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# Pharmacy Times®

PRACTICAL INFORMATION FOR TODAY'S PHARMACIST®

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## COPD Management Strategies and Minimizing Medication Waste in the Hospital Setting

Chronic obstructive pulmonary disease (COPD) is a common, preventable, progressive, and treatable illness characterized by persistent respiratory symptoms and airflow limitation due to abnormalities in the airways and alveoli. COPD is usually caused by exposure to noxious gases or particles.<sup>1</sup> In the United States, more than 15 million adults have been diagnosed with the condition.<sup>2,3</sup> The actual prevalence of COPD is likely much higher than estimated, however, with approximately half of all adults with the disease having not yet been diagnosed.<sup>2,4</sup> A higher prevalence of COPD has been reported in women and in adults aged 75 years or older.<sup>3</sup>

In 2014, COPD was ranked the third leading cause of death in the United States.<sup>2</sup> The disease also contributes to significant morbidity worldwide, creating a global burden of disease that is on the rise.<sup>5</sup> In 2010, after adjusting for demographics and 11 non-COPD-related comorbid conditions in patients with COPD, the direct medical costs of patients with the disease were \$32.1 billion.<sup>6,7</sup> A direct relationship between more severe COPD and higher costs of care has been established.<sup>1</sup>

In addition, costly hospitalizations and 30-day readmissions associated with COPD impact a variety of stakeholders.<sup>7</sup> Recent data estimates that in the United States, approximately 700,000 patients are hospitalized each year.<sup>7</sup> Furthermore, approximately 1 in 5 patients will experience a readmission for COPD within 30 days.<sup>7</sup> Efforts to reduce readmission rates are important to improve patient outcomes and decrease overall healthcare expenditures on hospitalizations.<sup>7</sup>

To facilitate COPD management, recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) report from the 2018 edition of the “*Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*” report recommends various pharmacologic therapeutic options for reducing symptoms, lessening the frequency and severity of exacerbations, and improving health status and exercise tolerance.<sup>1</sup> This paper discusses unit-dose products and strategies to minimize medication waste in the hospital setting.

### COPD TREATMENT

Various classes of medications are used for the treatment of COPD, including bronchodilator monotherapy, combination bronchodilators, anti-inflammatory agents, triple inhaled therapy, alpha-1 antitrypsin augmentation therapy, and antitussives. Within each class of medication, selection of a specific agent is based on availability, cost, and consideration of anticipated clinical response versus potential adverse effects (AEs).<sup>1</sup> Because severity of symptoms, airflow limitation, and severity of exacerbations can



**TABLE 1. CLASSIFICATION OF COPD BY THE GOLD REFINED ASSESSMENT TOOL<sup>1,a</sup>**

	<b>Exacerbation history (in last 12 months)</b>	<b>Symptom assessment</b>
<b>Group A</b>	≤1 exacerbation (not leading to hospitalization)	mMRC 0-1 CAT <10
<b>Group B</b>	≤1 exacerbation (not leading to hospitalization)	mMRC ≥2 CAT ≥10
<b>Group C</b>	≥2 exacerbations or ≥1 leading to hospitalization	mMRC 0-1 CAT <10
<b>Group D</b>	≥2 exacerbations or ≥1 leading to hospitalization	mMRC ≥2 CAT ≥10

CAT™ indicates COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council Dyspnea Scale.

<sup>a</sup>The GOLD refined assessment tool is used to guide treatment decisions in patients with spirometrically confirmed diagnoses (post-bronchodilator FEV<sub>1</sub>/FVC <0.7) and airflow limitation from mild to very severe [GOLD 1, FEV<sub>1</sub> ≥80%; GOLD 2, FEV<sub>1</sub> 50%-79%; GOLD 3, FEV<sub>1</sub> 30%-49%; GOLD 4, FEV<sub>1</sub> <30%]

vary among patients with COPD, treatment regimens should be individualized.<sup>1</sup>

Bronchodilators represent a major class of medication for both short- and long-term COPD maintenance therapy.<sup>1,8</sup> These medications alter the tone of airway smooth muscle, which widens the airways and improves expiratory flow; this results in an increase in forced expiratory volume in 1 second (FEV<sub>1</sub>) and/or changes in other spirometric variables.<sup>1</sup> Bronchodilators are generally used on a regular basis for the reduction of COPD symptoms. Regular use of short-acting bronchodilators for maintenance therapy is usually not recommended.<sup>1</sup>

Beta<sub>2</sub>-agonists, a class of bronchodilators, function by relaxing airway smooth muscle through the stimulation of beta<sub>2</sub>-adrenergic receptors, resulting in functional antagonism to bronchoconstriction. Beta<sub>2</sub>-agonists can be short acting (SABAs) or long acting (LABAs).<sup>1</sup> The adverse events associated with the class effects of beta<sub>2</sub>-agonist products include increased heart rate and, at higher doses, exaggerated somatic tremor.<sup>1</sup>

Antimuscarinic drugs also block bronchoconstrictor effects; however, these agents target M3 muscarinic receptors expressed in airway smooth muscle. Antimuscarinics can be short acting (SAMAs), including oxitropium and ipratropium, or long acting (LAMAs), including aclidinium, tiotropium, umeclidinium, and glycopyrrolate.<sup>1</sup> Treatment with both LABA and LAMA monotherapies has been reported to lead to improved FEV<sub>1</sub>, enhanced control of respiratory symptoms, and the reduction of COPD exacerbations and hospitalizations.<sup>1</sup>

Inhaled corticosteroids (ICS) have been used as anti-inflammatory agents for the treatment of COPD, with results from studies conducted prior to 2000 demonstrating symptomatic benefits and decreased moderate to severe exacerbations in patients with severe airflow limitation.<sup>9</sup> ICS monotherapy, as

an anti-inflammatory agent, has no effect on patients' long-term FEV<sub>1</sub> decline.<sup>1</sup> Combining an ICS with a LABA has been shown to improve lung function and reduce the risk of exacerbations in patients with moderate to very severe COPD.<sup>1</sup> However, use of ICS may be limited because of the unclear long-term safety of these medications.<sup>1</sup> Regular use of ICS has been associated with increased risk of pneumonia, especially in patients with severe disease.<sup>1</sup> The adverse events associated with the class effects of ICS therapy include oral candidiasis, hoarse voice, and skin bruising.<sup>1</sup>

The current GOLD 2018 report presents pharmacologic treatment algorithms for the initiation and subsequent escalation and/or de-escalation of COPD management based on individualized symptoms and exacerbation risk.<sup>1</sup> Maintenance therapy is initiated based on a patient's COPD classification: Group A, Group B, Group C, or Group D (TABLE 1).<sup>1</sup>

Patients in Group A should be offered either short- or long-acting bronchodilator therapy, based on its effect on breathlessness. The treatment is recommended for continuation if symptom improvement is observed.<sup>1</sup>

The recommended initial treatment for patients in Group B is a long-acting bronchodilator.<sup>1</sup> Long-acting bronchodilators are considered superior to short-acting bronchodilators taken as needed for maintenance therapy based on data demonstrating improved lung function, significantly fewer exacerbations, and improved quality-of-life scores.<sup>10</sup> However, no particular class of long-acting bronchodilator has been shown to be superior to another. Therefore, the choice of long-acting bronchodilator depends on the individual patient's needs. The use of 2 bronchodilators is recommended for patients receiving monotherapy who experience persistent breathlessness or as initial therapy in patients with severe breathlessness. If a patient does not experience additional symptom improvement with 2 bronchodilators, then it is recommended that treatment be stepped down again to a single bronchodilator. Additionally, patients in Group B are likely to have comorbidities that affect their symptoms and prognosis, and these potential variables should be explored.<sup>1</sup>

For patients in Group C, the recommended initial treatment is a single long-acting bronchodilator, with a preference for starting LAMA therapy over LABA therapy based on reduced rates of exacerbations with LAMAs. Adding a second long-acting bronchodilator or the use of combination LABA/ICS therapy may be beneficial in patients with persistent exacerbations. Because the use of ICS may increase a patient's risk of pneumonia, adding another LABA or LAMA is preferred over LABA/ICS combination therapy.<sup>1</sup>

A LABA/LAMA combination is recommended as initial therapy for patients in Group D; however, initial first-line therapy with LABA/ICS may be preferred in patients with a history and findings suggestive of asthma-COPD overlap.<sup>1</sup> Patients receiving LABA/LAMA therapy who develop further exacerbations may be escalated to LABA/LAMA/ICS treatment or

switched to LABA/ICS therapy. If a patient receiving LABA/ICS therapy continues to experience exacerbations and symptoms, then a LAMA can be added. Patients who do not respond to LABA/LAMA/ICS combination therapy may consider the addition of roflumilast if their FEV<sub>1</sub> is <50%, the addition of a macrolide such as azithromycin, or discontinuation of ICS therapy to reduce the risk for AEs associated with corticosteroid use.<sup>1</sup>

COPD exacerbations can be treated on an outpatient or inpatient basis, depending on the severity of the exacerbation and/or severity of the patient's underlying COPD.<sup>1</sup> COPD exacerbations are classified as mild, moderate, or severe.<sup>1</sup> Severe exacerbations often require hospitalization.<sup>1</sup> For patients experiencing acute exacerbations that require hospitalization, SABAs, with or without SAMAs, are recommended for initial control. Short-term (≤5 to 7 days) systemic corticosteroid therapy and antibiotics, if indicated, may be used to shorten recovery time and duration of hospitalization.<sup>1</sup> Recommendations include continuing treatment with long-acting bronchodilators (LABAs, LAMAs, or a combination), with or without ICS, during an exacerbation or to begin taking these medications prior to hospital discharge.<sup>1</sup>

Initial hospitalization for an acute COPD exacerbation has been associated with a high risk of recurrent exacerbations and increased mortality.<sup>1</sup> A recent study investigated the clinical practice and management of acute hospitalization for COPD in an effort to understand healthcare utilization for disease exacerbations. The study demonstrated that the use of COPD exacerbation action plan education and ongoing support was associated with decreased in-hospital healthcare utilization and increased corticosteroid and antibiotic use for the treatment of disease exacerbations.<sup>11</sup>

Studies have evaluated strategic approaches, such as implementing care bundles into hospital protocols, in an effort to influence readmission rates and/or short-term mortality.<sup>1</sup> A care bundle is protocolized care that is given to patients at hospital discharge and may include information on education, optimizing medication, and correct inhalation device technique.<sup>1</sup> Studies evaluating the effect of care bundles have found varying results. In one study, care bundle interventions did not demonstrate significant effects on reducing 30-day risk of hospital readmission.<sup>12</sup> However, a recent study demonstrated that receiving any part of a multicomponent COPD postdischarge integrated disease management program was associated with a significantly reduced 90-day readmission rate ( $P<0.05$ ).<sup>13</sup>

Despite the inconsistent results associated with these value-driven postdischarge care packages for patients following acute COPD exacerbations, as part of an incentive to promote their use, financial penalties have been imposed on hospitals that report higher-than-expected readmission rates. It is imperative to monitor the potential negative consequences of this approach, including the possibility of increased out-of-hospital mortality as a result of penalties for readmitting patients who might experience benefit from receiving additional in-hospital treatment.<sup>14</sup>

## ROLE OF LONG-ACTING BRONCHODILATORS

Recommendations within the GOLD report on combination therapy prior to 2017 did not distinguish between combination therapy with a LABA/ICS versus a LABA/LAMA for the reduction of COPD exacerbations in high-risk patients.<sup>15</sup> A notable change introduced in the 2017 GOLD report is the recommendation of LABA/LAMA combination therapy over combination LABA/ICS therapy based on findings from recent studies.<sup>1</sup> This change was based partially on results from the FLAME study, which demonstrated reduced COPD exacerbations in patients with a history of exacerbation during the previous year who received LABA/LAMA combination therapy compared with those who received LABA/ICS combination therapy.<sup>15</sup> Another study, SPARK, evaluated the effect of combination LABA/LAMA treatment compared with LAMA monotherapy on COPD exacerbations in patients with severe or very severe airflow limitation who had experienced ≥1 exacerbation in the prior year.<sup>16</sup> The results demonstrated significantly decreased COPD exacerbations in patients receiving LABA/LAMA combination treatment compared with LAMA monotherapy ( $P=0.038$ ).<sup>16</sup> Additional randomized controlled trials have reported a greater degree of improvement in lung function and COPD exacerbations in patients with stable COPD receiving LABA/LAMA combination therapy compared with either LABA or LAMA monotherapy.<sup>17</sup>

## USE AND ADMINISTRATION OF BRONCHODILATORS IN THE HOSPITAL SETTING

Several studies have evaluated the efficacy of long-acting bronchodilators in reducing the length of hospital stays and the rate of readmissions. Short-acting bronchodilators are recommended as initial treatment for acute COPD exacerbations; however, maintenance therapy should be initiated as soon as possible prior to hospital discharge.<sup>1</sup> A retrospective study of Medicare patients with COPD receiving LABA or SABA medications for maintenance therapy in the inpatient setting found that LABA-treated patients had a significantly shorter length of hospital stay and significantly lower overall healthcare costs compared with SABA-treated patients ( $P<0.001$  for both).<sup>18</sup> Although no studies have specifically evaluated LAMA medications compared with SAMA medications for the maintenance treatment of hospitalized patients with COPD, a 1-year randomized controlled trial that compared a LAMA (tiotropium) with a SAMA (ipratropium) demonstrated a significantly decreased number of exacerbations ( $P<0.01$ ) and significantly increased time to first exacerbation ( $P<0.01$ ) and to first hospitalization ( $P<0.05$ ) in patients receiving LAMA therapy.<sup>19</sup>

Results from a retrospective study that evaluated hospital length of stay and costs for patients treated with nebulized arformoterol (a LABA) compared with a nebulized SABA for maintenance therapy demonstrated that the average length of stay was significantly shorter ( $P<0.0001$ ) and total hospitalization

**TABLE 2. MDI DOSES DISPENSED VERSUS DOSES INHALED AND WASTED<sup>29</sup>**

Variable	Doses dispensed <sup>a</sup>	Doses inhaled	Doses wasted
Albuterol (Ventolin) <sup>b</sup>	1860	37	1823 (98%)
Ipratropium (Atrovent) <sup>c</sup>	–	–	–
Tiotropium (Spiriva)	1915	836	1079 (56%)
Formoterol (Foradil)	144	39	105 (73%)
Fluticasone (Flovent)	2760	52	2708 (98%)
Budesonide/ Formoterol (Symbicort)	10,080	675	9405 (93%)
Fluticasone/ Salmeterol (Advair)	3038	918	2120 (70%)
Total	19,797	2557	17,240 (87%)

<sup>a</sup>Each dose is equivalent to 1 inhalation unit. Per our hospital formulary, inhalers are dispensed as multidose MDI/DPI as follows: albuterol = 60 inhalations, ipratropium = 120 inhalations, tiotropium = 5 inhalation capsules, formoterol = 12 inhalation capsules, fluticasone = 120 inhalations, budesonide/formoterol = 60 inhalations, fluticasone/salmeterol = 14 inhalations.

<sup>b</sup>The majority of patients (97%) included in the study received nebulized albuterol (total doses = 8081) ± ipratropium (total doses = 6755).

<sup>c</sup>Per our hospital policy, all orders for ipratropium MDI are interchanged for tiotropium, which may explain why no ipratropium doses were dispensed.

costs were significantly lower in patients receiving arformoterol ( $P < 0.0001$ ).<sup>20</sup>

Inhaled medications for hospitalized patients with COPD can be administered via MDI, DPI, SMI, or nebulizer.<sup>1</sup> There is limited evidence available to guide the selection of delivery method for long-acting bronchodilators in the hospital setting because of a paucity of data on the comparison of different routes of bronchodilator delivery in this setting.<sup>21</sup> However, various inhalation devices are available to help improve ease of administration. Some inhalation devices have incorporated designs that provide audio and visual feedback to alert the patient and healthcare provider administering the medication that the device has been appropriately used.<sup>22</sup>

## VARIABILITY WITH DIFFERENT DELIVERY DEVICES AND METHODS

Adherence to medication is important to clinical outcomes over time and delaying further progression of COPD.<sup>23</sup> Poor adherence has been reported in >50% of the COPD population. This is thought to be the result of multiple comorbidities that require the use of an average of 6 medications.<sup>23</sup> Adherence may be affected by many factors, including difficulty with proper inhalation device use. For patients receiving inhaled therapy, current recommendations within the GOLD report emphasize the importance of education and training regarding inhalation device technique.<sup>1</sup> Patients enrolled in randomized controlled

trials routinely receive proper education and follow-up on appropriate inhalation technique, which may not reflect the usual clinical practice.<sup>1</sup>

Offering combination bronchodilator inhalation devices to patients may improve compliance by reducing the number of doses required. Fixed-dose combination inhalation devices include metered-dose inhalers (MDIs), soft-mist inhalers (SMIs), and dry-powder inhalers (DPIs).<sup>1</sup> In addition to issues with adherence, proper administration and technique when using the inhalation device is important for patient efficacy over time.<sup>24</sup> It is also important to be aware that each type of device is not available for all classes of inhaled drugs.

In an effort to improve medication delivery and inhalation technique, pharmaceutical companies have been developing devices that are designed to deliver inhaled medications more efficiently. Low-resistance inhalation devices have been designed to take into consideration the range of disease severity that patients with COPD may have. Additionally, feedback mechanisms can assist patients with COPD in proper administration technique.<sup>25</sup>

## COPD-RELATED MEDICATION WASTE IN THE HOSPITAL SETTING

Medication waste and cost may be important factors when determining delivery method in a hospital. Because most inhalation devices cannot be used by another patient, many MDIs, DPIs, and SMIs are often discarded once a patient has been discharged. On average, a patient hospitalized for COPD may have a length of stay of 4 to 6 days. Patients hospitalized for COPD may be prescribed a non-nebulized dosage form supplying enough medication for 14 to 28 days of therapy, and could potentially have 8 to 24 days of unused medication discarded after they are discharged.<sup>26-28</sup> In a single-center, retrospective study conducted at a university-affiliated teaching hospital, investigators assessed the amount of medications that were ordered via MDI or DPI and wasted after patients were discharged. Eligible patients were aged 40 years and older and hospitalized with COPD or COPD with asthma exacerbation. Of the 478 patients who met the study criteria, the mean length of hospital stay was 5 days. Results found that 87% of all MDI or DPI doses dispensed and 98% of dispensed doses of MDI albuterol and fluticasone were wasted. Reasons for medication waste included the length of hospitalization being shorter than the medication present in the inhalation device, errors of use, and patient-to-device mismatch. In the 478 eligible patients that were analyzed, it was estimated that costs associated with wasted medication doses amounted to approximately \$86,973.<sup>29</sup> Please see [TABLE 2](#) for more information on unused doses of medication from patients using MDI devices.<sup>29</sup> Limitations to this study included its design as a retrospective analysis and missing documentation of doses administered and wasted.<sup>29</sup>



## RISKS OF CANISTER SHARING

To address medication waste, some hospitals have implemented an MDI common canister (CC) program, in which a single canister can administer medication to multiple patients.<sup>29</sup> Before a hospital implements a CC protocol, several factors should be considered when developing a management strategy. Factors include the ability of the hospital staff to develop protocols that minimize the risk of contamination and contingency plans for how to manage patients who receive a CC protocol after a previous patient had positive microbial cultures.<sup>28</sup> Although these programs have been shown to produce a cost savings exceeding 50%, some evidence suggests that CC programs may spread bacteria and result in cross-infection of susceptible patients with COPD.<sup>30</sup> In CC programs, hospital staff may use isopropyl alcohol and thorough cleaning to sterilize MDI administration devices. However, as the same medication canister is used in more than one patient, there is a risk of cross-contamination associated with patients involved in CC programs.<sup>28,29</sup> Even with thorough cleaning, cross-contamination may occur when canisters become directly contaminated or staff members deviate from following protocols.<sup>30</sup> It has been estimated that in some settings, up to 5% of patients may experience cross-contamination. Furthermore, in one intensive care unit consisting of 15 beds, 11 cases of mixed bacterial infections were found and MDI devices were identified as the fomites.<sup>31</sup> Patients who inhale medication with contaminated equipment could potentially introduce pathogens into the lower respiratory tract and develop nosocomial infections or hospital-acquired pneumonia.<sup>28</sup>

Pharmaceutical companies have developed hospital unit-dose formulations for MDIs, DPIs, and nebulizers in order to help address medication waste and potentially reduce costs.

## CONCLUSION

Management costs for COPD are continuing to rise, with these expenditures including wasted medications and hospitalizations associated with COPD.<sup>29,32,33</sup> Results from studies have shown that costs due to wasting unused medications among patients hospitalized for COPD is an important issue for hospitals to address. Long-acting bronchodilators for maintenance treatment are used in hospitals for patients with stable COPD, which could potentially lead to shorter hospital stays and reduced readmission rates.<sup>18,20</sup> Prior to 2017, recommendations within the GOLD report did not distinguish between combination therapy with a LABA/ICS versus a LABA/LAMA for the reduction of COPD exacerbations in high-risk patients.<sup>15</sup> In addition, the GOLD committee updated the report to recommend LABA/LAMA combination therapy over LABA/ICS therapy.<sup>1</sup> Adherence to medication is important to improve long-term clinical outcomes, and inhalation devices that assist patients with their administration technique could help with patient

adherence over time.<sup>23</sup> Inhalation devices have been developed to include patient/provider feedback mechanisms that could aid patients with proper device use and medication administration.<sup>22</sup> Future studies are warranted to continue evaluating the benefits and costs associated with hospital unit-dose formulations for MDIs, DPIs, and nebulizers, to improve access to care, optimize patient outcomes, and decrease the economic burden of COPD.

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## NOTES

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