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Long-acting Medication Use in COPD: Opportunities for Minimizing Medication Waste in the Hospital Setting

Chronic obstructive pulmonary disease (COPD) is a condition characterized by obstruction to airflow.[1] More than 15 million Americans have been diagnosed with COPD. Although smoking is the primary risk factor for COPD, several others have been identified, including occupational exposure to dust, exposure to industrial chemicals and air pollution, as well as hereditary and genetic factors.[1] The incidence of COPD is higher in women than in men and adults aged 55 to 64 years are the largest affected population.[2]

COPD is the third most common cause of death in the United States[3] and is associated with substantial economic burden at both the individual and societal levels. Thirty-year projections indicate substantial worsening of this burden, including direct and indirect costs. Morbidity data are following a similar trend.[1] Continued use of tobacco and aging of the population are among the causes of these rising costs.[1]

The cost of COPD in the United States in 2010 was approximately $50 billion, including approximately $30 billion and $20 billion in direct and indirect costs, respectively. Because of the increasing prevalence of COPD, a mean cost of more than $4000 per patient per year is projected. These figures are expected to increase in the coming years. Direct costs, which include prevention, diagnosis, treatment, and rehabilitation, are related to disease severity. For example, patients with stage 1 COPD experienced the lowest direct cost, whereas those with stage 3 COPD had the highest cost. Hospitalization costs account for approximately half of direct costs and are the most important cost variable for all stages of disease.[1]

Of the approximately 700,000 COPD-related hospitalizations in the United States each year, an estimated 1 in 5 results in readmission within 30 days.[4] Costs were 18% higher for readmissions with COPD as principal diagnosis than those for the initial stay; costs were more than 50% higher for readmissions with COPD as any diagnosis or for all-cause readmissions.[5] Although the average length of stay in patients with COPD has decreased significantly over time, COPD-related hospitalization costs increased substantially from 2002 to 2010.[6]

The increasing costs associated with COPD management are a substantial burden on the health care system. To help manage COPD, current guidelines recommend the use of several long-acting medications for maintenance treatment of COPD and for the reduction of exacerbations.[7] This paper addresses the current management of COPD, including appropriate use of long- and short-acting treatments per the latest guidelines, information on available medication dosage forms, evidence for the use of treatments to minimize duration of hospitalization, and opportunities for hospitals and health systems to reduce the waste of medication and health care resources through appropriate use of available treatments.

COPD TREATMENTS

Available treatments for COPD include bronchodilators, such as beta$_2$-agonists and antimuscarinic drugs. ICS are not bronchodilators and are thought to induce anti-inflammatory effects. Antimuscarinic agents include short-acting muscarinic antagonists (SAMAs) and long-acting muscarinic agonists (LAMAs). Similarly, among the beta$_2$-agonists, there are short-acting beta$_2$-agonists (SABAs) and long-acting beta$_2$-agonists (LABAs). The effects of short-acting medications (eg, SABAs/SAMAs) typically last approximately 4 to 6 hours, whereas long-acting medications (eg, LABAs/LAMAs) last 12 or more hours.[7]

Beta$_2$-agonists and antimuscarinic agents work via differing mechanisms to produce bronchodilation. The main action of beta$_2$-agonists is to relax airway smooth muscle. These agents stimulate beta$_2$-adrenergic receptors, resulting in increased levels of cyclic adenosine monophosphate (cAMP) and reversal of bronchoconstriction. Antimuscarinic medications block the bronchoconstrictive effect of acetylcholine on M3 muscarinic receptors located in airway smooth muscle. LAMAs have prolonged binding to M3 receptors, which prolongs the duration of action.[7]

An ICS, in addition to a LABA or LAMA, may be prescribed to patients who experience frequent exacerbations or who have severe airflow limitations.[1] Importantly, the addition of ICS is known to increase the risk of pneumonia. However, in some patients with a combination of asthma and COPD, use of ICS therapy may be considered.[7]

The primary goal of COPD treatment is to stabilize the chronic disease and prevent exacerbations.[1] Although currently available treatments for COPD do not prevent disease progression, they do offer symptom control and help reduce risk of exacerbations.[1]

Guidelines have been developed to provide recommendations for management of COPD. The Global Strategy for the Diagnosis, Management, and Prevention of COPD is an evidence-based reference tool for the implementation of effective disease management plans and represents the current best practices for the treatment of people living with COPD. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 recommendations, a long-acting bronchodilator, such as a LAMA or LABA, is preferred as a maintenance medication over a short-acting bronchodilator, such as a SAMA or SABA, in patients who have stable COPD and occasional dyspnea. Moreover, although patients with stable COPD may initially receive a single long-acting bronchodilator or dual long-acting bronchodilator, in patients with persistent dyspnea, LABA/LAMA combination therapy is preferred. Importantly, GOLD recommends against use of long-term ICS monotherapy in patients with stable COPD and reserves ICS for use in combination with LABA therapy in patients with a history of COPD exacerbations despite treatment with a LABA. Long-term use of ICS alone in patients with COPD has not been shown to reduce the frequency of COPD exacerbations.[7]

In hospitalized patients with COPD, use of a long-acting bronchodilator such as a LABA or LAMA is recommended for maintenance treatment, starting as soon as possible before discharge from the hospital.[7] The important role of long-acting bronchodilator medications extends through the continuum of treatment from maintenance therapy, including patients with stable COPD, to hospitalized patients, to patients preparing for hospital discharge. Considering the importance of these therapies, it is also essential to consider how these medications can be used most efficiently to reduce treatment waste.

THE EFFECT OF LONG-ACTING MEDICATIONS ON LENGTH OF STAY AND REHOSPITALIZATION RATES

Available evidence regarding the value of COPD treatment in reducing length of stay and rehospitalization is strongest for long-acting inhaled COPD medications. GOLD recommends maintenance therapy with long-acting bronchodilators for patients with moderate to severe COPD and short-acting bronchodilators for intermittent symptoms and as rescue therapy for patients with mild COPD.[7] Several published studies have analyzed the efficacy of long-acting bronchodilators and combination therapy regimens in the reduction of hospital length of stay and rate of rehospitalizations.

In a retrospective study of Medicare beneficiaries with COPD who received treatment with LABA or SABA medications, LABA-treated patients experienced 1.53 fewer inpatient days (P=0.043) and 16% lower overall total health care costs compared with SABA-treated patients (P<0.001). Limitations of this study include its retrospective nature and the possibility of coding errors or data omissions in the medical record.[8]

Another retrospective study of readmission risk within 6 months postdischarge from a COPD-related hospitalization in patients receiving nebulized LABA or nebulized SABA found that patients who received nebulized LABA following hospitalization due to COPD had a 47% lower risk of readmission compared to those who received nebulized SABA. Limitations of the study include its retrospective design, the

possibility of data omission or coding errors, and lack of disease severity information.[9]

Similarly, a retrospective study conducted in the United Kingdom evaluated the benefits of combining a SABA and ICS versus those observed when adding a LABA to ICS in 2557 patients with COPD. In this study, over 1 year of follow-up, there was a 38% reduction ($P<0.007$) in the risk of rehospitalization or death within 1 year of initial hospitalization among patients who received a LABA and ICS relative to those who received a SABA and ICS. Study limitations include a lack of randomization and a lack of complete accounting for potential confounding variables, such as respiratory function, weight, and alcohol and tobacco consumption.[10]

The relationship between all-cause and COPD-related 30-day hospital readmission and COPD treatment regimen with a long-acting bronchodilator (either a LAMA or LABA) with or without an ICS was investigated in an analysis of prescription claims for 6066 patients hospitalized with a primary diagnosis of COPD. From 90 days prior to the index hospitalization through 30 days postdischarge, a total of 61.8% of patients filled a prescription for a LAMA or LABA with or without ICS; the remaining population did not have a prescription for these agents during the period surrounding index hospitalization. Despite having a similar rate of 30-day all-cause readmissions and ER visits between the 2 patient groups, those with a prescription for these therapies had a significantly higher 30-day rate of COPD-related hospital readmissions ($P<.0001$) and ER visits ($P<.0006$) compared with patients without a prescription for a LAMA or LABA agent with or without an ICS within the designated period surrounding the index hospitalization. As part of the study limitations, investigators noted that 30-day outcomes were investigated in a restricted population of patients with COPD who were fee-for-service Medicare Parts A, B, and D beneficiaries. Additionally, despite having a prescription claim for these medications during the period evaluated, a prescription claim is not indicative of medication utilization by the patient.[11]

Reducing the duration of hospitalization and the risk of rehospitalization is an important priority in the efficient and cost-effective management of COPD.[8-10] Additional studies exploring the effect of long-acting COPD medications on these outcomes may be important for the management of COPD.

COPD-RELATED MEDICATION WASTE IN HOSPITALS AND THE RISKS OF CANISTER SHARING

Pharmacotherapy may be ordered for hospitalized patients with COPD (TABLE 1[12-33]). These treatments may be administered via metered-dose inhalers (MDIs), soft-mist inhalers (SMIs), dry-powder inhalers (DPIs), or nebulizers.[7] An important concern with the use of MDIs, SMIs, or DPIs in hospitalized patients is that these dosage forms are often discarded after patients are discharged from the hospital, resulting in medication waste.[34] For example, in a patient with COPD prescribed a non-nebulized dosage form supplying enough medication for 14 to 28 days of therapy, 8 to 24 days of medication will be discarded unused, as the average length of COPD hospitalization is 4 to 6 days.[6,35,36]

In hospitalized patients with COPD, use of a long-acting bronchodilator such as a LABA or LAMA is recommended for maintenance treatment, starting as soon as possible before discharge from the hospital.

Unlike maintenance treatments administered using devices such as MDIs, SMIs, or DPIs, treatments with unit-dose nebulized medications are not subject to the potential challenges of medication waste or the potential for contamination that may be an issue with shared canister, or common canister (CC), programs. In CC programs, hospital staff may attempt to sterilize MDI administration devices using isopropyl alcohol and thorough cleaning but continue to use the same medication canister across patients.[36]

Several factors should be considered before a hospital implements a CC protocol. Practical considerations include the ability of the hospital and its staff to develop and execute protocols that minimize the risk of contamination. In addition, contingency protocols are needed to determine how to handle patients who receive a CC protocol after a previous patient had microbiological cultures that tested positive. Nosocomial infections or hospital-acquired pneumonia can result if pathogens enter the lower respiratory tract via inhalation through contaminated equipment.[36]

Although cost savings exceeding 50% have been realized through these programs, some evidence suggests that this practice may lead to the spread of bacteria and may result in cross-infection of medically vulnerable patients with COPD. In fact, it has been estimated that up to 5% of patients may experience cross-contamination in some settings.[37] In one intensive care unit of 15 beds, 11 cases of mixed bacterial infections were identified, with MDI devices identified as fomites.[38] Even with thorough cleaning of MDI devices, protocol deviations and direct contamination of the canisters themselves may be the source of cross-contamination.[37]

A single-center, retrospective study was conducted at a university-affiliated teaching hospital to assess the amount of wasted doses of medications ordered via MDI or DPI for patients aged 40 years and older hospitalized with COPD or COPD with asthma exacerbation. There were 555 admissions for COPD or COPD with asthma during the 18-month study period; among these, 478 patients met study criteria. A total of 63 patients were readmitted during this time. The mean length of hospital stay was 5 days. A total of 87% of all MDI or DPI doses dispensed were

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TABLE 1. AVAILABLE INHALER FORMULATIONS INDICATED FOR COPD TREATMENT[12-33]

	Active ingredient(s)	Available forms	Dosage, days supply
SAMA	Ipratropium	MDI	12.9 g canister, 200 inhalations ~25-day supply
SABA and SAMA combination	Albuterol and ipratropium	MDI	14.7 g canister, 200 inhalations ~25-day supply
		SMI/MDI	4 g canister, 120 inhalations ~30-day supply
LABAs	Arformoterol	Neb	Unit-dose 15 mcg/2 mL vial Cartons of 60 unit-dose vials (4 unit-dose vials in each of 15 pouches) ~30-day supply Cartons of 30 individually wrapped vials ~15-day supply **Unit dose may be provided as a single dose**
	Indacaterol	Single-dose DPI	Unit dose (blister pack), comes with 1 inhaler device ~30-day supply
	Formoterol	Neb	Unit-dose 20 mcg/2 mL vial Cartons of 60 individually wrapped vials ~30-day supply Cartons of 30 individually wrapped vials ~15-day supply **Unit dose may be provided as a single dose**
		DPI	Unit dose (blister pack) Box of 60 (strips of 6), comes with 1 inhaler device ~30-day supply Box of 12 (strips of 6), comes with 1 inhaler device ~6-day supply
	Olodaterol	SMI	60 inhalations (30 doses) ~30-day supply 28 inhalations (institutional pack) ~14-day supply
	Salmeterol	DPI	60-inhalation diskus ~30-day supply 28-inhalation diskus (institutional pack) ~14-day supply
LAMAs	Aclidinium	Breath-actuated DPI	60 inhalations ~30-day supply
	Glycopyrrolate	Single-dose DPI	Unit-dose box of 60, comes with 1 inhaler device ~30-day supply Unit-dose box of 6, comes with 1 inhaler device ~3-day supply (Hospital unit-dose formulation not yet available)

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table 1 continued from previous page

TABLE 1. AVAILABLE INHALER FORMULATIONS INDICATED FOR COPD TREATMENT[12-33] *(continued)*

LAMAs	Tiotropium	Single-dose DPI	Unit-dose packages in boxes of 5, 30, and 90, each comes with 1 inhaler device 5- to 90-day supply
		SMI	60 inhalations ~30-day supply
	Umeclidinium	DPI	30 inhalations ~30-day supply 7 inhalations ~7-day supply
LABAs and steroid combinations	Budesonide and formoterol	MDI	120 inhalations ~30-day supply 60 inhalations ~15-day supply
	Fluticasone and salmeterol	DPI	60 inhalations ~30-day supply 14 inhalations ~7-day supply
	Fluticasone and vilanterol	DPI	30 inhalations (60 blisters) ~30-day supply 14 inhalations (28 blisters) ~14-day supply
LABA and LAMA combinations	Glycopyrrolate and indacaterol	Single-dose DPI	Unit dose box of 60 capsules, comes with 1 inhaler device ~30-day supply Unit dose box of 6 capsules, comes with 1 inhaler device ~3-day supply (Hospital unit-dose formulation not yet available)
	Tiotropium and olodaterol	SMI	60 inhalations ~30-day supply
	Umeclidinium and vilanterol	DPI	30 inhalations (60 blisters) ~30-day supply 7 inhalations (14 blisters) ~7-day supply
	Glycopyrrolate and formoterol	MDI	120 inhalations ~30-day supply
LABA and LAMA in combination with ICS	Fluticasone furoate, umeclidinium and vilanterol	DPI	30 inhalations (60 blisters) ~30-day supply 14 inhalations (28 blisters; institutional pack) ~14-day supply

DPI = dry powder inhaler; neb = nebulized; MDI = metered dose inhaler; SMI = soft mist inhaler.

A total of 87% of all MDI or DPI doses dispensed were wasted.

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wasted. In addition, 98% of dispensed doses of MDI albuterol and fluticasone was wasted. Limitations to the study include its retrospective design and missing documentation of doses administered and wasted.[34]

TABLE 2[34] summarizes doses dispensed, inhaled, and wasted.[34] In this study, waste could be due to length of hospitalization versus the amount of medication present in the inhaler, errors of use, and patient-to-device mismatch.

TABLE 2. MDI DOSES DISPENSED VERSUS DOSES INHALED AND WASTED[34]

Variable	Doses dispensed[a]	Doses inhaled	Doses wasted
Albuterol (Ventolin)[b]	1860	37	1823 (98%)
Ipratropium (Atrovent)[c]	–	–	–
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%)

[a]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.
[b]The majority of patients (97%) included in the study received nebulized albuterol (total doses = 8081) ± ipratropium (total doses = 6755).
[c]Per our hospital policy, all orders for ipratropium MDI are interchanged for tiotropium, which may explain why no ipratropium doses were dispensed.
Reprinted with permission from Sage Publications.[34]

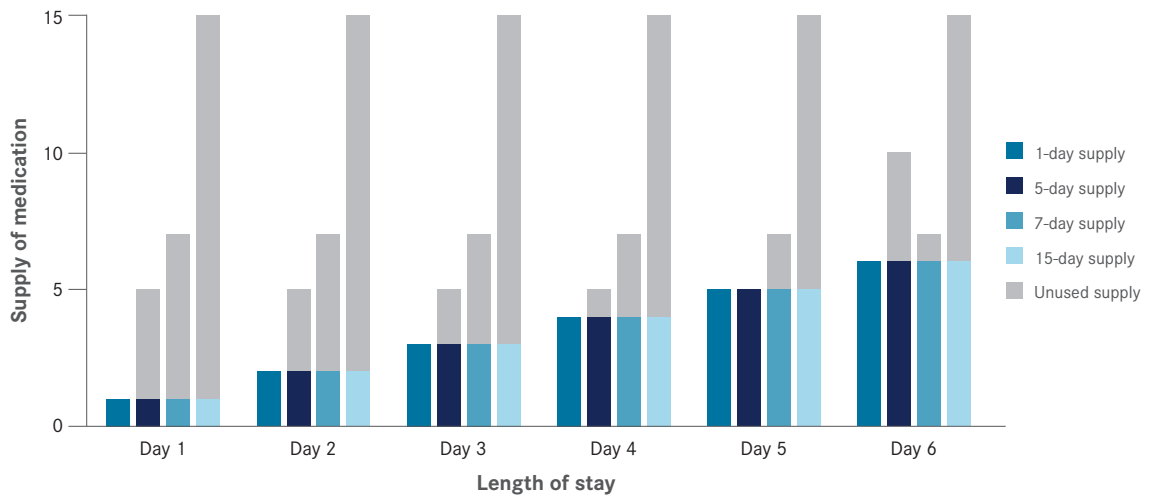
WASTE AS IT APPLIES TO DOSAGE SUPPLY OF LONG-ACTING MEDICATIONS

The FIGURE illustrates the relationship between various hospital lengths of stay and medication waste.[36] A patient hospitalized for COPD and prescribed the LABA and ICS combination MDI budesonide and formoterol would require a total of approximately 16 to 20 doses during the stay (2 inhalations twice daily), although this MDI is available in either 60 or 120 inhalation formulations (15- or 30-day supply). The amount of calculated waste would be approximately 40 doses and 100 doses for the 15- and 30-day supply MDIs, respectively. This translates to a 67% to 83% waste of medication for this hospital stay at a substantial cost to the facility. As demonstrated in the figure, the amount of unused medication is particularly substantial for shorter hospital stays and medications packaged in larger quantities. In contrast, for nebulized dosage forms, treatments may be dispensed in single-dose quantities, eliminating the potential for medication waste.

CONCLUSION

Costs related to management of COPD are substantial and are continuing to increase. Studies have demonstrated that medication waste among patients hospitalized for COPD is an important issue for hospitals. GOLD 2017 recommends the use of several long-acting medications for the maintenance treatment of COPD and short-acting medications for acute exacerbations

FIGURE. UNIT-DOSING FLEXIBILITY[36]



of COPD. Costs associated with the use of these agents, including waste associated with their real-world use, should be taken into consideration. Moreover, future studies should focus on determining methods to reduce medication waste and improve economic and clinical outcomes in patients with COPD. Through prudent use of available COPD treatments, we can mitigate the ever-increasing economic burden that COPD inflicts on the health care system.

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NOTES