

# Management of chronic obstructive pulmonary disease: A review focusing on exacerbations

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**Purpose.** Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality in the United States. Exacerbations—acute worsening of COPD symptoms—can be mild to severe in nature. Increased healthcare resource use is common among patients with frequent exacerbations, and exacerbations are a major cause of the high 30-day hospital readmission rates associated with COPD.

**Summary.** This review provides a concise overview of the literature regarding the impact of COPD exacerbations on both the patient and the healthcare system, the recommendations for pharmacologic management of COPD, and the strategies employed to improve patient care and reduce hospitalizations and readmissions. COPD exacerbations significantly impact patients' health-related quality of life and disease progression; healthcare costs associated with severe exacerbation-related hospitalization range from \$7,000 to \$39,200. Timely and appropriate maintenance pharmacotherapy, particularly dual bronchodilators for maximizing bronchodilation, can significantly reduce exacerbations in patients with COPD. Additionally, multidisciplinary disease-management programs include pulmonary rehabilitation, follow-up appointments, aftercare, inhaler training, and patient education that can reduce hospitalizations and readmissions for patients with COPD.

**Conclusion.** Maximizing bronchodilation by the appropriate use of maintenance therapy, together with multidisciplinary disease-management and patient education programs, offers opportunities to reduce exacerbations, hospitalizations, and readmissions for patients with COPD.

**Keywords:** chronic obstructive pulmonary disease, exacerbations, hospitalizations, patient care

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with airway obstruction and is characterized by persistent respiratory symptoms.<sup>1</sup> COPD is estimated to affect about 16 million adults in the United States.<sup>2</sup> Incidence of COPD is highest in patients who smoke or have a history of tobacco use, those older than 40 years, and men.<sup>1</sup> Despite recommendations that maintenance pharmacotherapy be used for patients with moderate-to-severe COPD,<sup>1</sup> up to 71% of patients from a Medicare population did not receive maintenance therapy, highlighting opportunities for improvements in patient management and care.<sup>3</sup>

COPD is defined as being “stable” when symptoms are well managed and pulmonary decline is minimized, while management of “unstable” COPD (in patients who experience frequent or severe exacerbations and a faster decline in pulmonary function) can be more challenging. Exacerbations of COPD are a major contributor to the economic burden and, depending on severity, can result in the need for emergency department (ED) visits and hospitalizations.<sup>4-7</sup> Also, there is a positive correlation between disease severity and higher treatment costs.<sup>1</sup> The expansion of the Affordable Care Act Hospital Readmissions Reduction

Program in 2014 to include COPD has highlighted the need for better management to reduce frequent hospitalizations and readmissions associated with severe disease.<sup>8</sup> This review provides an overview of the impact of COPD on patients and, more broadly, the impact on the health system overall, and reviews the latest management guidelines for patients with COPD. We discuss how appropriate treatment can improve patient outcomes and reduce healthcare use and associated costs.

### Impact of exacerbations on patients

Increases in exacerbation frequency, severity, and length of recovery period have all been shown to significantly reduce health-related quality of life for patients with COPD.<sup>9,10</sup> In one prospective trial, the mean recovery time for symptoms to return to baseline levels following an exacerbation event was ~14.5 days, while the recovery of peak expiratory flow to patient baseline levels did not occur within 99 days for ~7% of exacerbations.<sup>9</sup> This suggests that lung function may undergo accelerated decline and may not fully recover following an exacerbation. Furthermore, recovery of lung function and symptoms to baseline levels following an exacerbation was found to occur more slowly with each additional year of disease, making it harder for patients to recover from exacerbations over time.<sup>11</sup> In two separate studies, frequent exacerbations contributed to a long-term decline in lung function (measured as forced expiratory volume in 1 second [FEV<sub>1</sub>]) in patients with moderate-to-severe COPD.<sup>12,13</sup> In another study, symptom burden and exacerbation frequency were strongly correlated with the health-related quality of life in patients with moderate or severe COPD.<sup>14</sup> These results suggest that treatments that reduce exacerbation frequency could have a significant impact on health status and disease progression. Interestingly, even a single exacerbation could result in a significant increase in the rate of decline

in lung function<sup>15</sup> and a sustained worsening of health status in patients with acute exacerbation of chronic bronchitis who likely had COPD as well.<sup>16</sup>

### KEY POINTS

- Frequent exacerbations in patients with chronic obstructive pulmonary disease (COPD) are a major cause of the high hospital readmission rates and can result in deteriorated patient health-related quality of life and accentuated health-care costs.
- Appropriately administered maintenance pharmacotherapy can significantly reduce symptoms and prevent exacerbations in patients with COPD.
- Increased awareness of treatment recommendations among prescribers and COPD aftercare programs that provide patient support through education and inhaler technique training, in addition to pulmonary rehabilitation and follow-up appointments, also have been shown to improve patient outcomes and reduce hospitalizations.

Numerous studies have documented the association between exacerbation history and future exacerbation events (Table 1).<sup>4,17-22</sup> Exacerbations are a major contributor to disease progression, with accelerated lung-function decline in patients who experience exacerbations, and the greatest decline seen in patients with mild disease.<sup>23</sup> Severe exacerbations are also associated with a significant increase in mortality,<sup>24</sup> making prevention of exacerbations the key goal in management of COPD.<sup>1</sup> Furthermore, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations place a major focus on the role of exacerbations in

determining treatment options with the updated ABCD disease risk stratification tool (Figure 1).<sup>1</sup>

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### Management of COPD

**Stable COPD.** Reduction in the risk of exacerbation, along with symptom management, is the cornerstone of the current strategy for management of COPD.<sup>1</sup> The main components of COPD management are appropriate pharmacotherapy (that addresses both symptom management and exacerbation prevention), promotion of smoking cessation, pulmonary rehabilitation, and regular follow-up monitoring for disease progression.

The GOLD ABCD tool combines symptom severity, using either the COPD Assessment Test score or the modified Medical Research Council scale, together with exacerbation risk, determined by either spirometry-defined airflow limitation or exacerbation history, to categorize patients into disease “risk stratification” groups ABCD to guide pharmacotherapy (Figure 1).<sup>25</sup>

Bronchodilators are central to management of COPD at all levels of severity. GOLD recommends specific treatment options for the initial therapy upon diagnosis of COPD in patients based on their ABCD classification (Figure 2A). This initial therapy differs from the follow-up treatment, which is based on current medication(s) and the most treatable trait (e.g., dyspnea or exacerbation; Figure 2B) after ensuring correct inhaler technique and adherence to the initial treatment regimen.<sup>1</sup>

The preference for long-acting muscarinic antagonist (LAMA)/long-acting  $\beta_2$ -agonist (LABA) combinations over inhaled corticosteroid (ICS)-containing regimens is supported by evidence from several studies.<sup>26-29</sup> In the LANTERN<sup>26</sup> and ILLUMINATE<sup>27</sup> studies, a combination of glycopyrronium/indacaterol (LAMA/LABA) significantly improved lung function compared with salmeterol/fluticasone (LABA/ICS) and decreased the incidence of pneumonia in patients with moderate-to-severe

**Table 1.** Summary of the Association Between Exacerbation History and Prediction of Future Events<sup>a</sup>

Author	Study Design	Exacerbation-Related Outcomes	Results
AbuDagga et al. <sup>5</sup>	Retrospective study of claims-based data ( <i>n</i> = 17,382); 1-year baseline, 1-year follow-up	Annual moderate and/or severe exacerbation rate and exacerbation-related costs during follow-up year	Patients experienced ~29.6% more exacerbations during follow-up year for each additional exacerbation during the previous year (RR, 1.2963; 95% CI, 1.2794-1.3134; <i>p</i> < 0.0001)
Hurst et al. <sup>18</sup>	Observational study (ECLIPSE) in patients with moderate-to-severe COPD ( <i>n</i> = 2,138); 3-year study	Rate of moderate or severe exacerbations	An exacerbation that had been treated during the year before study entry was predictive of an exacerbation within the first year of study (OR, 4.30; 95% CI, 3.58-5.17; <i>p</i> < 0.001)
Husebø et al. <sup>22</sup>	Prospective cohort 3-year study ( <i>n</i> = 403)	Exacerbation rate	≥2 exacerbations in the previous year were associated with higher moderate or severe annual exacerbation rate (incidence rate ratio, 1.65; 95% CI, 1.24-2.21; <i>p</i> < 0.001)
Kerkhof et al. <sup>20</sup>	Retrospective analysis of health-care database ( <i>n</i> = 16,565); 1-year baseline data, 1-year follow-up	Exacerbation frequency	Number of exacerbations in year prior to COPD diagnosis were predictive of exacerbations during follow-up year: 1 exacerbation (OR, 2.42; 95% CI, 2.18-2.69); 2 exacerbations (OR, 4.39; 95% CI, 3.89-4.95); 3 exacerbations (OR, 7.28; 95% CI, 6.25-8.48); ≥4 exacerbations (OR, 17.83; 95% CI, 15.12-21.03)
Müllerová et al. <sup>19</sup>	Retrospective medical records study ( <i>n</i> = 58,589); 1-year baseline data, 1-year follow-up	Rate of moderate or severe exacerbations	1 moderate exacerbation in year prior to study vs none was associated with 1 (OR, 1.89; 95% CI, 1.79-1.99) or ≥2 moderate-to-severe exacerbations during follow-up year (OR, 3.31; 95% CI, 3.12-3.51) ≥2 moderate exacerbations in the year prior to study vs none was associated with ≥2 moderate-to-severe exacerbations during follow-up (OR, 13.64; 95% CI, 12.67-14.68)
Müllerová et al. <sup>21</sup>	Observational study (ECLIPSE) in patients with moderate-to-severe COPD ( <i>n</i> = 2,138); 3-year study	Time to first hospital admission for an exacerbation	Patients who had a severe exacerbation that resulted in hospitalization during the first year of the study were at increased risk of being hospitalized for an exacerbation during the next 2 years (HR, 2.71; 95% CI, 2.24-3.29; <i>p</i> < 0.001)
Pasquale et al. <sup>4</sup>	Retrospective analysis of claims data from patients with COPD and chronic bronchitis ( <i>n</i> = 8,554); 1-year baseline data, 1-year follow-up	Rate of moderate or severe exacerbations	Exacerbations were significantly higher during follow-up for patients with ≥1 (mean ± S.D.: 1.26 ± 1.64) or ≥2 (1.77 ± 1.90) exacerbations during baseline year after diagnosis (1.04 ± 1.51)

<sup>a</sup>CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio; RR = rate ratio.

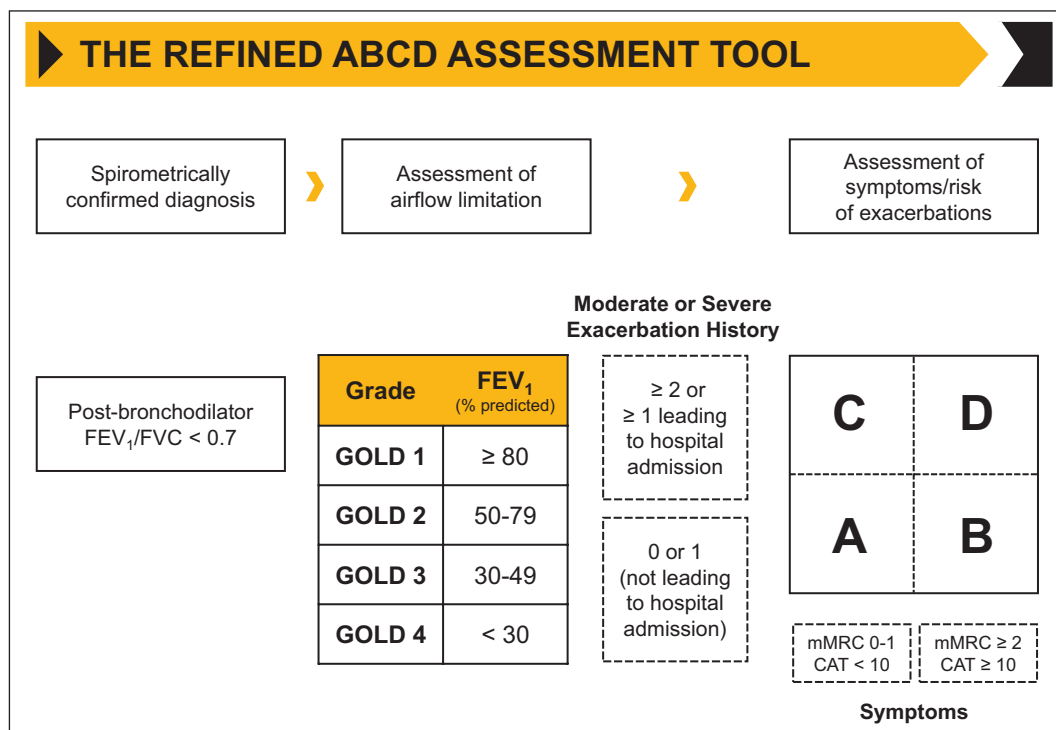
COPD. Similarly, a LAMA/LABA combination of tiotropium/olodaterol provided a greater improvement in lung function than salmeterol/fluticasone in patients with moderate-to-severe COPD in the ENERGITO<sup>®</sup> study.<sup>28</sup> In the FLAME study,<sup>29</sup> glycopyrronium/indacaterol was more effective than salmeterol/fluticasone in reducing the rate of

COPD exacerbations and increasing the time to first exacerbation in patients with a history of exacerbations in the previous year. Notably, compared with LABA/ICS, LAMA/LABA combination therapy significantly reduced the rate of COPD exacerbations by 31%<sup>26</sup> and 11%, respectively, in patients with moderate-to-severe COPD who experienced either

up to 1 or at least 1 exacerbation in the previous year.

A switch from LABA/ICS to LAMA/LABA is recommended if patients do not respond to ICS or where risks associated with ICS are a concern.<sup>1</sup> If patients have persistent exacerbations despite being on the LAMA/LABA or LABA/ICS treatment regimens, LAMA/

**Figure 1.** Updated GOLD classification of COPD severity.<sup>1</sup> The GOLD guidelines updated in 2019 use exacerbation history and symptom burden to classify patient’s future exacerbation risk stratification (ABCD tool). However, the use of spirometry is vital to properly diagnose and gauge a prognosis for the disease. CAT = COPD Assessment Test, COPD = chronic obstructive pulmonary disease, GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity. Reproduced with permission from Global Initiative for Chronic Obstructive Lung Disease 2019 report (copyright © 2019 Global Initiative for Chronic Obstructive Lung Disease, Inc.).



LABA/ICS triple therapy should be considered. A switch from LAMA/LABA to a triple therapy should be guided by the biomarker assessment (i.e., patients with eosinophil counts of ≥100 cells/μL are more likely to benefit from the triple therapy). For patients with eosinophil counts of <100 cells/μL, roflumilast and azithromycin should be considered in patients with chronic bronchitis with severe airflow limitation (FEV<sub>1</sub> < 50%) and who are former smokers, respectively.<sup>1</sup>

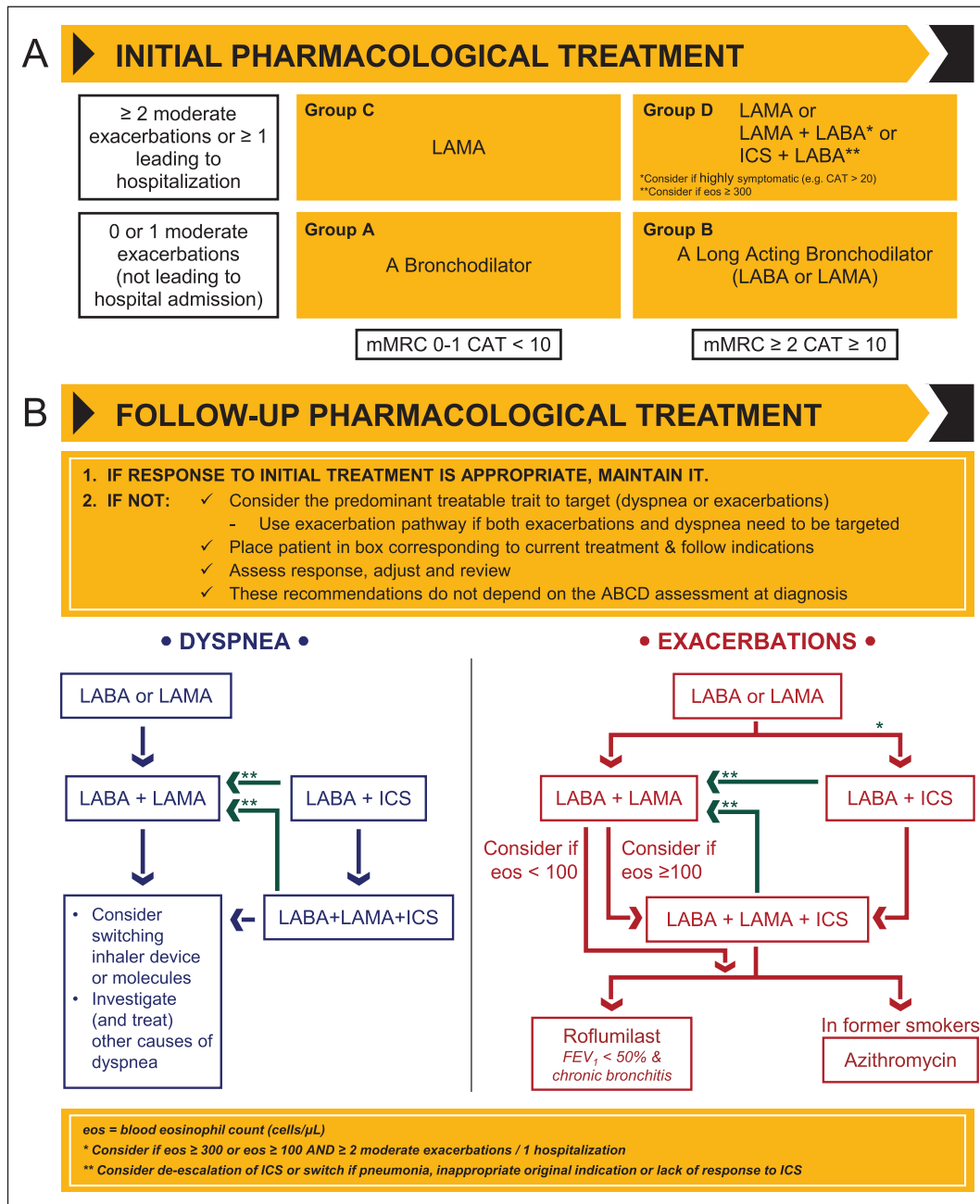
Trials assessing LAMA/LABA/ICS triple therapy have shown improved bronchodilator effects compared with LABA/ICS and LAMA alone.<sup>30-32</sup> Furthermore, triple therapy was shown to reduce exacerbations by 23% to 35% in patients who had experienced exacerbations in the previous year compared with LABA/ICS alone.<sup>31,32</sup> Escalation to triple therapy

is recommended in the GOLD strategy document for patients who experience further exacerbations on LAMA/LABA or LAMA/ICS regardless of their ABCD assessment at diagnosis; however, GOLD recommendations note that there is a lack of direct evidence to indicate whether triple therapy will offer any further benefits to LAMA/LABA in absence of a biomarker assessment.<sup>1</sup> The GOLD guidelines include (since the 2017 update) guidance for de-escalation of treatment should additional therapies not result in incremental benefits, particularly with regard to removing ICS from treatment if no benefit is seen, if pneumonia is noted, or if ICS was prescribed for an inappropriate original indication, as deemed by a physician.<sup>1</sup> This is novel, because historical approaches to treating COPD have tended to be chronic and cumulative because of the progressive nature

of the disease. An individual treatment approach should always be taken because patients show varied responses to available therapies.

**Acute exacerbation.** Short-acting bronchodilators, particularly short-acting β<sub>2</sub>-agonists, are recommended for treatment of exacerbations and can be combined with short-acting anticholinergics.<sup>1</sup> The addition of a systemic corticosteroid to the treatment regimen may be required for moderate-to-severe COPD exacerbations or those that do not respond to short-acting bronchodilators. European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines recommend oral corticosteroids over intravenous corticosteroids for patients hospitalized with an exacerbation.<sup>33</sup> Although oral corticosteroid therapy is beneficial in resolving exacerbations, duration of corticosteroid use should be kept to

**Figure 2.** Recommended initial (A) and follow-up (B) treatment options. CAT = COPD assessment test, COPD = chronic obstructive pulmonary disease, eos = eosinophil counts (cells/ $\mu$ L), FEV<sub>1</sub> = forced expiratory volume in 1 second, ICS = inhaled corticosteroid, LABA = long-acting  $\beta_2$ -agonist, LAMA = long-acting muscarinic antagonist, mMRC = modified Medical Research Council. Reproduced with permission from Global Initiative for Chronic Obstructive Lung Disease 2019 report (copyright © 2019 Global Initiative for Chronic Obstructive Lung Disease, Inc.).



a minimum to avoid possible side effects, including pneumonia.<sup>1</sup> ERS/ATS guidelines recommend treatment with corticosteroids for up to 14 days, whereas GOLD recommends a shorter time of 5 days.<sup>1,33</sup> The REDUCE trial<sup>34</sup> found that shorter courses of systemic

corticosteroids (5 days) were noninferior to longer courses (14 days) for patients experiencing an exacerbation, with both treatments resulting in similar re-exacerbation rates within 6 months and similar lung-function recovery times. Antibiotics are recommended as

an additional treatment for patients with increased sputum purulence that is indicative of bacterial infection.<sup>1</sup> GOLD provides little guidance regarding the choice of antibiotic other than recommending to consider local bacterial resistance patterns.<sup>1</sup>

Factors that indicate the need for inpatient admission following onset of an exacerbation include patient inability to cope within the home environment, severe dyspnea and/or lack of response to initial treatment, and acute respiratory failure.<sup>1</sup>

**Opportunities for transitional care management.** According to Hurst and colleagues,<sup>35</sup> exacerbations in COPD are not random events but occur in a high-risk period for recurrent exacerbation in the 8-week period following an initial exacerbation. This finding presents a therapeutic window for healthcare providers for preventative interventions. Reduction in the risk of future exacerbations is a key goal of COPD management, and patients should be started on appropriate maintenance therapy following an exacerbation.<sup>1</sup> Follow-up appointments after hospitalization for acute exacerbation are recommended for all patients within 1 to 4 weeks and 12 to 16 weeks postdischarge. These appointments should focus on areas including treatment regimen, inhaler technique, and measurement of symptoms.

Inhaler technique is often poor among patients with COPD, a factor that is associated with increased risk of ED visits and hospitalization.<sup>36</sup> Thus, initial and repeated reinforcement of patient education on inhaler technique is critical for COPD management.<sup>1,36</sup> Selection of an appropriate inhaler is also important for managing COPD, because patient satisfaction with the inhaler is thought to influence adherence.<sup>37</sup> Follow-up visits and patient education should also cover adherence to medication.<sup>1</sup> Poor adherence to maintenance therapies is common among patients with COPD and is often multifactorial. As the disease progresses, COPD typically requires more than 1 medication, which may not be delivered with similar inhalers. The use of multiple inhalers can be confusing to patients and lead to poor inhaler technique.<sup>38</sup> Also, the lack of generic inhaled options can affect cost, which also can negatively influence adherence. Poor adherence is associated with increased

mortality rates, whereas higher adherence is associated with reduced hospitalizations.<sup>39</sup> In addition, errors related to inhaler handling are associated with an increased rate of severe COPD exacerbations.<sup>40</sup> Consequently, GOLD 2019 report, for the first time, highlights the importance of assessing inhaler technique and adherence in patients with poor symptom control before adjusting patients' medications/treatment regimen.<sup>1</sup> Community, clinical, and hospital pharmacists can provide medication-related education for patients with COPD, including the purpose and value of taking maintenance medications, the importance of adherence, proper inhaler technique, and how to troubleshoot and maintain their inhalers. A review of studies conducted during a 10-year period showed that inhaler training education and medication adherence by community pharmacists had a positive impact, resulting in significant reduction in inhalation errors, improvement in the choice of inhalers, and better adherence to inhaled medication.<sup>41</sup>

### Implications for the health system and managed care community

Exacerbations of COPD are a major cause of healthcare resource use because they increase physician office visits, ED visits, hospitalizations, and pharmacy use compared with stable COPD.<sup>4-7</sup> Data from large prospective and retrospective studies suggest that ~37% to 71% of patients with COPD experience at least 1 exacerbation annually.<sup>4,6,17,42</sup> Exacerbations can also occur in patients with mild COPD but are underreported.<sup>43</sup> Among patients who experience a COPD exacerbation, ~9% to 31% require an ED visit and ~14% to 35% require hospitalization.<sup>4,6,7,17,42</sup>

Milder exacerbations can often be treated on an outpatient basis, but those which are moderate to severe in nature may prompt ED visits or hospitalization, leading to higher treatment costs with increased exacerbation frequency and severity (Table 2).<sup>4,6,18,42,44-49</sup> Mean cost of treatment for a severe

exacerbation that requires hospitalization can range from \$7,000 to \$39,200, with costs substantially elevated for patients who require mechanical ventilation (Table 2). Comorbidities, including cardiovascular disease and lung cancer, are common in patients with COPD and are significantly associated with both higher costs and increased mortality following hospitalization for a COPD exacerbation.<sup>45</sup> Survival rates at 5 years after a hospitalization for a COPD exacerbation are estimated to be only 45%.<sup>24</sup>

Hospital readmissions within 30 days of discharge after an acute COPD exacerbation occur in ~20% of patients.<sup>8</sup> Studies have shown that factors associated with re-exacerbation and readmission include longer duration of hospital stay, low FEV<sub>1</sub>, comorbidities, high modified Medical Research Council dyspnea score, and previous admissions.<sup>50,51</sup> A study of 90-day readmission rates following acute exacerbations found that readmission was ~35% and was significantly associated with increased mortality (13.4% in readmitted versus 2.3% in nonreadmitted patients).<sup>50</sup>

Patients who experience numerous readmissions may have a phenotype known as the "frequent exacerbator."<sup>52</sup> It is hypothesized that patients with this phenotype have an altered adaptive (CD4 and CD8 T cell) immune system that attenuates an inflammatory response, facilitating COPD exacerbations.<sup>53</sup> However, this phenotype is not only seen in patients with the most severe airflow obstruction. The ECLIPSE study found that 22%, 33%, and 47% of patients with moderate, severe, and very severe airflow obstruction, respectively, were frequent exacerbators.<sup>18</sup> This high prevalence of the frequent-exacerbator phenotype, even among patients with moderate airflow obstruction, is particularly concerning because of the detrimental effects that exacerbations exert, including accelerating lung-function decline, reducing quality of life, and increasing hospitalizations and mortality.<sup>52</sup> These factors, together with implementation of the Affordable Care Act Hospital Readmissions

**Table 2.** Estimates of the Costs of Treating COPD Exacerbations in the United States<sup>a</sup>

Authors	Study Design	Findings
AbuDagga et al. <sup>5</sup>	Retrospective, claims based. Patients with COPD with chronic bronchitis ( <i>n</i> = 17,382), 2004-2012	<b>Cost per exacerbation, mean ± S.D.</b> Moderate: \$269 ± \$748 Severe: \$18,120 ± \$31,592 <b>Annual exacerbation costs, mean ± S.D.</b> ≥1 moderate: \$405 ± \$1,169 ≥1 severe: \$25,364 ± \$43,493
Dalal et al. <sup>46</sup>	Retrospective, claims based ( <i>n</i> = 71,493), 2005-2009	<b>Cost per visit for exacerbation, mean ± S.D.</b> ED visit: \$647 ± \$445 Simple admissions (no ICU/intubation): \$7,242 ± \$7,987 Complex admissions (general/surgical/medical ICU and/or intubation): \$20,757 ± \$41,370 (5.8% of all admissions)
Dalal et al. <sup>49</sup>	Retrospective, claims based on commercial ( <i>n</i> = 51,210) and Medicare plans ( <i>n</i> = 42,166), 2006-2009	<b>Per visit COPD-related healthcare costs (2009), mean</b> ED visit (commercial): \$345 ED visit (Medicare): \$429 Standard hospitalization (commercial): \$10,170 Standard hospitalization (Medicare): \$7,430 Intensive care hospitalization (commercial): \$39,229 Intensive care hospitalization (Medicare): \$14,112
Dhamane et al. <sup>6</sup>	Retrospective, claims based ( <i>n</i> = 52,459), 2007-2012	<b>Mean COPD-related total costs over 24 months</b> No exacerbations: \$1,605 ≥1 exacerbation: \$3,707 ≥2 exacerbations: \$6,712 ≥3 exacerbations: \$12,257
Ke et al. <sup>42</sup>	Retrospective, claims based ( <i>n</i> = 754), 2011-2014	<b>Annual COPD-related healthcare costs for all patients,<sup>b</sup> mean ± S.D. (median)</b> ED visits: \$257 ± \$1,039 (\$0) Hospitalizations: \$7,625 ± \$21,785 (\$0)
Pasquale et al. <sup>4</sup>	Retrospective, claims based. Patients with COPD and chronic bronchitis on maintenance medications ( <i>n</i> = 8,554), 2007-2011	<b>COPD-related annual total costs, mean (95% CI)</b> No exacerbations: \$1,425 (1,404-1,447) ≥1 moderate or severe exacerbation: \$7,022 (6,926-7,119)
Perera et al. <sup>45</sup>	Retrospective study of U.S. inpatient discharge records ( <i>n</i> = 1,254,703), 2006	<b>Cost per hospitalization for acute exacerbation, mean ± S.D.</b> Overall (COPD or chronic bronchitis ICD-9 code with pneumonia or procedure code for mechanical ventilation): \$9,545 ± \$12,700 Principal diagnosis of COPD: \$7,015 ± \$8,289 With mechanical ventilation: \$24,374 ± \$26,608 Without mechanical ventilation: \$7,569 ± \$7,434
Yu et al. <sup>47</sup>	Retrospective, claims based ( <i>n</i> = 228,978), 2004-2009	<b>Total healthcare cost per patient quarter (90 days), mean ± S.D.</b> No exacerbations: \$4,762 ± \$13,082 Mild-to-moderate exacerbation: \$6,628 ± \$18,188 Severe exacerbation: \$17,016 ± \$24,675 <b>COPD-related total cost per patient quarter (90 days), mean ± S.D.</b> No exacerbation: \$658 ± \$3,336 Mild-to-moderate exacerbation: \$1,522 ± \$11,505 Severe exacerbation: \$7,014 ± \$13,278
Wallace et al. <sup>48</sup>	Retrospective, claims based ( <i>n</i> = 1,505), 2011-2015	<b>Annual COPD-related healthcare costs for all patients,<sup>b</sup> mean ± S.D.</b> ED visits: GOLD 1: \$186 ± \$1,100 GOLD 2: \$144 ± \$588 GOLD 3: \$193 ± \$651 GOLD 4: \$534 ± \$1,059 Hospitalizations: GOLD 1: \$3,853 ± \$12,462 GOLD 2: \$4,449 ± \$12,728 GOLD 3: \$6,277 ± \$12,970 GOLD 4: \$12,139 ± \$15,599

<sup>a</sup>CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = emergency department, GOLD = Global Initiative for Chronic Obstructive Lung Disease, ICD-9 = International Classification of Diseases 9th revision, ICU = intensive care unit, S.D. = standard deviation.

<sup>b</sup>Costs calculated from whole population including patients who did not use the service. GOLD airflow limitation severity classification: GOLD 1 (mild), forced expiratory volume in 1 second (FEV<sub>1</sub>) ≥80% predicted; GOLD 2 (moderate), FEV<sub>1</sub> 50% to 79% predicted; GOLD 3 (severe), FEV<sub>1</sub> 30% to 49% predicted; GOLD 4 (very severe), FEV<sub>1</sub> < 30% predicted.

Reduction Program, whereby hospitals with higher-than-expected 30-day readmission rates for COPD are financially penalized, have highlighted the need for strategies to reduce readmissions and improve overall patient care.<sup>8</sup>

Several studies have assessed readmission characteristics and trialed ways to reduce readmissions following discharge after acute exacerbation. A disease-management program for COPD, which provided follow-up in the community after hospital discharge, was found to reduce COPD-related and all-cause 60- and 90-day readmission rates.<sup>54</sup> This program included home visits, clinical assessment, medication review, inhaler technique training, and disease-education components. Care team members typically included a nurse practitioner, a registered nurse, and a respiratory therapist.<sup>53</sup> Patients discharged to skilled nursing facilities were found to be less likely to be readmitted to a hospital within 30 days of discharge than those discharged home, with or without home care (18.8%, 27.7%, and 31.1% readmission rates, respectively).<sup>8</sup> In a prospective, observational study, a COPD care bundle, involving a multidisciplinary team of respiratory therapists, pulmonologists, pharmacists, critical care physicians, general internists, and nurses, was also found to improve care of patients with COPD exacerbations.<sup>55</sup> This bundle included standard nursing protocols, patient education on inhaler use and medication, and postdischarge referrals to pulmonologists and was found to significantly reduce 30- and 60-day readmissions compared with control (9.1% versus 54.4% for 30-day and 22.7% versus 77.0% for 60-day). Length of hospital stay was also reduced following implementation of the care bundle, as were the total aggregate hospital costs at 90 days postdischarge, which were reduced from \$19,954 to \$7,652.

In contrast, others have found that use of care bundles did not result in reduced readmission rates in patients with acute exacerbations of COPD.<sup>56,57</sup> In a single-center randomized study,

a care bundle that included smoking cessation counseling, patient education, and telephone follow-up did not reduce 30- and 60-day readmission rates.<sup>56</sup> Similarly, a Medicare Bundled Payments for Care Improvement Initiative, in which patients were more likely to receive telephone follow-up, pulmonary rehabilitation, pulmonologist appointments, and home care, did not significantly reduce 30- or 90-day readmissions and was found not to be cost-effective.<sup>57</sup>

Pulmonary rehabilitation programs that involve a multidisciplinary approach, including exercise therapy and patient education, have been shown to improve health-related quality of life in patients with COPD.<sup>58</sup> A 5-year study of the use of a pulmonary rehabilitation program with negative pressure ventilation found that during the first 4 years, patients with pulmonary rehabilitation and negative pressure ventilation had increased exercise capacity and reduced lung-function decline.<sup>59</sup> Furthermore, in patients who received pulmonary rehabilitation and negative pressure ventilation, risk of exacerbations requiring ED visit or hospitalization was reduced by 66% and 54%, respectively, and annual total medical costs were reduced when compared with patients who were assigned to an exercise program alone (\$3,274 ± \$1,604 versus \$4,335 ± \$3,269). ERS/ATS guidelines recommend starting pulmonary rehabilitation within 3 weeks of hospital discharge.<sup>33</sup> Limited access to pulmonary rehabilitation remains an issue for many patients who could otherwise benefit from this resource.<sup>1</sup>

Maintenance medication therapy remains a key strategy to reduce hospitalizations due to acute COPD exacerbations. The timing of maintenance therapy initiation following an acute exacerbation in naive patients can significantly affect outcomes, with patients who started maintenance more than 30 days postdischarge having significantly higher risk (43%) of COPD-related hospitalization or ED visit in the following year.<sup>60</sup> Others have agreed with these findings and found that initiating

maintenance therapy within the first 30 days of discharge resulted in significantly reduced COPD-related ED visits (36.7%), office visits (12.1%), and outpatient costs (39.0%) in the following year.<sup>61</sup> A large retrospective study of claims data found that after a moderate exacerbation requiring a prescription for an oral corticosteroid, only 25% of patients were prescribed maintenance therapy.<sup>62</sup> Based on data from the TORCH trial, adherence to maintenance medication is also vitally important in reducing hospitalizations and mortality.<sup>39</sup>

## Conclusion

COPD exacerbations, particularly those that require ED visits or hospitalization, lead to substantial economic burden. Patients who have frequent exacerbations have reduced quality of life and accelerated disease progression. Appropriate therapy with maintenance bronchodilators has been shown to reduce exacerbation frequency but is underused, highlighting a need for increased awareness of treatment recommendations among treating physicians, prescribers, and healthcare organizations in which patient care could be improved. Several studies have found that COPD aftercare programs that increase patient support are beneficial in improving outcomes and reducing hospitalizations. Programs that include referrals to pulmonologists, patient education and inhaler technique training, and pulmonary rehabilitation have been shown to be successful and, in combination with appropriate maintenance therapy, could improve the lives of patients with frequent exacerbations. This highlights that continuing the move toward integrated care of COPD is the way to achieve better outcomes.

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