
5. Rogliani P, Calzetta L, Coppola A, et al. Optimizing drug delivery in COPD: the role of inhaler devices. *Respir Med*. 2017;124:6-14.
6. Lavorini F, Fontana GA, Usmani OS. New inhaler devices - the good, the bad and the ugly. *Respiration*. 2014;88(1):3-15.
7. Ibrahim M, Verma R, Garcia-Contreras L. Inhalation drug delivery devices: technology update. *Med Devices (Auckl)*. 2015;8:131-139.
8. Barrons R, Pegram A, Borries A. Inhaler device selection: special considerations in elderly patients with chronic obstructive pulmonary disease. *Am J Health Syst Pharm*. 2011;68(13):1221-1232.
9. Dal Negro RW. Dry powder inhalers and the right things to remember: a concept review. *Multidiscip Respir Med*. 2015;10(1):13.
10. Mahler DA, Waterman LA, Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus® dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2013;26(3):174-179.
11. Sharma G, Mahler DA, Mayorga VM, Deering KL, Harshaw O, Ganapathy V. Prevalence of low peak inspiratory flow rate at discharge in patients hospitalized for COPD exacerbation. *Chronic Obstr Pulm Dis*. 2017;4(3):217-224.
12. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal inspiratory flow rates are associated with chronic obstructive pulmonary disease and all cause readmissions. *Ann Am Thorac Soc*. 2017;14(8):1305-1311.
13. Le V, Hoang Thi TH, Robins E, Flament M. Dry powder inhalers: study of the parameters influencing adhesion and dispersion of fluticasone propionate. *AAPS PharmSciTech*. 2012;13(2):477-484.
14. Dalby RN, Eicher J, Zierenberg B. Development of Respimat® Soft Mist™ Inhaler and its clinical utility in respiratory disorders. *Med Devices (Auckl)*. 2011;4:145-155.
15. Lavorini F, Mannini C, Chellini E, Fontana GA. Optimising inhaled pharmacotherapy for elderly patients with chronic obstructive pulmonary disease: the importance of delivery devices. *Drugs Aging*. 2016;33(7):461-473.
16. Tashkin DP. A review of nebulized drug delivery in COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2585-2596.
17. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. *Br J Clin Pharmacol*. 2003;56(6):588-599.
18. Chrystyn H. Anatomy and physiology in delivery: can we define our targets? *Allergy*. 1999;54(suppl 49):82-87.
19. Biddiscombe M, Meah S, Barnes P, Usmani O. Drug particle size and lung deposition in COPD. *Eur Respir J*. 2016;48(Suppl 60):Abstract. doi: 10.1183/13993003.congress-13992016.PA13993313.
20. Demoly P, Hagedoorn P, de Boer AH, Frijlink HW. The clinical relevance of dry powder inhaler performance for drug delivery. *Respir Med*. 2014;108(8):1195-1203.
21. Dhand R. Inhaled drug therapy 2016: the year in review. *Respir Care*. 2017;62(7):978-996.
22. de Boer AH, Gjaltema D, Hagedoorn P, Frijlink HW. Can 'extrafine' dry powder aerosols improve lung deposition? *Eur J Pharm Biopharm*. 2015;96:143-151.
23. Vincken W, Dekhuijzen PR, Barnes P; ADMIT Group. The ADMIT series - Issues in inhalation therapy. 4) How to choose inhaler devices for the treatment of COPD. *Prim Care Respir J*. 2010;19(1):10-20.
24. Roggeri A, Micheletto C, Roggeri DP. Inhalation errors due to device switch in patients with chronic obstructive pulmonary disease and asthma: critical health and economic issues. *Int J Chron Obstruct Pulmon Dis*. 2016;11:597-602.
25. Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: systematic literature review and meta-analysis. *NPJ Prim Care Respir Med*. 2017;27(1):22.
26. Melani AS, Bonavia M, Cilenti V, et al; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control [published correction appears in *Respir Med*. 2012;106(5):757]. *Respir Med*. 2011;105(6):930-938.
27. Sanchis J, Gich I, Pedersen S; Aerosol Drug Management Improvement Team (ADMIT). Systematic review of errors in inhaler use: has patient technique improved over time? *Chest*. 2016;150(2):394-406.
28. Sulaiman I, Seheult J, Sadasivuni N, et al. The impact of common inhaler errors on drug delivery: investigating critical errors with a dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2017;30(4):247-255.
29. Chapman KR, Love L, Brubaker H. A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects. *Chest*. 1993;104(5):1332-1337.
30. van der Palen J, Thomas M, Chrystyn H, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. *NPJ Prim Care Respir Med*. 2016;26:16079.
31. Chrystyn H, Price DB, Molimard M, et al. Comparison of serious inhaler technique errors made by device-naïve patients using three different dry powder inhalers: a randomised, crossover, open-label study. *BMC Pulm Med*. 2016;16:12.
32. Crane MA, Jenkins CR, Goeman DP, Douglass JA. Inhaler device technique can be improved in older adults through tailored education: findings from a randomised controlled trial. *NPJ Prim Care Respir Med*. 2014;24:14034.
33. Ohbayashi H, Kudo S, Ishikawa M. Inhaler operability and patient satisfaction regarding Genuair® and Respimat® inhalers for chronic obstructive pulmonary disease: a randomized crossover sudy. *Pulmon Ther*. 2017;3(1):173-185.
34. Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax*. 2008;63(9):831-838.
35. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care*. 2005;50(10):1360-1374; discussion 1374-1375.
36. Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int J Chron Obstruct Pulmon Dis*. 2012;7:495-502.
37. Dhand R, Dolovich M, Chipps B, Myers TR, Restrepo R, Farrar JR. The role of nebulized therapy in the management of COPD: evidence and recommendations. *COPD*. 2012;9(1):58-72.
38. Roche N, Gerhard S, Pritchard JN, et al. Patient focus and regulatory considerations for inhalation device design: report from the 2015 IPAC-RS/ISAM Workshop. *J Aerosol Med Pulm Drug Deliv*. 2017;30(1):1-13.
39. Al-Showair RA, Tarsin WY, Assi KH, Pearson SB, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? *Respir Med*. 2007;101(11):2395-2401.
40. Janssens W, VandenBrande P, Hardeman E, et al. Inspiratory flow rates at different levels of resistance in elderly COPD patients. *Eur Respir J*. 2008;31(1):78-83.
41. Jarvis S, Ind PW, Shiner RJ. Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age Ageing*. 2007;36(2):213-218.
42. Lavorini F, Levy ML, Corrigan C, Crompton G; ADMIT Working Group. The ADMIT series - issues in inhalation therapy. 6) Training tools for inhalation devices. *Prim Care Respir J*. 2010;19(4):335-341.
43. Pauwels R, Newman S, Borgström L. Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. *Eur Respir J*. 1997;10(9):2127-2138.
44. Everard ML, Devadason SG, Le Souëf PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. *Respir Med*. 1997;91(10):624-628.
45. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49(2):doi: 10.1183/13993003.13901794-2016.
46. Jones V, Fernandez C, Diggory P. A comparison of large volume spacer, breath-activated and dry powder inhalers in older people. *Age Ageing*. 1999;28(5):481-484.
47. Ho SF, O'Mahony MS, Steward JA, Breay P, Burr ML. Inhaler technique in older people in the community. *Age Ageing*. 2004;33(2):185-188.
48. Taffet GE, Donohue JF, Altman PR. Considerations for managing chronic obstructive pulmonary disease in the elderly. *Clin Interv Aging*. 2014;9:23-30.
49. Melani AS, Bonavia M, Mastropasqua E, et al; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri (AIPO). Time required to rectify inhaler errors among experienced subjects with faulty technique. *Respir Care*. 2017;62(4):409-414.
50. Dal Negro RW, Povero M. Dry-powder inhalers in patients with persistent airflow limitation: usability and preference. *Multidiscip Respir Med*. 2016;11(1):31.
51. Price D, Chrystyn H, Kaplan A, et al. Effectiveness of same versus mixed asthma inhaler devices: a retrospective observational study in primary care. *Allergy Asthma Immunol Res*. 2012;4(4):184-191.
52. Dantic DE. A critical review of the effectiveness of 'teach-back' technique in teaching COPD patients self-management using respiratory inhalers. *Health Ed J*. 2014;73(1):41-50.
53. Bosnic-Anticevich SZ, Sinha H, So S, Reddel HK. Metered-dose inhaler technique: the effect of two educational interventions delivered in community pharmacy over time. *J Asthma*. 2010;47(3):251-256.
54. Adnan M, Karim S, Khan S, Al Wabel N. Critical errors found during metered dose inhaler technique demonstration by pharmacists. *Saudi Pharm J*. 2016;24(5):625.
55. Capstick TG, Clifton IJ. Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert Rev Respir Med*. 2012;6(1):91-101; quiz 102-103.
56. Chan AH, Harrison J, Black PN, Mitchell EA, Foster JM. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract*. 2015;3(3):335-349.e1-e5.

Treatment Options for Stable Chronic Obstructive Pulmonary Disease: Current Recommendations and Unmet Needs

Barbara Yawn, MD, MSc, FAAFP; and Victor Kim, MD

Introduction

Chronic obstructive pulmonary disease (COPD) is common, often seen in primary care daily practice, and places a substantial burden on patients, their families, and society.[1-4] Although dyspnea, cough, wheezing, chest tightness, and/or sputum production are typical symptoms of COPD, some patients present with less obvious issues, such as a highly sedentary lifestyle, adjusted to match their limitations and fatigue.[5-7]

Both pharmacologic and nonpharmacologic treatment options can reduce symptoms, treat comorbidities, prevent exacerbation, and improve quality of life, exercise tolerance, and health status in patients with COPD.[3] Patients require initial therapy based on symptoms, history, and their own treatment goals, with regular monitoring to determine when to enhance or discontinue unnecessary therapy, and when to refer to a pulmonologist.

Primary care physicians manage the care of approximately 80% of patients with COPD.[8] This provides the opportunity to engage patients in management goal-setting that facilitates more tailored treatments, and can improve adherence to therapy, which is historically poor in patients with COPD, thereby improving outcomes.[9-11]

Current COPD management guidelines

Both the Global Initiative for Obstructive Lung Disease (GOLD) and COPD Foundation guidelines recommend individualized care for patients with COPD.[3,12] This individualized care is based on comprehensive assessment of symptoms (including assessment of whether symptoms are persistent or worsening) and/or continuation of exacerbations to escalate therapy. COPD phenotypes, such as individuals with frequent exacerbations, chronic bronchitis, and asthma–COPD overlap syndrome (ACO) can also guide treatment.[13-15]

GOLD 2017 strategy: key updates

The 2017 GOLD guidelines are based on a simplified approach that uses respiratory symptoms and exacerbations to assign GOLD A–D categories, and guide individualized pharmacologic treatment (**FIGURE 1**)[3]:

- GOLD A – low symptoms, low exacerbation frequency
- GOLD B – high symptoms, low exacerbation frequency
- GOLD C – low symptoms, high exacerbation frequency
- GOLD D – high symptoms, high exacerbation frequency.

Postbronchodilator spirometry confirms the diagnosis of COPD by a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of less than 0.7, and denotes levels of airflow limitation severity based on the postbronchodilator FEV_1 percentage predicted (**FIGURE 1**).

Barbara Yawn, MD, MSc, FAAFP, Department of Family and Community Health, University of Minnesota, Blaine, MN

Victor Kim, MD, Department of Thoracic Medicine and Surgery, Temple University School of Medicine, Philadelphia, PA

ACKNOWLEDGMENTS AND FINANCIAL DISCLOSURES

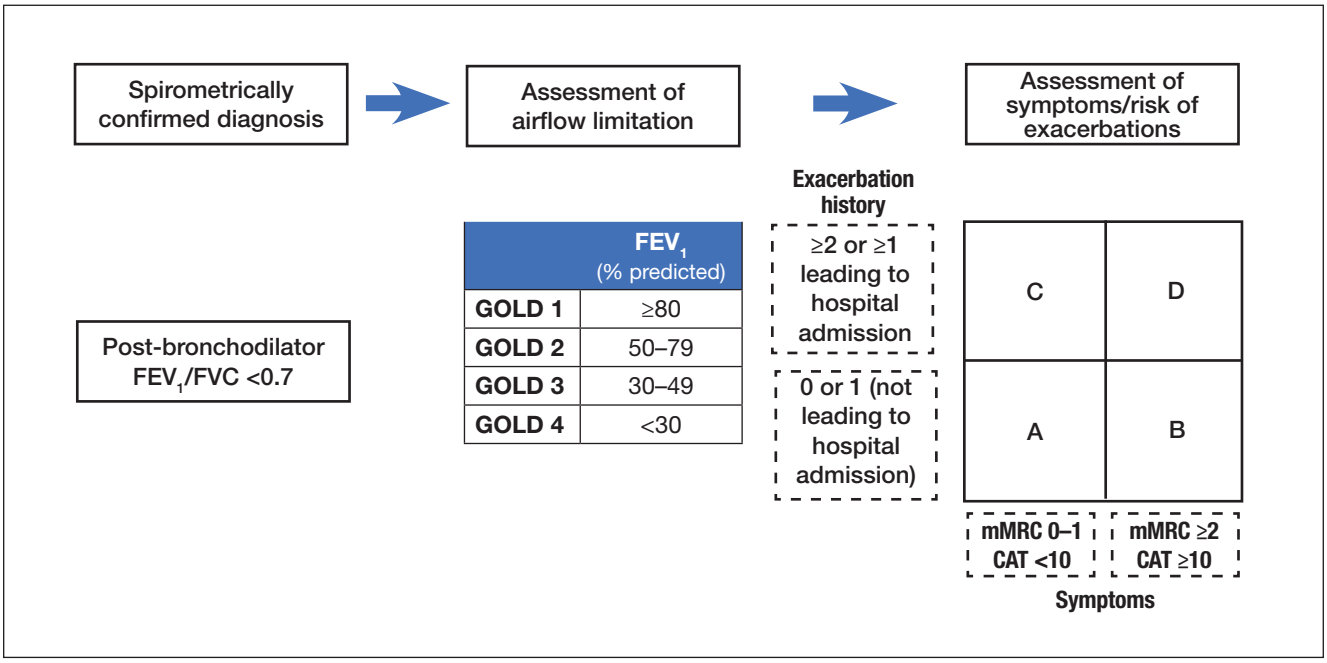
Dr. Yawn reports receipt of personal payments for COPD-related advisory boards for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; and GlaxoSmithKline; and COPD-related research grant funding from Boehringer Ingelheim Pharmaceuticals, Inc. She has served as a content developer and peer reviewer for Medscape and UpToDate, and has grant support from the National Heart, Lung, and Blood Institute and the Patient-Centered Outcomes Research Institute for COPD-related research.

Dr. Kim has attended advisory board meetings for AstraZeneca; Concert Pharmaceuticals Inc.; CSA Medical Inc.; and Gala Therapeutics Inc. He has been a peer reviewer for Medscape, and has received grant support from the National Heart, Lung, and Blood Institute.

Funding for this article was provided by AstraZeneca LP (Wilmington, DE, USA). Medical writing support was provided by Hannah Burke, BSc, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip, of Core (London, UK), which were funded by AstraZeneca LP (Wilmington, DE, USA), in accordance with Good Publication Practice guidelines ((Battisti WP et al. *Ann Intern Med*. 2015;163:461–464. doi: 10.7326/M15-0288).

This article is being co-published in *The Journal of Family Practice* and *Cleveland Clinic Journal of Medicine.*
doi: 10.3949/ccjm.85.s1.05

FIGURE 1 2017 updates to the GOLD ABCD assessment tool[3]



Abbreviations: CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council.

Reproduced with permission from: the Global Initiative for Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of COPD, 2017.

Repeated spirometry assessment can identify individuals with rapidly declining lung function who are appropriate for referral to a pulmonologist.

Nonpharmacologic treatment approaches

Smoking cessation and pulmonary rehabilitation are central to effective COPD disease management.[3] Smoking cessation has the greatest capacity to influence the natural history of COPD.[3] Nicotine replacement products, as well as varenicline and bupropion, have been shown to increase long-term smoking cessation rates.[16]

Pulmonary rehabilitation (which includes exercise training, education, and self-management interventions aimed at behavior change) should be considered a fundamental part of COPD care.[3] Pulmonary rehabilitation is recommended for any COPD patient of GOLD grades B–D (postbronchodilator FEV_1/FVC ratio <0.70 and FEV_1 <80% of predicted).[3] The 2015 Cochrane Review of pulmonary rehabilitation for COPD assessed 65 randomized controlled trials involving 3822 participants, and concluded that pulmonary rehabilitation relieved dyspnea and fatigue, resulting in statistically improved functional exercise, maximal exercise capacity, and quality of life.[17] Inclusion of pulmonary rehabilitation in treatment regimens may provide greater benefit than other more commonly used therapies alone.[17]

Long-term oxygen therapy has been shown to improve survival in COPD patients with severe resting hypoxemia (defined as a partial pressure of arterial oxygen [PaO_2] of ≤55 mm Hg, or an oxyhemoglobin saturation level [SpO_2] of ≤88%[18]), and is recommended in the current GOLD guidelines for selected patients.[3] However, there is no clinical evidence demonstrating a mortality benefit with oxygen therapy in patients with stable COPD who have only moderate arterial oxygen desaturation (PaO_2 of 56–59 mm Hg or SpO_2 between 88%–90%[18]) at rest or with exercise.[3] The **L**ong-Term **O**xygen **T**reatment **T**rial (LOTT) investigated the impact of the prescription of long-term supplemental oxygen in 738 patients with COPD and moderate resting (SpO_2 between 89%–93%) or exercise-induced (SpO_2 ≥80% for ≥5 min and <90% for ≥10 seconds during exercise) desaturation. Long-term oxygen supplementation did not result in either a longer time to death or first hospitalization.[19] In a Cochrane Review published in 2016, Ekström et al conclude with moderate confidence that oxygen can relieve breathlessness when given during exercise to mildly hypoxemic and nonhypoxemic individuals with COPD, but does not improve health-

related quality of life.[20] Consultation with a pulmonologist is appropriate if when and how to prescribe oxygen therapy is not clear.

Pharmacologic treatment recommendations

Recent updates of the GOLD recommendations acknowledge the discordance between lung function and symptoms in patients with COPD. The 2017 recommendations use symptoms and exacerbation risk to define the ABCD categories that guide therapy selection. However, the GOLD authors still acknowledge the importance of spirometry in diagnosis, prognostic evaluation, and treatment with nonpharmacologic interventions in patients with COPD.[3]

The GOLD grades (A–D) guide treatment initiation, and modifications over time including escalation, or de-escalation, such as stopping inhaled corticosteroids (ICS) in those with infrequent exacerbations or whose exacerbations continue with ICS treatment (**FIGURE 2**). Stopping a second long-acting bronchodilator in patients whose levels of dyspnea do not improve following escalation from monotherapy may also be considered[3]; however, as COPD is a progressive disease, it is important to note that levels of symptom improvement can be difficult to determine, and symptoms may not continue at the improved level following de-escalation. Evidence for the impact of escalation and de-escalation remains modest[3]:

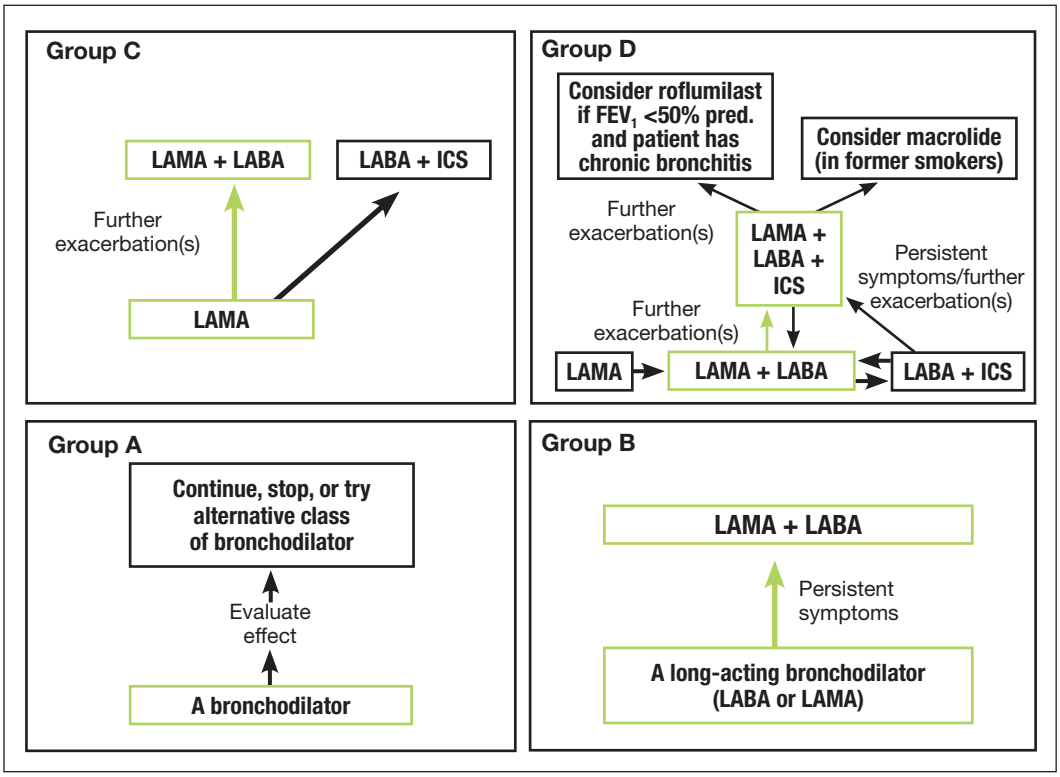
- GOLD A patients: initial treatment with a short- or long-acting bronchodilator
- GOLD B patients: initial treatment with a single long-acting muscarinic receptor antagonist (LAMA) or long-acting β_2-agonist (LABA). If symptoms (such as dyspnea) are severe at initiation of therapy, or persistent with use of 1 long-acting bronchodilator, LAMA/LABA combination is recommended
- GOLD C patients: initial treatment with a LAMA (LAMA is the preferred treatment due to superior exacerbation prevention versus LABA), with preferred escalation to LAMA/LABA if further exacerbations occur. Escalation to ICS/LABA combination may be considered (although is not preferred due to possible risk of pneumonia[21])
- GOLD D patients: initial treatment with LAMA/LABA; initial treatment with ICS/LABA may be preferred in patients with a history and/or findings suggestive of asthma–COPD overlap or high blood eosinophil counts (but consider the risk of pneumonia). Escalation to ICS/LAMA/LABA triple therapy may be considered if symptoms persist or further exacerbations occur.

GOLD grades provide a valuable guide for initiating therapy and continuing assessment and care. Initial therapy may provide sufficient disease control in some patients, but disease progression and persistent symptoms despite therapy often require treatment escalation. Assessing and escalating therapy should be based on changes in functional status and symptom burden, which can be identified by asking appropriate questions, or performing tests to evaluate functional capacity, such as the 6-minute walk test.[3] The modified Medical Research Council (mMRC) dyspnea scale is also a good example of a quick tool for baseline assessment of the patient's functional status. This assessment must be coupled with appropriate follow-up. During follow-up visits, it is important to ask patients about their typical daily activities, and assess how these compare to what has been reported previously. Follow-up visits can also be an opportunity to check that a patient is using their inhaler device correctly.

Regular assessment of patients' health status is important for optimal disease management.[22] The COPD Assessment Test (CAT) is a short, simple, COPD patient-completed questionnaire, designed to inform the clinician about the severity and impact of a patient's disease. Changes in patients' functional abilities and symptoms over time can be monitored with regular use of the CAT at COPD visits.[23] Although the CAT test facilitates prediction of COPD exacerbations,[24] it is not intended to identify comorbidities; for example, the mental health comorbidities of COPD (including anxiety, sleep disturbances, and depression) are often unreported by patients and so can be difficult for clinicians to detect.[25] Awareness of possible comorbid conditions, and appropriate screening for conditions such as depression (PHQ-2), anxiety (GAD-7), or osteoporosis (BMD) is recommended.[26] Further details of PHQ-2 and GAD-7 are provided in the second article (*Anxiety and Depression in Chronic Obstructive Pulmonary Disease: Recognition and Management*) of this supplement.

Physicians need to make decisions about whether (and how) treatment should be escalated using parameters in addition to frequency of exacerbations, such as a lack of improvement or worsening of symptoms or functional status.[3] For example, the addition of a second bronchodilator is recommended for a GOLD B patient with continued breathlessness on a single bronchodilator, and escalating from 1 to 2 long-acting bronchodilators is recommended for GOLD C patients with persistent exacerbations despite monotherapy with a LABA or LAMA. LAMA/LABA combinations that are currently approved for the treatment of COPD by the US Food and Drug Administration are umeclidinium/vilanterol, tiotropium/olodaterol, glycopyrrolate/formoterol, and glycopyrrolate/indacaterol.[27-30]

FIGURE 2 Current pharmacologic treatment algorithms by GOLD grades A–D[3]



Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor antagonist.

Reproduced with permission from: the Global Initiative for Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of COPD, 2017.

For patients with high symptom burden (mMRC ≥2, CAT ≥10) experiencing frequent exacerbations, defined as 2 or more exacerbations per year, or 1 or more exacerbations per year that lead to a hospitalization (ie, GOLD D patients), LAMA/LABA is recommended as first-choice treatment. A recent study showed LAMA/LABA to be superior to ICS/LABA for preventing exacerbations; while it should be noted that the majority of exacerbations in this study were mild, LAMA/LABA was also found to be significantly more effective at reducing exacerbations classed as moderate or severe than ICS/LABA.[31] However, these findings may not be broadly generalizable, owing to limitations associated with the study's exclusion criteria and the high discontinuation rate reported during the study's run-in phase, which may have introduced a selection bias.[31]

ICS/LABA may be considered for treating persistent exacerbations in some GOLD C patients, and may be first choice in GOLD D patients with asthma-like features, or possibly high blood eosinophil counts.[3] Patients who remain symptomatic on LAMA/LABA may also be considered for triple therapy (ICS/LAMA/LABA), as per the GOLD recommendations.[3] Care must be taken to use ICS appropriately, as ICS treatment may increase a patient's risk of developing pneumonia, although risk profiles for pneumonia vary depending on the ICS treatment selected.[32] Increased risk of other adverse effects associated with ICS treatment should also be considered, including oral candidiasis (odds ratio [OR], 2.65; 95% confidence interval [CI], 2.03–3.46 [note, oral candidiasis can be avoided by mouth-rinsing[33]]), hoarse voice (OR, 1.95; 95% CI, 1.41–2.70), and skin bruising (OR, 1.63; 95% CI, 1.31–2.03) compared with placebo in patients with COPD.[21] Nonetheless, use of ICS is not associated with a mortality risk,[34] and a 2017 study by Crim et al reported that the risk of pneumonia was not increased with ICS compared with placebo in patients with moderate airflow limitation who had/were at high risk of cardiovascular disease.[35] Physicians should therefore consider both the potential risks and benefits of ICS before prescribing them to patients with COPD.

While careful consideration of ICS is warranted, ICS/LABA combinations are often prescribed inappropriately in many patients with COPD in clinical practice, including those at low exacerbation risk.[15] Treatment de-escalation by stopping ICS may be appropriate in patients receiving ICS/LAMA/LABA who suffer from fewer than 2 exacerbations per year (ie, receiving ICS inappropriately),[36] or in those who continue to experience persistent exacerbations despite ICS.[3] The use of systemic steroids in stable COPD is not recommended.[37]

At any stage of disease, patients may benefit from a referral by primary care to a pulmonologist for further

evaluation.[38] Reasons include uncertain diagnosis, severe COPD, assessment for oxygen therapy, trouble finding or referring to pulmonary rehabilitation, and COPD in patients younger than 40 years of age (who may be suffering from α_1-antitrypsin deficiency).[38] Referring patients with significant emphysema or other co-existing lung diseases also allows evaluation for surgical interventions such as lung transplantation, lung volume reduction surgery (LVRS), or other therapies.

Patients with COPD may gain particular benefit from comanagement by primary care physicians and pulmonologists.[39] For example, primary care physicians may require guidance from pulmonologists regarding the management of patients with severe disease whose therapy requirements are becoming more complex. Similarly, pulmonologists may not be comfortable managing the comorbidities often encountered in COPD (eg, anxiety and depression), so would require support from the primary care physician to provide the patients with effective, holistic management.

Surgical and bronchoscopic interventions

Surgical and bronchoscopic interventions have the potential to significantly benefit carefully selected patient groups with emphysema.[3] LVRS resects parts of the lungs to reduce hyperinflation, and improves lung function and reduces exacerbations in patients with advanced emphysema.[3] It can prolong mortality in selected patients,[40] but can increase the risk of death in those with low FEV_1 and either homogenous emphysema or very low carbon monoxide diffusing capacity.[41]

Nonsurgical bronchoscopic interventions continue to improve; they have been designed to achieve similar results to LVRS (but with less morbidity), and provide a possible intervention for patients with heterogenous or homogenous emphysema, and significant hyperinflation refractory to optimized medical care.[3] Use of endobronchial one-way valves and lung volume reduction coils has resulted in significant improvements in patients' quality of life, exercise capacity, and pulmonary function for select patients with severe emphysema.[42,43] Other therapies, such as adhesives (where a biologic sealant collapses targeted areas of the lung to induce the formation of scar tissue, thus reducing lung tissue volume), and vapor therapy (where heated water vapor is used to deliver thermal energy to the lungs, inducing an inflammatory response that causes contraction fibrosis and atelectasis, and subsequently lung volume reduction) are also in development.[44] Consideration of surgical or nonsurgical interventions require referral to a pulmonologist.

Lung transplantation may be an option for patients with very severe COPD without significant comorbidities. Lung transplantation improves quality of life, but does not prolong survival.[3,45,46] The procedure is limited by donor availability, high cost, and potential complications.[3]

COPD Foundation guidelines

The COPD Foundation guidelines provide recommendations for first- and second-line therapy based on diagnosis, and the assessment of severity domains (spirometry grade, regular symptoms, high exacerbation risk, oxygenation status, emphysema, chronic bronchitis, and comorbidities; **TABLE 1**).[47,48] Each of the domains requires separate treatment consideration. These guidelines align well with the GOLD recommendations for assessment of symptoms, exacerbations, chronic bronchitis, and comorbidities in all patients with COPD. The COPD Foundation also provides useful tools for health care professionals, most notably the Pocket Consultant Guide (PCG) for the Diagnosis and Management of COPD (**FIGURE 3**). Last updated in November 2016, the PCG serves as a resource to help physicians in a point-of-care context.

The COPD Foundation and GOLD make similar treatment recommendations, but there are a number of differences between the 2 guidelines. For example, GOLD is most suited as a desk reference, whereas the COPD Foundation guidelines and PCG are designed for use at the bedside; therapy recommendations are based on the ABCD methodology in GOLD, whereas the COPD Foundation's management approach requires evaluation of seven severity domains (**TABLE 1**); spirometry grades are also organized differently.

The COPD Foundation guidelines note that some spirometry results are normal, but do not rule out the presence of chronic bronchitis, emphysema, or other lung disease; or are neither normal nor consistent with COPD or other lung disease. The guidelines therefore define 2 additional spirometric grades, referred to as SG 0 (representing patients with normal spirometry) and SG U (representing patients who have a FEV_1/FVC ratio >0.7 but FEV_1 <80% predicted). At present, neither SG 0 nor SG U are associated with therapeutic options distinct from other spirometric grades, but this may change as we learn more from clinical studies.[47,48]

Importance of managing COPD comorbidities

Comorbidities are common among patients with COPD, and COPD itself may increase the risk of developing other diseases.[3,49-52] It can be difficult to recognize the many comorbidities in patients with COPD, due to the diverse nature of these comorbidities, a lack of understanding of their underlying causes, patients' failure to recognize or share symptoms, or misdiagnosing them as adverse effects associated with COPD medication.[53] Failure to recognize and treat comorbidities can increase risk of hospitalizations or exacerbations, worsen prognosis, increase morbidity, lower the chances

TABLE 1 COPD Foundation treatment guidelines[48]

	Short-acting bronchodilator	LAMA or LABA or LAMA plus LABA	ICS/LABA	Roflumilast	Oxygen	Exercise/ pulmonary rehabilitation	Lung volume reduction surgery	Azithromycin[a]
Spirometry grade[b]								
SG1 Mild	First line as needed	Possibly second line						
SG2/3 Moderate/ Severe	First line as needed	First line	Second line	Second line[c]				
Regular symptoms	First line as needed	First line	Second line			First line		
Exacerbation risk high		First line[d]	First line[d]	Second line[c]				Second line
Oxygenation								
Severe hypoxemia					First line			
Episodic hypoxemia					Possibly second line			
Emphysema							Second line in selected cases	
Chronic bronchitis				Second line[c]				
Comorbidities	Evaluate and treat identified comorbid conditions as part of first-line therapy							

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor antagonist; SG, spirometric grade.

[a]Off-label use.

[b]"SG1 Mild" obstruction: post bronchodilator FEV_1/FVC ratio <0.7, FEV_1 ≥60% predicted; "SG2 Moderate" obstruction: post bronchodilator FEV_1/FVC ratio <0.7, 30%≤ FEV_1 ≤60% predicted; "SG3 Severe" obstruction: post bronchodilator FEV_1/FVC ratio <0.7, FEV_1 <30% predicted.

[c]Indicated if chronic bronchitis, high exacerbation risk, and spirometry grades 2/3 are all present.

[d]LAMA, ICS/LABA, LAMA plus LABA, or LAMA plus ICS/LABA are all potential options depending on frequency of exacerbations and severity of COPD.

Introducing the COPD Foundation Guide for Diagnosis and Management of COPD, recommendations of the COPD Foundation. Rennard S, Thomashow B, Crapo J, et al. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2013;10(3):378-389, reprinted by permission of the publisher Taylor & Francis Ltd, http://www.tandfonline.com.

of treatment adherence, and place a greater burden on the patient, family, and health care resources.[51,52,54-56] Common comorbidities include cardiovascular disease, musculoskeletal dysfunction, metabolic syndrome, anxiety/depression, osteoporosis, lung cancer, and heart failure.[3,51,52]

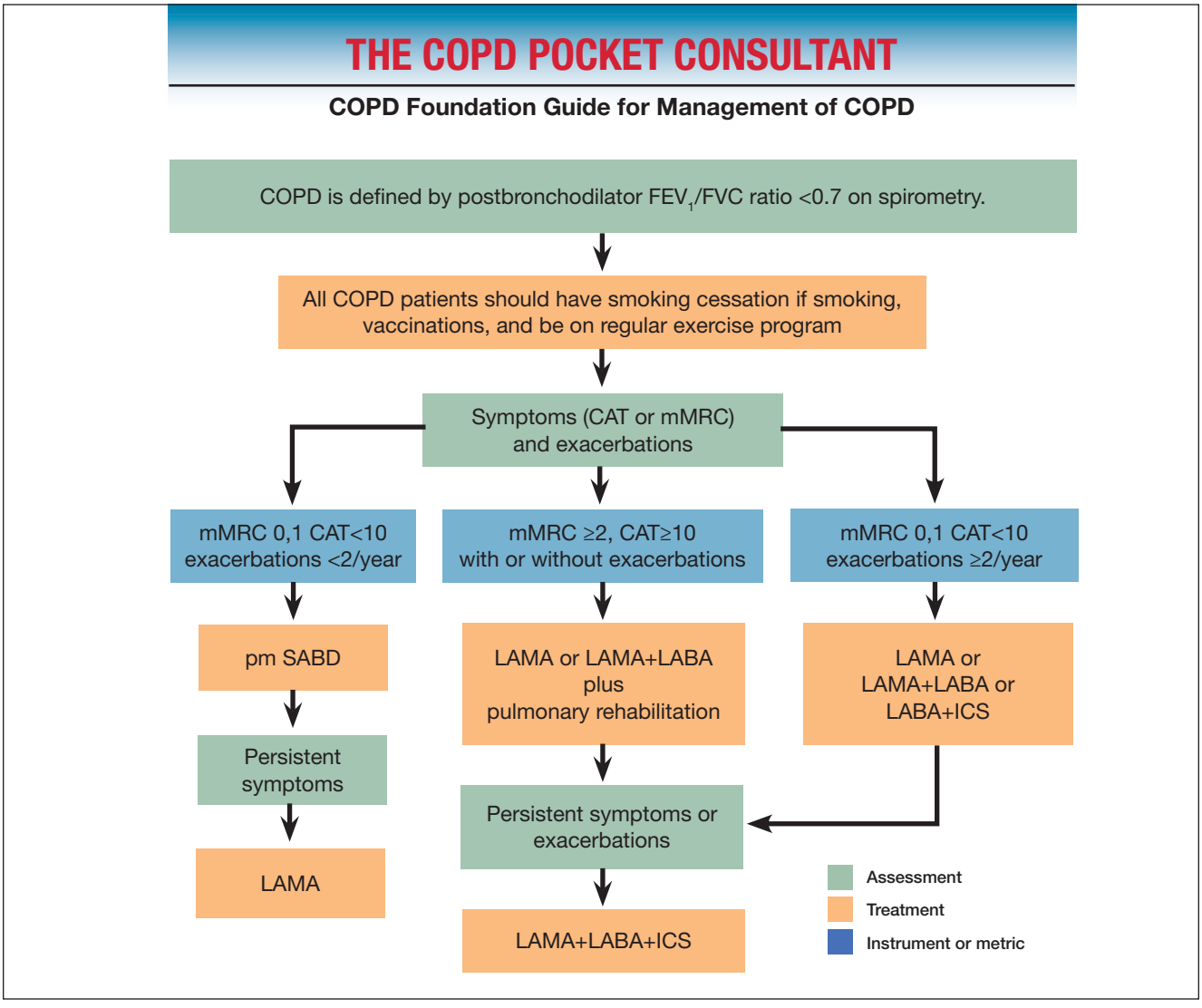
The value of effectively managing comorbidities in improving outcomes and adherence to therapy is well documented. For example, personalized management of patients with COPD and comorbid anxiety and/or depression has been shown to reduce both the mental health symptoms and COPD-related outcomes (eg, exercise tolerance, disability).[57-59]

Comorbidity burden may impact adherence to COPD medication. Depression, for instance, is a known risk factor for nonadherence to treatment. Patients with multiple untreated or uncontrolled comorbid conditions may also be less likely to benefit from pulmonary rehabilitation.[60] It is therefore important that comorbidities are managed effectively to improve adherence to therapy, and enhance the benefits of pulmonary rehabilitation.

Patient monitoring

Routine follow-up of patients with COPD is essential as lung function may worsen over time, even with the best

FIGURE 3 **COPD Foundation Pocket Consultant Guide**



Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic agent; mMRC, dyspnea assessment test; SABD, short-acting bronchodilator (includes SABA, short-acting β_2-agonist); SAMA, short-acting muscarinic agent, and combined SAMA/SABA.

Reprinted with permission from: *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*.[47]

available care.[3] Worsening of symptoms, activity limitation, and disease progression should be monitored closely to determine when to modify management/pharmacotherapy, and to identify any complications and/or comorbidities that may develop.[3] When patients with COPD do not receive the appropriate level of treatment or monitoring, it can be due to: under-reporting of disease severity, symptoms, and exacerbations during consultation; lack of information on the impact of the disease on the patient's quality of life; and failure to recognize comorbidities.[23,25,53] Continued use of the patient questionnaires described previously is recommended, and the GOLD strategy advises that symptoms are assessed at each visit. These follow-up visits also provide an opportunity to monitor patients with COPD for key comorbidities, including heart failure, ischemic heart disease, arrhythmias, osteoporosis, depression/anxiety, and lung cancer, as well as to determine a patient's current smoking status, taking appropriate action as needed.[3]

Unmet needs

COPD remains underdiagnosed in the United States, with only 50% of individuals with impaired lung function reported to receive a formal diagnosis of COPD.[61,62] Opportunities for diagnosing COPD earlier in its course are being missed; 85% of patients consult primary care for lower respiratory symptoms in the 5 years before diagnosis of COPD, and might have been candidates for further evaluation of those symptoms, including spirometry testing.[63] Initiating treatment at early stages of COPD has the potential to improve patients' health-related quality of life, and may provide opportunities to slow disease progression through interventions such as smoking cessation.[64] Practical approaches to improving early diagnosis in primary care involve the use of questionnaires and clinical suspicion to identify those appropriate for spirometry, the most reliable method for identifying patients with COPD.[3,9,65] Such methodology is currently under investigation, with early studies demonstrating the potential benefit of the **C**OPD **A**ssessment in **P**rimary Care **T**o Identify **U**ndiagnosed **R**espiratory Disease and **E**xacerbation Risk (CAPTURE) questionnaire in conjunction with peak expiratory flow to gauge whether a patient requires further diagnostic evaluation.[66]

In addition, the GOLD strategy and COPD Foundation guidelines emphasize that correct assessment of symptoms is of paramount importance in determining the most appropriate therapy (both pharmacologic and nonpharmacologic) for patients with COPD, but traditionally has not been used to inform management choices. Both guidelines therefore highlight the importance of symptom assessment ahead of therapeutic decision-making.

Poor adherence to prescribed therapies and inadequate patient monitoring also need addressing. Two studies analyzing refill adherence data in patients with COPD and asthma in Sweden reported that only 28%–29% of prescribed treatments were dispensed with refill adherence that covered more than 80% of prescribed treatment time[67,68]; a study in 5504 patients in the United States with a prescription of fluticasone propionate/salmeterol combination therapy found that more than half of patients only refilled their prescription once over the course of the 1-year study.[69] With studies showing incorrect use of inhalers in more than 50% of patients with COPD, incorrect inhaler technique is a significant contributor to poor treatment adherence.[70,71] Inhaler technique should be reviewed regularly with direct observation of patients' technique. Assessment of the patients' ability to use their current prescribed inhaler(s) is recommended before considering a change in treatment.[70] Errors in inhaler use are also associated with an increased rate of severe COPD exacerbations, increased risk of hospitalization, and poor disease control.[71,72] Important factors affecting inhaler use include age, education, product design, costs (copays and deductibles) for medications, and instruction and inhaler technique education from the health care providers.[70,72,73] Recent data support improvements in product design, training by the health care provider, and "self-training" by the patient (assisted by instructional video or other digital media) to increase adherence and reduce the frequency of handling errors.[10,70,74] Electronic monitoring devices, messaging systems, and cell phone applications are also being considered as ways to increase adherence.[75]

Maintenance medication is an essential component of COPD management. However, patients with COPD often report that their preference is for medication that they can "feel" working, which may be implicated in their motivation to adhere to therapy.[76] Conversely, while maintenance medication may reduce exacerbations, and lessen a patient's decline in lung function,[77] it may not have a significant impact on how they "feel." As a result, patients may not take it as prescribed, contributing to poor adherence. It is therefore important for primary care physicians to acknowledge that the impact of taking the maintenance medication may not be felt immediately, and articulate the importance of maintenance therapy to their patients, as failure to adhere to treatment can have significant implications for longer-term outcomes such as symptom burden, quality of life, and exacerbation risk.[11]

Regular patient follow-up is necessary to reinforce such information: patients with milder or stable COPD may be followed at 6-month intervals, while patients with severe or frequent exacerbations, or patients who have recently been hospitalized, require follow-up at 2- to 4-week intervals.[78]

Conclusions

Defining personal treatment goals for patients with COPD can enhance patient and physician communication and encourage continued collaboration to improve adherence and outcomes. Regularly monitoring symptoms, exacerbations, and comorbidities via patient-focused questionnaires, and closely examining patient adherence and technique, form a fundamental part of care for patients with COPD. Recent updates to the GOLD and the COPD Foundation guidelines have emphasized the importance of symptom assessment in initiating COPD therapy, and continued assessment to appropriately escalate treatment. Nonpharmacologic therapies such as smoking cessation and pulmonary rehabilitation are recommended at all stages of COPD alongside pharmacologic treatment.

REFERENCES

1. Janson C, Marks G, Buist S, et al. The impact of COPD on health status: findings from the BOLD study. *Eur Respir J*. 2013;42(6):1472-1483.
2. Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. *Int J Tuberc Lung Dis*. 2008;12(7):703-708.
3. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2017. Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Accessed July 2017.
4. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*. 2016;21(1):14-23.
5. Wheaton AG, Cunningham TJ, Ford ES, Croft JB; Centers for Disease Control and Prevention (CDC). Employment and activity limitations among adults with chronic obstructive pulmonary disease--United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):289-295.
6. Rennard S, Decramer M, Calverley PM, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J*. 2002;20(4):799-805.
7. Troosters T, van der Molen T, Polkey M, et al. Improving physical activity in COPD: towards a new paradigm. *Respir Res*. 2013;14:115.
8. Perez X, Wisnivesky JP, Lurslurchachai L, Kleinman LC, Kronish IM. Barriers to adherence to COPD guidelines among primary care providers. *Respir Med*. 2012;106(3):374-381.
9. Price D, Crockett A, Arne M, et al. Spirometry in primary care case-identification, diagnosis and management of COPD. *Prim Care Respir J*. 2009;18(3):216-223.
10. van Boven JF, Ryan D, Eakin MN, Canonica GW, Barot A, Foster JM; Respiratory Effectiveness Group. Enhancing respiratory medication adherence: the role of health care professionals and cost-effectiveness considerations. *J Allergy Clin Immunol Pract*. 2016;4(5):835-846.
11. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Mölken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med*. 2014;108(1):103-113.
12. COPD Foundation. Pocket Consultant Guide for the Diagnosis and Management of COPD. 2016.
13. Lange P, Halpin DM, O'Donnell DE, MacNee W. Diagnosis, assessment, and phenotyping of COPD: beyond FEV_1. *Int J Chron Obstruct Pulmon Dis*. 2016;11 Spec Iss3-12.
14. Miravitlles M, Soler-Cataluña JJ, Calle M, et al. A new approach to grading and treating COPD based on clinical phenotypes: summary of the Spanish COPD guidelines (GesEPOC). *Prim Care Respir J*. 2013;22(1):117-121.
15. Patalano F, Banerji D, D'Andrea P, Fogel R, Altman P, Colthorpe P. Addressing unmet needs in the treatment of COPD. *Eur Respir Rev*. 2014;23(133):333-344.
16. van Eerd EAM, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2016(8):CD010744.
17. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;(2):CD003793.
18. Ekström M. Clinical usefulness of long-term oxygen therapy in adults. *N Engl J Med*. 2016;375(17):1683-1684.
19. Albert RK, Au DH, Blackford AL, et al; Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med*. 2016;375(17):1617-1627.
20. Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database Syst Rev*. 2016;(11):CD006429.
21. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;(7):CD002991.
22. Jones PW, Price D, van der Molen T. Role of clinical questionnaires in optimizing everyday care of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2011;6:289-296.
23. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648-654.
24. Lee SD, Huang MS, Kang J, et al; Investigators of the Predictive Ability of CAT in Acute Exacerbations of COPD (PACE) Study. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. *Respir Med*. 2014;108(4):600-608.
25. Sonetti DA, Hospenthal AC, Adams SG. Integrated management strategies for chronic obstructive pulmonary disease. *J Multidiscip Healthc*. 2010;3:181-188.
26. Miyazaki M, Nakamura H, Chubachi S, et al; Keio COPD Comorbidity Research (K-CCR) Group. Analysis of comorbid factors that increase the COPD assessment test scores. *Respir Res*. 2014;15:13.
27. Anoro Ellipta [highlights of prescribing info]. Research Triangle Park, NC: GlaxoSmithKline group of companies; 2013.
28. Stiolto Respimat [highlights of prescribing info]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015.
29. Bevespi Aerosphere [highlights of prescribing info]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
30. Utibron Neohaler [highlights of prescribing info]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
31. Wedzicha JA, Banerji D, Chapman KR, et al; FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222-2234.
32. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68(11):1029-1036.
33. Dempsey OJ, Coutie WJ, Wilson AM, Williams P, Lipworth BJ. Evaluation of the buccal component of systemic absorption with inhaled fluticasone propionate. *Thorax*. 1999;54(7):614-617.
34. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(20):2407-2416.
35. Crim C, Calverley PMA, Anderson JA, et al; SUMMIT Investigators. Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: The SUMMIT trial. *Respir Med*. 2017;131:27-34.
36. Rossi A, Guerriero M, Corrado A, OPTIMO/AIPO Study Group. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res*. 2014;15:77.
37. Falk JA, Minai OA, Mosenifar Z. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2008;5(4):506-512.
38. British Thoracic Society Standards of Care Committee. BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease. *Thorax*. 2008;63(Suppl 1):i1-i16.
39. Benfante A, Messina R, Milazzo V, Scichilone N. How to unveil chronic respiratory diseases in clinical practice? A model of alliance between general practitioners and pulmonologists. *Pulm Pharmacol Ther*. 2017;44:106-110.
40. Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med*. 2003;348(21):2059-2073.
41. Fishman A, Fessler H, Martinez F, et al. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med*. 2001;345(15):1075-1083.
42. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. *Thorax*. 2014;69(11):980-986.
43. Slebos DJ, Shah PL, Herth FJ, Valipour A. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. *Respiration*. 2017;93(2):138-150.
44. Browning RF, Parrish S, Sarkar S, et al. Bronchoscopic interventions for severe COPD. *J Thorac Dis*. 2014;6(suppl 4):S407-S415.
45. Stavem K, Bjørtuft Ø, Borgan Ø, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant*. 2006;25(1):75-84.
46. Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet*. 1998;351(9095):24-27.
47. Yawn B, Thomashow DM, Mannino D, et al. A statement of the COPD Foundation: The 2017 update to the COPD Foundation COPD Pocket Consultant Guide. *Chronic Obstr Pulm Dis*. 2017;4(3):177-185.
48. Rennard S, Thomashow B, Crapo J, et al. Introducing the COPD Foundation Guide for Diagnosis and Management of COPD, recommendations of the COPD Foundation. *COPD*. 2013;10(3):378-389.
49. Dal Negro RW, Bonadiman L, Turco P. Prevalence of different comorbidities in COPD patients by gender and GOLD stage. *Multidiscip Respir Med*. 2015;10(1):24.
50. Chetty U, McLean G, Morrison D, Agur K, Guthrie B, Mercer SW. Chronic obstructive pulmonary disease and comorbidities: a large cross-sectional study in primary care. *Br J Gen Pract*. 2017;67(658):e321-e328.
51. Westerik JA, Metting EI, van Boven JF, Tiersma W, Kocks JW, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. *Respir Res*. 2017;18(1):31.
52. Putcha N, Han MK, Martinez CH, et al; the COPDGene Investigators. Comorbidities of COPD have a major impact on clinical outcomes, particularly in African Americans. *Chronic Obstr Pulm Dis*. 2014;1(1):105-114.
53. Koskela J, Kilpeläinen M, Kupiainen H, et al. Co-morbidities are the key nominators of the health related quality of life in mild and moderate COPD. *BMC Pulm Med*. 2014;14:102.
54. Clini EM, Boschetto P, Lainscak M, Janssens W. Comorbidities in chronic obstructive pulmonary disease from assessment to treatment. *Biomed Res Int*. 2014;2014:414928.
55. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J*. 2008;32(4):962-969.
56. Schwab P, Dhamane AD, Hopson SD, et al. Impact of comorbid conditions in COPD patients on health care resource utilization and costs in a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*. 2017;12:735-744.
57. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. *Eur Respir Rev*. 2014;23(133):345-349.

58. Alexopoulos GS, Kiosses DN, Sirey JA, et al. Untangling therapeutic ingredients of a personalized intervention for patients with depression and severe COPD. *Am J Geriatr Psychiatry*. 2014;22(11):1316-1324.
59. Eiser N, Harte R, Spiros K, Phillips C, Isaac MT. Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. *COPD*. 2005;2(2):233-241.
60. Crisafulli E, Costi S, Luppi F, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax*. 2008;63(6):487-492.
61. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. *Respir Care*. 2002;47(10):1184-1199.
62. Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance--United States, 1999-2011. *Chest*. 2013;144(1):284-305.
63. Jones RC, Price D, Ryan D, et al; Respiratory Effectiveness Group. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. *Lancet Respir Med*. 2014;2(4):267-276.
64. Welte T, Vogelmeier C, Papi A. COPD: early diagnosis and treatment to slow disease progression. *Int J Clin Pract*. 2015;69(3):336-349.
65. Price D, Freeman D, Cleland J, Kaplan A, Cerasoli F. Earlier diagnosis and earlier treatment of COPD in primary care. *Prim Care Respir J*. 2011;20(1):15-22.
66. Martinez FJ, Mannino D, Leidy NK, et al; High-Risk-COPD Screening Study Group. A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(6):748-756.
67. Krigsman K, Nilsson JL, Ring L. Refill adherence for patients with asthma and COPD: comparison of a pharmacy record database with manually collected repeat prescriptions. *Pharmacoepidemiol Drug Saf*. 2007;16(4):441-448.
68. Krigsman K, Moen J, Nilsson JL, Ring L. Refill adherence by the elderly for asthma/chronic obstructive pulmonary disease drugs dispensed over a 10-year period. *J Clin Pharm Ther*. 2007;32(6):603-611.
69. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol*. 2006;118(4):899-904.
70. Chrystyn H, Price DB, Molimard M, et al. Comparison of serious inhaler technique errors made by device-naïve patients using three different dry powder inhalers: a randomised, crossover, open-label study. *BMC Pulm Med*. 2016;16:12.
71. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49(2):pii: 1601794.
72. Melani AS, Bonavia M, Cilenti V, et al; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105(6):930-938.
73. Han MK, Martinez CH, Au DH, et al. Meeting the challenge of COPD care delivery in the USA: a multiprovider perspective. *Lancet Respir Med*. 2016;4(6):473-526.
74. Plaza V, Peiró M, Torrejón M, et al; PROMETHEUS Study Group. A repeated short educational intervention improves asthma control and quality of life. *Eur Respir J*. 2015;46(5):1298-1307.
75. Craven VE, Morton RW, Spencer S, Devadason SG, Everard ML. Electronic monitoring and reminding devices for improving adherence to inhaled therapy in patients with asthma. *Cochrane Database Syst Rev*. 2015;(3):CD011554.
76. Kawata AK, Kleinman L, Harding G, Ramachandran S. Evaluation of patient preference and willingness to pay for attributes of maintenance medication for chronic obstructive pulmonary disease (COPD). *Patient*. 2014;7(4):413-426.
77. Ferguson GT. Maintenance pharmacotherapy of mild and moderate COPD: what is the evidence? *Respir Med*. 2011;105(9):1268-1274.
78. BMJ Best Practice. COPD. http://bestpractice.bmj.com/best-practice/monograph/7.html. Updated November 2017. Accessed May 30, 2017.