Asthma and COPD

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LEARNING OBJECTIVES

1. Given patient information, distinguish between and assess the status of asthma, severe asthma, chronic obstructive pulmonary disease (COPD) (and its complications), and asthma-COPD overlap syndrome (ACOS).
2. Design an initial therapeutic regimen consistent with current treatment guidelines for asthma, severe asthma, COPD, and ACOS, and revise as appropriate according to therapeutic response.
3. Evaluate a patient's asthma or COPD therapy to maximize outcomes and justify adjunctive therapy and modifications based on individuals' needs, skill level, and preferences.
4. Judge the patient-specific effect of new and emerging therapies according to current understanding of the pathophysiology, available evidence, and drug-specific properties.

ABBREVIATIONS IN THIS CHAPTER

ACOS	Asthma-COPD overlap syndrome
BT	Bronchial thermoplasty
CAMP	Childhood Asthma Management Program
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
DLCO	Carbon monoxide diffusion in the lung
ENDS	Electronic nicotine delivery systems
EPR-3	Third Expert Panel Report of the National Heart, Lung, and Blood Institute
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 antagonist
mMRC	Modified Medical Research Council respiratory questionnaire
NRT	Nicotine replacement therapy
PDE	Phosphodiesterase
PFT	Pulmonary function test
PPSV23	Pneumococcal polysaccharide vaccine

INTRODUCTION

Prevalence and Health Care Use

Respiratory diseases are common, affecting 300 million people worldwide (GINA 2016). The prevalence of asthma is increasing worldwide (GINA 2016; Maio 2016), including in the United States, where the prevalence rose by 14.8% in 2001–2010 (CDC 2012). This rise in prevalence was especially seen in children (GINA 2016). Asthma also affects population health because of increased morbidity and mortality. The WHO estimates that 13.8 million disability-adjusted life-years and 346,000 deaths worldwide are attributable to asthma annually (GINA 2016). As a result, the economic impact of asthma on expenditures is quite large, including both direct (e.g., medication and routine and urgent care) and indirect (e.g., decreased quality of life [QOL] and productivity, missed school/workdays) health care costs (GINA 2016). Because effective therapies exist, asthma-related morbidity and mortality can be blunted. Health care efforts should focus on optimizing therapy to prevent chronic symptoms and educating individuals to minimize symptoms and avoid exacerbations so that they can live normal lives.

The prevalence of chronic obstructive pulmonary disease (COPD) is reported to be less than that of asthma (in most nations, less than 6%), but this figure is likely low because of underdiagnosis (GOLD 2016). The incidence of COPD is higher in those who currently smoke or have a history of tobacco use, those older than 40, and men (GOLD 2017). Chronic respiratory diseases, including COPD, were the third leading cause of death in the United States after heart disease and cancer in 2013 (CDC 2016). The direct and indirect costs of COPD approach $50 billion in the United States. Because most health care costs are related to treatment of exacerbations, costs rise

PCV13	Pneumococcal conjugate vaccine
QOL	Quality of life
SABA	Short-acting β_2-agonist

Table of other common abbreviations.

dramatically with the increasing frequency of exacerbations that accompany COPD progression (GOLD 2017). Readmissions for COPD exacerbations are common and expensive. Thus, the Centers for Medicare & Medicaid Services has made 30-day readmissions after COPD exacerbations a focus for cost-containment in its Hospital Readmissions Reduction Program (CMS 2016). Although there is a slight genetic component, COPD can largely be prevented by avoiding tobacco smoke and other noxious respiratory particles (e.g., occupational and environmental exposure). Therefore, health care efforts should focus on tobacco use prevention, tobacco cessation to lower frequency and slow disease progression, and optimal therapeutic strategies to prevent and limit the severity of exacerbations and disability associated with COPD.

Overview of Therapeutic Issues

There are significant barriers to the optimal management of asthma and COPD. Until recently, the treatment of respiratory diseases had not received the same attention as other chronic diseases such as hypertension, diabetes, and hyperlipidemia. As a result, providers may be less knowledgeable regarding treatment guidelines. Providers under-assess asthma severity, which results in the under-prescribing of asthma controller medications (Scichilone 2010; Moonie 2005), as well as underdiagnose COPD. Lack of insurance or inadequate insurance can limit access to health care and medications (Scichilone 2010; Seid 2009). Accessibility and affordability of inhaled medications are negatively affected by the current lack of generic options. Nonadherence is common (CDC 2012). The causes are multifactorial and will be discussed later in the chapter. Patients need to understand the purpose and value of taking maintenance medications in order to comprehend the personal implications of their nonadherence on overall control and frequency and severity of exacerbations, as well as the impact of disease on their QOL. Treatment with inhaled instead of systemic medications limits adverse effects but complicates drug delivery to the lung. Initial instruction and repeated reinforcement are necessary for patients to demonstrate and maintain correct device techniques to optimize drug delivery and deposition in the lung (Broeders 2009). Longer-acting medications in newer delivery devices are now available, resulting in therapeutic options of varying expense. Providers must be familiar with the cost of medications on institutional and health plan formularies to select cost-effective options for a specific patient. However, providers should seek and incorporate patient views on therapy to maximize adherence (Scichilone 2010). Both providers and patients should aspire to the maximum disease control possible.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- The underlying pathophysiology of asthma versus that of COPD
- The concepts behind and interpretation of common pulmonary function tests: FEV_1, FEV_1/FVC, DLCO, Sao_2, and arterial blood gases
- The pharmacology, therapeutic regimens, adverse effects, and relative role of β_2-agonists, muscarinic receptor antagonists, and corticosteroids in the chronic treatment of COPD and asthma

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2016.
- Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 Global Strategy for Diagnosis, Management, and Prevention of COPD.

ASSESSMENT OF ASTHMA VS. COPD VS. ASTHMA-COPD OVERLAP SYNDROME

Asthma and COPD have the same general symptoms (e.g., wheezing, shortness of breath, bronchoconstriction). Thus, distinguishing asthma from COPD requires a combination of pattern of symptoms, symptom-inducing triggers, clinical history and complications, and results of pulmonary function tests (PFTs) (Table 1-1). Those with asthma tend to present at younger ages (usually in childhood) and have intermittent (but not progressive) symptoms that are often associated with trigger exposure, underlying atopy, and PFTs showing reversible airway obstruction (either spontaneously or with treatment). The most common complication of asthma is exacerbations. Although serious and even fatal asthma exacerbations can occur, most individuals with asthma have a normal life span and QOL, especially with optimal controller therapy.

In contrast to asthma, COPD usually begins later in life, is most commonly associated with a history of tobacco use or occupational exposures to noxious respiratory particles, consists of progressive symptoms over months to years, and has some degree of irreversible airflow obstruction by spirometry

Table 1-1. Comparison of Features of Asthma, COPD, and ACOS

Clinical Feature	Asthma	COPD	Suggestive of ACOS
Pattern of signs and symptoms	Dry cough, wheezing or shortness of breath, chest tightness Intermittent episodes: Symptoms may be nocturnal and are often related to trigger exposure	Chronic bronchitis: Productive cough worse on awakening; wheezing, shortness of breath, and chest tightness usually with effort Emphysema: Progressive dyspnea over months to years	Symptoms are persistently exertion related but also variable in severity
Triggers	Atopic: Mold, pollen, furry animal dander, latex/food allergies, etc. Irritants: Perfumes, household chemicals, tobacco smoke, etc. Weather: Poor air quality days; often seasonal (spring or fall) Exercise: Symptoms occur typically several minutes into activity; symptoms improve with or prevented by warmup before exercise	Weather: Poor air quality days, change of seasons (e.g., cold "snaps," rainy periods) Exertion: Onset of symptoms typically "fixed" to level of effort/distance (e.g., onset of shortness of breath after walking one block or flight of stairs and improves with rest)	Mixed features
PFTs	FEV_1 may be normal (at least 80% of predicted) in mild or well-controlled asthma or "reverse" (i.e., > 12% or 400-mL improvement) after bronchodilators FEV_1/FVC usually > 70% of predicted Methacholine challenge test may be used to confirm asthma if baseline FEV_1 is normal (drop in FEV_1 to < 80% of predicted) DLCO is usually normal	Post-bronchodilator FEV_1 may improve, but not necessarily normalize. Severity (% of predicted) • Mild/grade 1 (> 80%) • Moderate/grade 2 (50%–79%) • Severe/grade 3 (30%–49%) • Very severe/grade 4 (< 30%) • In a COPD subset, FEV_1 may meet the criteria for "responsive" to bronchodilators (i.e., change of 12% or 200 mL) Post-bronchodilator FEV_1/FVC remains < 70% of predicted DLCO is decreased with emphysema	FEV_1: May "reverse" (asthma-like) or be "responsive" post-bronchodilators as in a subset of COPD Post-bronchodilator FEV_1/FVC may persist as < 70% of predicted (similar to COPD) FENO (> 50 ppb) in nonsmoking individuals is consistent with eosinophilic airway inflammation Blood eosinophilia may be present
Complications	Exacerbations: Range from mild to life threatening and can be fatal	Exacerbations: Cardinal signs are an increase in dyspnea, sputum production or purulence. Exacerbations increase in severity and frequency as COPD progresses. Complications associated with hypoxia: • Polycythemia (Hct > 55%) may cause CVA, VTE, or PE • Pulmonary hypertension (pressures > 25/12 mm Hg) • Cor pulmonale (i.e., features of right-sided failure with absence of signs of left-sided heart failure) • Arrhythmias (e.g., multifocal atrial tachycardia) • (Those with chronic bronchitis develop complications earlier in the disease course [i.e., at a higher FEV_1])	Compared with COPD: May develop similar complications; frequency of exacerbations may impair QOL

Table 1-1. Comparison of Features of Asthma, COPD, and ACOS (*continued*)

Clinical Feature	Asthma	COPD	Suggestive of ACOS
History	Family history of atopy (e.g., asthma, allergic rhinitis, eczema) Exposure to tobacco in utero	20+ pack-year personal history of tobacco use Occupational/industrial exposure to noxious particles (e.g., grain dust, steel mills)	History of occupational exposure and/or personal or family history of asthma
Time course/ prognosis	Onset often in childhood Symptoms respond to acute or chronic therapy and/or trigger avoidance Normal QOL and life span possible for most with optimal therapy	Onset of symptoms in fourth to fifth decade with diagnosis usually in the fifth to sixth decade of life Symptoms become more continuous and limiting over time, even with chronic therapy May stabilize with tobacco cessation Progressive decrease in QOL; premature death	Onset of symptoms usually in fourth decade Symptoms partly respond to therapy, but they progress and are less responsive to treatment over time Can develop COPD-like complications over time
Underlying pathophysiology	Airway obstruction because of bronchoconstriction and Th2-driven eosinophilic inflammation Mediators: Histamine, IL-4, IL-5, LTD_4, LTB_4, PAF, ECF	Neutrophilic/lymphocytic inflammation from Th1 and Th17 combined with eosinophilic inflammation during exacerbations Airway obstruction because of increased production and decreased clearance of mucus, inflammation, and airway collapse Ventilation-perfusion mismatch causes chronic hypoxic complications Mediators: Elastase, IL-1, IL-6, IL-8, TNFα; LTB_4; TGFβ	Unknown; may vary by clinical phenotype. Likely a mixture of features (e.g., combination of eosinophilic and neutrophilic inflammation)

ACOS = asthma-COPD overlap syndrome; CVA = cerebrovascular accident; DLCO = carbon monoxide diffusion in the lung; ECF = eosinophil chemotactic factor; FENO = fractional excretion of nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IL = interleukin; LT = leukotriene; LTB_4 = leukotriene B_4; PAF = platelet-activating factor; PE = pulmonary embolism; PFT = pulmonary function test; QOL = quality of life; TGF = transforming growth factor; Th = helper T cell; TNF = tumor necrosis factor; VTE = venous thromboembolism.

testing. Historically, COPD has been categorized into chronic bronchitis and emphysema subtypes. Chronic bronchitis has productive cough and earlier development of hypoxia and carbon dioxide retention, resulting in complications such as right-sided heart failure/cor pulmonale with edema (i.e., "blue bloater" in appearance). In contrast, emphysema initially presents with exertional dyspnea that progresses over time to dyspnea at rest. Patients may be thinner because of the caloric expenditure from the increased respiratory rate and work to breathe. The ratio of ventilation to perfusion is better preserved in emphysema. A patient with emphysema ("pink puffer") is generally better oxygenated than a patient with chronic bronchitis having a similar a FEV_1. As a result, the complications attributable to hypoxia occur later in the course of lung function decline (i.e., at a lower FEV_1). Many to most patients with COPD present with combined features of both chronic bronchitis and emphysema. In general, chronic bronchitis and emphysema treatments are the same; thus, distinguishing between the two COPD subsets has small therapeutic implication at this time.

Asthma and COPD have underlying airway obstruction, and inflammation in common, but the mechanisms and complications are different (see Table 1-1). In asthma, bronchoconstriction and eosinophil-related inflammation are primarily responsible. Because lung acini are not involved, oxygen or carbon dioxide exchange is not normally affected. Hypoxia is rare outside serious exacerbations. In contrast, neutrophils are the main cause of inflammation in COPD; eosinophils have a secondary role during exacerbations and play an increasing role as lung function declines. Obstruction occurs from increased mucus production and decreased clearance; in addition, airways can collapse on exhalation because of damaged airway infrastructure. Direct bronchoconstriction plays a minor role in airway obstruction in COPD. Damage to acini impairs gas exchange, resulting in ventilation and blood perfusion

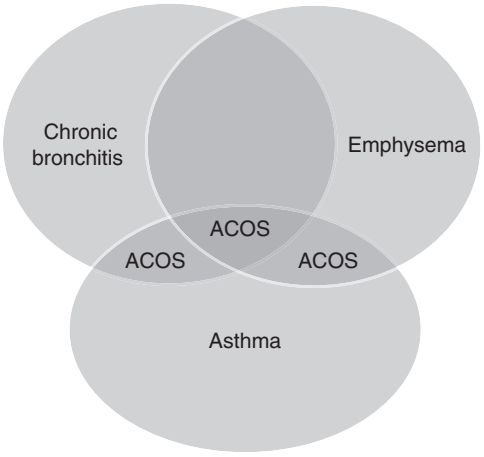

Figure 1-1. Overlapping presentation of asthma, chronic obstructive pulmonary disease, and asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS).

mismatch. As lung damage progresses, hypoxic complications such as cor pulmonale occur.

Although asthma and COPD are distinct conditions, some patients have features of both. Classically, this relationship was shown by a Venn diagram (Figure 1-1) of interlocking circles for asthma, chronic bronchitis, and emphysema. In recent years, some have explored and defined this clinical observation, calling it asthma-COPD overlap syndrome (ACOS). Because both COPD and asthma are marked by airflow obstruction and airway inflammation, it is still unclear whether ACOS is a separate distinct respiratory process with an underlying pathophysiology that differs from either condition alone or several phenotypes of coexisting asthma and COPD (Nielsen 2015). For example, the previously reversible airway obstruction of asthma can become "fixed" or irreversible over time, especially in those with severe, poorly controlled asthma; or those with asthma who smoke for many years may present with a new diagnosis of COPD (Kiljander 2015). Another possible overlap includes those with asthma who have a productive cough similar to that in chronic bronchitis, rather than the typical dry asthma cough. These clinical scenarios could be considered asthma–COPD ACOS phenotypes. In contrast, an example of a COPD-asthma ACOS phenotype could include those with COPD whose obstruction after bronchodilators on PFTs meets the criteria for reversibility (forced expiratory volume in 1 second [FEV_1] improvement of 12% or 400 mL) or responsiveness (improvement of 12% or 200 mL) and who have atopic triggers (Kiljander 2015).

The specific diagnosis of COPD, asthma, or ACOS has many significant clinical implications. None of these conditions can be diagnosed according to the type or even the pattern of symptoms alone. Doing PFTs is important to differentiate between, and confirm, an asthma diagnosis and a COPD diagnosis. Not all individuals with a chronic cough and wheezing have COPD, even if the individual has a long-term history of tobacco use. Other conditions such as heart failure and tuberculosis can also masquerade as COPD or even asthma. Although similar medication categories such as inhaled bronchodilators and inhaled corticosteroids (ICS) are used, the underlying pathophysiology of asthma and COPD translates to significant differences in prognosis, complications, and treatment algorithms.

Currently, there are no standardized diagnostic criteria for ACOS (see Table 1-1). Hence, current guidelines (GINA ACOS 2015) recommend categorizing a condition as asthma or COPD when the characteristics of one condition are present without the features of the other. A diagnosis of ACOS can be applied if a similar number of features of asthma and COPD are present. The incidence of ACOS is currently unknown, but it is estimated to occur in 10%–50% of patients with COPD (GINA ACOS 2015). Similarly, the prevalence of ACOS is unknown, but it is thought to increase with age (Kiljander 2015). However, it is important to determine whether a patient falls in the ACOS category because this can negatively affect the progression of lung deterioration, response to therapy, and overall prognosis (Barnes 2016). Thus, the lack of standardized diagnostic criteria for ACOS hinders the accurate measurement of disease incidence, understanding of the underlying pathophysiology, and conductance of therapeutic research (van der Berge 2016).

CURRENT GUIDELINES AND UPDATES

Compare and Contrast GINA and EPR-3 Guidelines

Stepwise Approach to Therapy in Adults

The Global Initiative for Asthma (GINA) guidelines are evidence-based international guidelines that are updated annually. Although a Working Group has done a needs assessment (NHLBI 2014), the Third Expert Panel Report of the National Heart, Lung, and Blood Institute (EPR-3) on asthma was last updated in 2007 (NAEPP 2007). The similarities and differences between the two recommendations are summarized in Table 1-2. Both guidelines recommend an inhaled short-acting β_2-agonist (SABA), such as albuterol, as a "quick-relief" medication to treat intermittent symptoms. In some countries, a low-dose ICS such as beclomethasone or mometasone plus a formoterol combination product is also approved for use as a quick-relief medication. The theory for using a combination product for quick relief of symptoms is that promptly increasing the ICS dose in the short term can lessen the severity of an acute exacerbation. An added benefit is that the patient needs only one inhaler product for both controller and quick reliever, which can decrease confusion over which inhaler to use. Disadvantages to this approach are the higher cost of the combination product and potential for greater ICS

Table 1-2. Comparing the GINA and EPR-3 Stepwise Approach to Asthma Treatment in Adolescents > 12 and Adults[a]

Medication Class	Step 1[b]	Step 2[c]	Step 3[c]	Step 4[c]	Step 5[c]	Step 6[c]
Controller(s)	None	Low-dose ICS	Low-dose ICS + LABA or Medium-dose ICS (EPR-3)	Medium-dose ICS + LABA High-dose ICS + LABA (GINA 2016) Add tiotropium (GINA 2016)	High-dose ICS + LABA (EPR-3) Consider omalizumab (GINA 2016) Consider mepolizumab (GINA 2016) Add tiotropium (GINA 2016) Add low-dose oral steroid (GINA 2016)	High-dose ICS + LABA + oral corticosteroid (EPR-3) Consider omalizumab (EPR-3)
Quick relief	As-needed SABA					
			As-needed SABA or low-dose ICS/formoterol[d] (GINA 2016)			

[a]Recommendations are from both EPR-3 and GINA 2016 unless otherwise indicated.

[b]Intermittent asthma.

[c]Persistent asthma: symptoms or quick-relief inhaler use > 2 days/week or nocturnal symptoms more than twice a month.

[d]Not an approved indication in the United States.

EPR-3 = Third Expert Panel Report of the National Heart, Lung, and Blood Institute; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist.

exposure, increasing the risk of long-term adverse events. The GINA guidelines include this option of the combination product as an alternative to a SABA as a quick-relief medicine.

Patients with persistent asthma (symptoms occurring or use of quick-relief medication more often than 2 days/week or nocturnal symptoms more than twice a month) should be prescribed a daily controller medication (step 2 therapy), usually a low-dose ICS (see Table 1-2). If asthma remains uncontrolled (defined as symptoms occurring or use of quick-relief medication more often than 2 days/week or nocturnal symptoms more than twice a month and with any activity limitation) despite adherence to initial controller therapy, controller therapy should be stepped up further. The next step-up in therapy (step 3) can be achieved by increasing the ICS dose (number of puffs per day) or the ICS strength (e.g., from low to moderate or from moderate to high), adding a long-acting β_2-agonist (LABA), or both. The GINA guidelines recommend adding the LABA first before increasing the ICS dose. Combining an ICS and a LABA into a single device increases patient convenience and potentially adherence. There is little benefit to increasing the dose of LABAs because the dose-bronchodilation response curve is fairly flat (Cazzola 2012). Thus, the dose of LABAs in these products is constant. A further step-up in therapy (step 4 and step 5) is accomplished by making additional increases in the dosage of the ICS component. Combination products are discussed later in the chapter.

Because the GINA guidelines have been more recently updated to include newer information, recommendations for tiotropium and mepolizumab are mentioned. These are alternatives in step 5. In more severe asthma, oral corticosteroids can be given daily, despite the likelihood of adverse effects. Despite the cost of omalizumab ($500–2700 per month, depending on the dosage required), omalizumab can be cost-effective by decreasing hospitalizations and urgent care visits for individuals with high immunoglobulin (Ig) E concentrations whose asthma is uncontrolled by step 4 therapy (GINA 2016). The EPR guidelines follow the same general order of agents for therapy, but they break the therapy into six steps (rather than five, as in GINA). Omalizumab and oral corticosteroids are reserved for the sixth step. The dosing strategy for omalizumab is based on the patient's weight and baseline IgE concentration (eFacts).

The GINA guidelines now define asthma severity by the therapy step required to achieve asthma control. Mild asthma is controlled with step 1 or 2 therapy. Moderate asthma is well controlled with step 3 therapy. Severe asthma requires step 4 or 5 therapy to achieve control.

Both guidelines recommend that before stepping up therapy, patient adherence, adequacy of device technique, trigger

management, and comorbid conditions should be assessed and addressed, if problematic (EPR-3 and GINA 2016); these are common reasons for inadequate response to or failures of therapy. Monotherapy with a LABA alone as controller therapy is not indicated for persistent asthma. Failure to treat underlying lung inflammation can result in serious exacerbations.

If asthma remains well controlled for at least 3 months, a step-down in therapy may be indicated to limit long-term medication exposure (GINA 2016). Oral corticosteroids should slowly be tapered to the lowest possible dose and/or prescribed every other day. Ideally, oral corticosteroid therapy is discontinued and therapy transitioned back to high-dose ICS. Discontinuing alternative therapies (e.g., tiotropium) should be considered before changing the ICS or LABA regimen. For combination therapy, the ICS dose is usually decreased first (by 50%) and the LABA continued because the risk of losing control is greater when continuing therapy with an ICS alone. In general, controller ICS therapy with at least a low dose is continued indefinitely. Corticosteroids with a shorter duration such as beclomethasone, mometasone, or ciclesonide can be dosed once daily instead of the usual twice daily to lower the ICS dose. Discontinuing an ICS, resulting in monotherapy with LABA, is never indicated for asthma. The GINA guidelines strongly suggest that all step-downs in therapy be considered trials with close monitoring. Patients should have a written action plan so that if asthma flares, the patient knows how to manage symptoms and restarts the previous step in controller therapy. Throughout the GINA guidelines, comprehensive asthma self-management (which includes action plans) is emphasized because of the documented decrease achieved in pediatric and adult morbidity and mortality from asthma. The American Lung Association and the Asthma and Allergy Foundation of America have examples of asthma action plans on their websites. Action plans have also been developed for patients with low health literacy (Yin 2016).

Asthma Recommendations for Children vs. Adults

Both guidelines (GINA and EPR-3) have specific recommendations for asthma treatment in children 6–12 years of age. Although similar in the general stepwise approach for adults, the treatment algorithm for children has some differences. For children younger than 12 years, the preferred step-up approach is to increase the ICS from low to medium dose before adding a LABA. Theophylline and ipratropium are not indicated for individuals younger than 18 years. Montelukast is generally not recommended as a preferred controller agent. For ICS plus LABA therapy, only combination inhalers are to be used in children (FDA 2010). Using two separate devices could result in inadvertent monotherapy with a LABA if the child is nonadherent to ICS therapy. When stepping down therapy, the LABA is usually discontinued before the ICS dose is lowered. With adequate instruction, children can be taught to use dry powder inhalers (DPIs) and metered dose inhalers (MDIs) (with or without a holding chamber) correctly. See the guidelines for detailed recommendations for children younger than 6 years.

GOLD Guidelines for Stepwise Approach to COPD

Evidence-based treatment recommendations for COPD are summarized by the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, which are updated yearly (GOLD 2017) (Figure 1-2). Until recently, COPD was staged as grades 1–4, and therapy was recommended according to the post-bronchodilator FEV_1 (percentage of predicted). A limitation of this staging system is that although the degree of lung impairment and clinical status is related, symptom severity is not directly proportional to FEV_1 impairment. As previously mentioned, those with chronic bronchitis tend to be more symptomatic and have more hypoxic complications at the same degree of FEV_1 impairment than do those with emphysema.

Pharmacists should be familiar with two validated questionnaires used to assess and quantify COPD symptoms: the modified Medical Research Council respiratory questionnaire (mMRC) and the COPD Assessment Test (CAT) as well as their respective cut points. Fewer symptoms is an mMRC score of 0 or 1 (range 0–4) or a CAT score less than 10 (range 0–40), and more symptoms is an mMRC or CAT score of at least 2 or 10, respectively. Of the two questionnaires, the CAT is preferred because it provides a more comprehensive assessment of symptoms, whereas the mMRC only assesses dyspnea (GOLD 2017).

A few years ago, the GOLD guidelines changed the COPD classification/staging system to incorporate recent exacerbation history with the symptom/breathlessness score and the post-bronchodilator FEV_1 to provide a composite picture of a patient's clinical status. As the classification further evolves, the 2017 GOLD guidelines still use post-bronchodilator FEV_1 to stage COPD into grades 1–4. But only an individual's symptom score and exacerbation history (GOLD 2017) are used to evaluate current COPD status and divide into groups A, B, C, and D (see Figure 1-2). For example, COPD in a patient with a CAT score of 12 and one hospitalization for a COPD exacerbation in the past year would be classified as having group D COPD, regardless of the FEV_1 results. If PFTs show a post-bronchodilator FEV_1 of 35% of predicted, the full assessment will be grade 3, group D COPD. When COPD grade severity and symptom/exacerbation history significantly change or appear disparate, further testing or assessments may be necessary. For example, a patient with prior grade 3, group C COPD unexpectedly appears more symptomatic (i.e., have a higher CAT score). Questioning may reveal the symptom worsening is likely due to an increase in physical activity (rather than a worsening of the underlying lung function.) In another example, a patient assessed with only grade 2 COPD based on FEV_1, but group D based on symptoms. Further

<table>
<tr><th colspan="3">Staging[a]</th><th colspan="2">Initial Therapy Recommendations</th><th>Exacerbation History (past 12 months)</th></tr>
<tr><td>Grade 4 very severe</td><td rowspan="3">FEV$_1$/FVC < 70%
Post-bronchodilator FEV$_1$</td><td>< 29%</td><td rowspan="2">Group C[b]
• LAMA</td><td rowspan="2">Group D[c]
• LABA + LAMA</td><td rowspan="2">High risk
≥ 2 or
≥ 1 leading to hospitalization</td></tr>
<tr><td>Grade 3 severe</td><td>30%–49%</td></tr>
<tr><td>Grade 2 moderate</td><td>50%–79%</td><td rowspan="2">Group A[d]
• SAMA or SABA as needed</td><td rowspan="2">Group B[e]
• LAMA or
• LABA</td><td>Low risk
1 (not requiring hospitalization)</td></tr>
<tr><td>Grade 1 mild</td><td>≥ 80% of predicted</td><td>0</td></tr>
<tr><td colspan="3" rowspan="5"></td><td colspan="2">Symptoms score</td><td rowspan="5"></td></tr>
<tr><td>CAT[f] < 10
low symptoms</td><td>CAT ≥ 10
high symptoms</td></tr>
<tr><td colspan="2">Degree of breathlessness</td></tr>
<tr><td>mMRC[g] 0–1
less breathless</td><td>mMRC ≥ 2
more breathless</td></tr>
</table>

Figure 1-2. GOLD 2017 treatment recommendations according to symptoms and exacerbation history.

[a]Staging is used to establish the COPD diagnosis and assesses the grade according to the degree of airflow obstruction. But the grade (1–4) is no longer used to determine recommendations for maintenance therapy (i.e., groups A-D).

[b]LAMAs may be more effective at preventing exacerbations; they are thus recommended over LABAs in group C. LAMA + LABA is the preferred therapeutic escalation if exacerbations remain frequent. LABA + ICS may be an alternative to escalate therapy, but this combination can also increase the risk of pneumonia.

[c]To decrease symptoms and frequency/severity of exacerbations, therapy may be escalated by a trial with LABA + LAMA + ICS. However, more data are needed to assess whether an ICS adds benefit to LABA + LAMA therapy. If COPD is of the chronic bronchitis type and the FEV$_1$ is less than 50% of predicted, therapeutic escalation by adding roflumilast may be considered. However, in those with ACOS, LABA + ICS may be used as initial therapy.

[d]Continue initial SABA, or try the alternative bronchodilator class, depending on response. LAMA or LABA may also be considered as initial therapy.

[e]Either bronchodilator class (LABA or LAMA) may be used initially in group B because neither has been shown to be more effective in this group. Escalate to LAMA + LABA as needed to control symptoms. With severe breathlessness before therapy, may initiate therapy with LABA + LAMA.

[f]Ranges for CAT scores 0–40.

[g]mMRC scores 0–4.

CAT = COPD Assessment Test; FEV$_1$ = forced expiratory volume in 1 second; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council respiratory questionnaire; SAMA = short-acting muscarinic antagonist.

testing might reveal a previously unidentified concurrent condition (e.g., heart failure or sleep apnea) that contributes to the increased symptoms.

The general stepwise approach begins with a SABA or a short-acting muscarinic antagonist for intermittent symptoms. As symptoms increase in frequency, a long-acting bronchodilator (either a LABA or a long-acting muscarinic antagonist [LAMA]) is added for better symptom management and maintenance of activity level. Long-acting agents are preferred because they provide better symptomatic management than short-acting agents. The 2017 GOLD guidelines recommend LAMA over LABA as initial monotherapy for group C COPD because LAMA better improves exacerbation rates. But either a LABA or a LAMA can be recommended for initial therapy in group B because no difference in exacerbation rates has been shown in this group. Initial drug selection can also be influenced by situational factors such as patient device preference, clinician experience, and formulary restrictions. If clinical response is insufficient, a second long-acting bronchodilator (in the opposite drug class) is added.

Therapy with ICS early in the course of COPD does not provide clinical benefit; however, as lung function progressively declines (group C or D), moderate-dose ICS therapy may slightly decrease symptoms and have a modest effect on decreasing exacerbations. The response to ICS therapy likely corresponds to the increasing contribution of eosinophils to

the underlying lung inflammation as lung function declines. Because of the cost of ICS therapy, these agents should generally be reserved for patients most likely to benefit (i.e., symptoms uncontrolled or continued exacerbations on LAMA plus LABA therapy). It is well known that ICS are often overused in patients with COPD. As many as 40% of patients in one study classified as having risk category A or B were receiving an ICS inappropriately (Watz 2016). Unnecessary use of ICS adds not only to the cost of therapy, but also to the risk of adverse events from long-term exposure, such as bone fracture and pneumonia. Individuals at higher risk of pneumonia with ICS therapy include those who currently smoke, are older than 55, have a history of pneumonia, have a BMI less than 25 kg/m^2, and have severe airflow limitation (GOLD 2017). Other risks of ICS include poor diabetes control, cataracts, and mycobacterial infections. Monotherapy with ICS is not recommended by GOLD because long-acting bronchodilators are more effective at controlling symptoms and have fewer associated risks.

For patients with group D COPD, pharmacotherapy targets reducing the frequency and severity of exacerbations, which significantly increase health care expenditures, worsen prognosis and increase risk of death (GOLD 2017). Both tiotropium and ICS-LABA combinations reduce exacerbation rates in this risk category. A retrospective cohort study assessed the impact of triple-drug therapy (ICS-LABA plus a LAMA) compared with double therapy with ICS-LABA on real-life outcomes, evaluating mortality, hospital admission, and exacerbation frequency (Short 2012). A total of 2853 patients were included, with 1857 receiving triple therapy and 996 receiving double therapy. Significant improvement in all-cause mortality was shown for patients receiving triple therapy versus double therapy, with an adjusted HR of 0.65 (95% CI, 0.57–0.75), which was a 35% risk reduction. For COPD exacerbations, the adjusted HR for an oral steroid prescription was 0.71 (95% CI, 0.63–0.80), which equated to a 29% risk reduction for triple- versus double-drug therapy. Similarly, the adjusted HR for hospital admission as the result of respiratory disease was 0.85 (95% CI, 0.73–0.99), which was a 15% risk reduction with triple therapy versus double therapy (Short 2012). In this study, triple-drug therapy was achieved by adding a LAMA to LABA plus ICS therapy. However, if the GOLD treatment algorithm is followed, more patients with severe COPD (i.e., groups C and D) will be escalated to double bronchodilator (LABA plus LAMA) therapy before an ICS is initiated. An unanswered question is the benefit, if any, to adding an ICS to double bronchodilator therapy to achieve triple-drug therapy.

Another logical question is, which two-drug therapy may be more effective with an ICS plus a LABA or a LABA plus a LAMA. A recent study was designed to study this question (Wedzicha 2016). After a 4-week run-in period with tiotropium, patients with COPD having an FEV_1 less than 60% and an mMRC of 2 or more received either indacaterol 100 mcg plus glycopyrronium 50 mcg once daily or salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily for 52 weeks. The primary outcome of this study was the annual rate of COPD exacerbations, which was 11% lower (p=0.003) in the indacaterol/glycopyrronium group at 3.59 (95% CI, 3.28–3.94) than at 4.03 in the salmeterol/fluticasone group (95% CI, 3.68–4.41). The difference was also significant, according to a modified intention-to-treat analysis. Secondary outcomes of time to first exacerbation, annual rate of moderate to severe COPD exacerbations, improvement in QOL scores, and decrease in rescue medication use also favored the LABA plus LAMA group. The difference in moderate to severe exacerbations favored the LABA plus LAMA group, regardless of initial blood eosinophil counts. The incidence of adverse events was no different between the groups. However, the incidence of pneumonia was 3.2% in the LABA plus LAMA group but 4.8% in the ICS plus LABA group (p=0.02).

There are a few interesting aspects to this study. First, a better response to an ICS might have been expected in those with a higher eosinophil count (2% or greater). Yet the LABA plus LAMA group also had better results in this population. Second, the rate of pneumonia was higher in the ICS group. However, a higher fluticasone dose (500 mcg twice daily) was used than was recommended for COPD (250 mcg twice daily), which may have contributed to this result. Finally, the indacaterol/glycopyrronium regimen was a higher-dose once-daily regimen than the product currently approved in the United States (indacaterol 27.5 mcg plus glycopyrronium 15.6 mcg) dosed twice daily. The U.S.-approved product may not provide the same efficacy results as in this trial. But it is reassuring that the higher daily dose appeared to be well tolerated.

Because of the risks of ICS therapy and lack of data regarding the benefits of adding ICS to LABA plus LAMA therapy, the 2017 GOLD guidelines take a more cautious approach to ICS use. Starting with LAMA therapy (in group C) and escalating to double LAMA plus LABA therapy, as necessary, is preferred to initiating or escalating to ICS plus LABA therapy. Similarly, initiating those in group D on double bronchodilator therapy for symptom control before adding an ICS is recommended by the available data. The role of ICS therapy in the treatment of COPD will likely continue to evolve as more data become available.

Roflumilast, an oral phosphodiesterase type 4 (PDE4) inhibitor, is another option for patients in GOLD group C or D with frequent exacerbations despite a LAMA plus a LABA or a LABA plus ICS therapy (GOLD 2017). Data are lacking on the benefits of adding roflumilast versus adding ICS to double bronchodilator therapy. The dose is one 500-mcg tablet daily. In general, candidates for therapy have predominant chronic bronchitis subtype and a chronic productive cough with daily sputum production because roflumilast can decrease the number of sputum neutrophils and eosinophils (eFacts). However, common adverse effects limit its clinical usefulness, including weight loss, sleep disorders, headaches, diarrhea, and nausea. Potential for weight loss can be of particular concern in those with a low BMI (i.e., less than 25 kg/m^2),

discouraging roflumilast use in the very thin patient with the classic emphysema presentation. Postmarketing surveillance has shown that roflumilast can also worsen depression and even be associated with suicidal ideation. Major drug interactions may occur with roflumilast because it is a substrate of CYP3A4 (eFacts); inhibitors of CYP3A4 and dual inhibitors of CYP1A2 and CYP3A4 should be avoided (e.g., clarithromycin, ketoconazole, verapamil, cimetidine, some HIV retroviral agents). According to the package insert for roflumilast, strong inducers of CYP such as rifampin, phenobarbital, carbamazepine, and phenytoin should also be avoided. Pharmacists should carefully check for drug interactions and other comorbid conditions like depression and weight loss before initiating roflumilast. This drug should be reserved for patients with a history of frequent exacerbations despite double bronchodilator therapy, in whom the modest benefit on exacerbation frequency can justify its considerable cost (GOLD 2017; Mehta 2016).

Theophylline was only recommended in the 2016 GOLD guidelines if other bronchodilators are unavailable or unaffordable. Drug interactions, adverse effects, and limited efficacy curb its use when other agents are available. The 2017 guidelines do not provide any suggested situations for theophylline use.

The GOLD 2017 guidelines also briefly mention the possibility of de-escalating therapy, but they do not discuss specific situations or make recommendations for changes in therapy. However, patients who successfully quit tobacco may need less therapy to maintain the same level of symptoms (e.g., CAT score less than 10). Until more data are available, it is logical to follow similar principles in de-escalating therapy (i.e., discontinuing ICS or roflumilast therapy in preference to maintaining double bronchodilator therapy). Similarly, the timing and level of symptoms at which to consider de-escalation also require further study. Before modifying therapy, symptom scores should be lower and stable with less frequent and severe exacerbations for a considerable period (e.g., 1 year). Close monitoring is also advised, especially in those with a history of severe exacerbations.

β-Adrenergic receptor–blocking drugs have traditionally been avoided in COPD because of concerns for inducing bronchospasm and worsening symptoms. However, these concerns may result in the under-prescribing of these agents in patients with concurrent COPD and a strong cardiac indication for their use, such as heart failure and coronary artery disease. Data analyses support the safe use of β-adrenergic receptor–blocking agents in this population (GOLD 2016; Lipworth 2016; Lopez-Campos 2016; Salpeter 2005). Additional long-term data are needed, especially to detect potential differences among agents (e.g., whether there are differences between agents with an indication for heart failure [i.e., bisoprolol, carvedilol, and metoprolol]). In the meantime, selective β-adrenergic–blocking drugs can be used with close monitoring in patients with a strong cardiac indication for their use.

Adjunctive Therapy for COPD and Asthma

Vaccinations

Patients with COPD and asthma should receive vaccinations to prevent influenza and pneumococcal respiratory infections. Annual influenza vaccinations prevent acute exacerbations of COPD (Criner 2015). The inhaled influenza vaccination is not recommended for those with respiratory conditions or those older than 50 years (Kobayashi 2015).

Patients with COPD (age 19–64) should receive the pneumococcal polysaccharide vaccine (PPSV23) (Pneumovax 23). After age 65, if a patient has not received a pneumococcal vaccination, administer a dose of the pneumococcal conjugate vaccine (PCV13), followed by PPSV23 6–12 months later. Similarly, if a patient with COPD received a dose of PPSV23 after age 65, but not PCV13, administer a dose of PCV13 at least 1 year after PPSV23 was given.

Adult patients with COPD age 65 and older who have not received PCV13 but have received one or more doses of PPSV23 before age 65 should receive PCV13 at least 1 year after the most recent PPSV23 dose. In addition, patients who have been vaccinated with PPSV23 before age 65 should receive a final dose of PPSV23 (ensuring that at least 5 years have elapsed since the original dose of PPSV23). Further pneumococcal vaccinations after the sequence at age 65 are unnecessary (CDC 2015).

Similar to patients with COPD, those with asthma should receive an annual influenza vaccination. In addition, asthma was recently added as an indication for vaccination against pneumococcal disease. The same vaccines, dosing, and intervals should be followed as mentioned earlier for patients with COPD (Kim 2016b).

Tobacco Cessation and Avoidance

All patients with COPD should be encouraged to quit smoking; this is a modifiable risk factor. Quitting can stabilize and even slightly improve lung function. Patients with asthma should also be encouraged to avoid personal tobacco use. Exposure to smoke in the home and workplace by others should also be avoided because tobacco smoke is a common irritant trigger for asthma. Tobacco exposure in utero and in young children is a risk factor for developing asthma; avoidance of tobacco use during pregnancy and exposure during the first year of life is one of the few known measures that can prevent asthma.

The U.S. Surgeon General recently released a report summarizing the risks of use of electronic nicotine delivery systems (ENDS) (also known as electronic cigarettes or "vaping") by youth and young adults (DHHS 2016). Nicotine can harm the developing brain. Use of ENDS can result in nicotine addiction; close to 60% of adolescent ENDS users also use other tobacco products, including cigarettes. The ENDS device can also potentially be used for illicit drugs. Although e-cigarette vapor contains fewer chemicals than conventional cigarettes, the vapor contains carbonyl and volatile organic compounds known to have adverse effects; the health effects

of the many other chemicals in these products are not well studied. Given these concerns, ENDS should not be viewed as "safe cigarettes"; youth and adults should strongly be discouraged from using them.

Updated tobacco cessation guidelines continue to recommend the regular use of the 5A's approach by all health care professionals (i.e., Ask about tobacco use, Advise quitting, Assess willingness to quit, Assist in quit attempt, Arrange follow-up) (Siu 2015). Pharmacists are well positioned to facilitate these steps: the community pharmacist when patients obtain medications, ambulatory care pharmacists at follow-up visits, and hospital-based pharmacists at the time of admission and discharge. Pharmacologic options include nicotine replacement therapy (NRT), varenicline, and sustained-release bupropion. Varenicline has the highest cessation rates versus placebo at 1 year (28%); however, combining two forms of NRT (e.g., the long-acting patch and the short-acting gum) can increase cessation rates as well. Combining pharmacotherapy with intensive counseling or behavioral support (for at least a total of 90 minutes) increases the effectiveness of tobacco cessation at 6 months. Inhaler NRT devices should be avoided in those with asthma or COPD because of the potential for bronchospasm; other forms of NRT can be used (eFacts).

Updated guidelines do not recommend using the ENDS for tobacco cessation because of the lack of sufficient data to support their use (Siu 2015). The only two randomized controlled trials using ENDS for tobacco cessation had mixed results. The safety and toxicity of the components, including the aerosols and nicotine in these products, are not known. There is also a concern for the potential poisoning of children who obtain access to these products.

In 2009, the FDA was granted regulatory authority over smokeless tobacco products (FDA 2009). More recently, the FDA was given additional authority to regulate ENDS, cigars, pipe tobacco, hookah (water pipe) tobacco, nicotine gels, and dissolvables (FDA 2016b). Manufacturers and distributors of such products are now also required to maintain the set standards as well as clearly label nicotine products with the following statement: "WARNING: This product contains nicotine. Nicotine is an addictive chemical" (FDA 2016b).

Adjunctive Therapies Specifically for COPD

Pulmonary Rehabilitation Programs

Benefits from completing a comprehensive pulmonary rehabilitation program include increased exercise capacity, reduced depression, improved QOL, decreased length of hospital stay, and improved recovery after a COPD exacerbation (GOLD 2017; Mehta 2016). The most effective programs last 6–8 weeks and include exercise training, smoking cessation, nutritional counseling, and education (GOLD 2017). Longer programs (e.g., 12 weeks or more) have not been shown to provide additional benefit. A higher health status after program completion can be maintained if exercises are continued at home. Major barriers to program attendance/completion and hence programmatic effectiveness include insufficient patient access (lack of transportation or locally available programs), lack of health care payer support, and health care providers' unfamiliarity with the programs and benefits, limiting referrals (Vogiatzis 2016). On the one hand, even those with severe lung disease may benefit with increased exercise capacity and improved QOL (GOLD 2017). On the other hand, patients in GOLD grade 3 or 4 may be unable to complete the program and therefore not receive the full effect. Therefore, rehabilitation should be recommended in early disease stages (e.g., group B). Despite the labor intensity required to provide such programs, pulmonary rehabilitation is cost-effective (GOLD 2017).

Pharmacists can provide the medication-related educational component in such programs, including the importance of adherence and use of proper device technique as well as how to troubleshoot and maintain pulmonary devices. Pharmacists should be knowledgeable regarding the availability of programs in their area in order to refer patients early in the COPD disease course.

Oxygen

Candidates for long-term oxygen therapy (more than 15 hours per day) include those with resting hypoxemia (Sao_2 less than 88%) and those with COPD complications such as pulmonary hypertension, right-sided heart failure with edema, or polycythemia (i.e., hematocrit more than 55%) if Sao_2 is 88% or less (GOLD 2016). With these criteria, continuous oxygen therapy can improve survival, activity level, and QOL. Although oxygen may play a role in the palliative treatment of severe dyspnea in the absence of hypoxemia (i.e., Sao_2 above 92%), the survival benefits may not occur in this situation (GOLD 2017). Ambulatory oxygen therapy is not recommended for those who do not meet these criteria. Patients should be involved in the decision-making regarding the use of oxygen because motivation for use is key for adherence. If oxygen is used less than 15 hours/day, the survival benefits of oxygen may not be achieved.

Surgery

Surgical removal of parts of the lung to reduce hyperinflation is generally considered last line for severe COPD. A lung volume reduction surgery can be advantageous for patients with a post-bronchodilator FEV_1 of 20% of predicted or less and either severe upper-lobe emphysema on CT or carbon monoxide diffusion in the lung (DLCO) of 20% of predicted or less. In this population, lung volume reduction surgery can improve survival rates, exercise capacity, and QOL (GOLD 2017). The costs of lung volume reduction surgery, insurance coverage, and patient buy-in are perceived barriers to this surgery.

Bronchoscopic lung volume reduction (BLVR) is another option for patients with severe emphysema who may not wish to undergo surgery. A variety of BLVR methods include the use of valves, coils, foam, or stents to improve lung

function, exercise tolerance, and symptoms (van Agteren 2016). Slight improvements in lung function, activity levels, and symptoms have been observed. However, exacerbations and pneumonia may be more frequent. More data are needed to determine the best candidates for BLVR and compare the benefits with those achieved in lung volume reduction surgery (GOLD 2017).

Augmentation of α_1-Antitrypsin

Severe deficiency of α_1-antitrypsin, even without a history of smoking, can result in early-onset emphysema. Lung parenchymal damage from deficiency of this protease inhibitor can further be exacerbated with smoking. Augmenting α_1-antitrypsin can regain a more natural balance in lung parenchymal damage and construction. α_1-Antitrypsin replacement products are only FDA approved in patients with a documented α_1-antitrypsin deficiency (below 11 micromoles/L) who are also nonsmoking and likely to be adherent (Stoller 2016). Although weekly, biweekly, and monthly regimens have been studied, only the weekly infusion regimen (60 mg/kg) is FDA approved. Replacement therapy is generally well tolerated, although rare anaphylactic events are possible. Use should be restricted to those likely to benefit because of the high cost of the medication and need for administration at an infusion center.

Palliative and End-of-Life Care

Because COPD is usually progressive, the GOLD 2017 guidelines briefly outline important aspects of palliative care for those with severe COPD. Data suggest that patients with COPD are less likely to receive such services than are those with cancer and other end-of-life conditions. Dyspnea may improve with pulmonary rehabilitation, opiates, and oxygen. Increased work to breathe may result in malnutrition; those with a low BMI may require nutritional supplementation. Anxiety and depression may respond to pulmonary rehabilitation, yoga, and relaxation therapies. End-of-life care and advanced directives should be proactively discussed to identify patient preferences. Palliative care teams are an important resource in addressing the special needs of patients with severe COPD.

Adjunctive Therapies for Asthma

Trigger Management and Avoidance

Patients should learn to recognize their triggers for asthma symptoms. Common triggers include viral or bacterial infections; irritants like tobacco smoke, perfumes, household cleaners, and high levels of air pollution; and allergens such as animal dander, bird feathers, mold, or pollen. Other triggers include occupational exposure to chemicals, exercise, and food preservatives. Aspirin and other NSAIDs and β-adrenergic receptor–blocking agents may also be triggers in some patients. An allergy to latex is a trigger for some with asthma; cross-reactions to a variety of foods including avocados, bananas, kiwis, tomatoes, potatoes, and mangos have been noted (Kahn 2016). Treatment of gastroesophageal reflux and allergic rhinitis may also improve asthma symptoms.

Not all triggers occur in all patients with asthma. A comprehensive screen to identify personal triggers should be done. Pharmacists should also assist patients in developing a practical trigger management plan, including avoidance strategies and pretreatment with a SABA before exposure to a known trigger. A comprehensive management plan makes trigger avoidance more likely (Rank 2010). Trigger management should also be discussed routinely during admissions for or follow-up visits after asthma exacerbations to prevent future events.

Bronchial Thermoplasty

Bronchial thermoplasty (BT) involves distributing radiofrequency energy into the airways by flexible bronchoscopy to reduce airway smooth muscle mass, decrease bronchoconstriction (Wahidi 2012; Thomson 2011), and decrease bronchial hyper-reactivity (Trivedi 2016). Thermal energy is delivered to the airway wall through electrodes; it is then converted to heat when it comes in contact with tissue (Wahidi 2012). When heat is introduced to the smooth muscle of the airway, the interaction of actin with myosin is disrupted, quickly inactivating muscle cells (Gildea 2011). Airway smooth muscle is a logical target because of its role in bronchoconstriction, promotion of airway inflammation and remodeling, and expelling mucus from the lungs.

In a sham-controlled trial, BT decreased the frequency of severe exacerbations requiring corticosteroids, ED visits, and time lost from work/school and improved QOL scores (Castro 2010). Similarly, a trial assessed the safety of BT 5 years after treatment and found that the rate of oral corticosteroid use and the proportion of subjects requiring oral corticosteroid pulse therapy did not worsen in the BT group. At 5 years, 57% of the BT group reported a decrease in LABA use over time; fewer in the BT group were no longer receiving a LABA (Thomson 2011). After BT, there was a sustained reduction in exacerbations and health care use, despite the lack of changes in lung function or airway structure (Trivedi 2016).

In 2010, the FDA approved BT for treating those older than 18 years with severe persistent asthma not well controlled with ICS and LABA (Wahidi 2012). Bronchial thermoplasty is an additional option for treating patients with severe asthma or asthma refractory to high-dose ICS and LABA therapy. Interventional pulmonologists with advanced bronchoscopist training, skill, and expertise are needed to provide this therapy.

Immunotherapy

Allergic rhinitis is a known risk factor for developing asthma. Controlling allergy symptoms can improve asthma control in some patients. Allergen immunotherapy decreases the immune system's response to a specific antigen (e.g., dust mites) over time by creating tolerance to specific antigens (Hanci 2016). Both subcutaneous and sublingual

immunotherapy can improve asthma symptoms in as few as 12 months and reduce the need for medications. However, immunotherapy does not generally improve PFT results (Mener 2016). Immunotherapy may be considered for those with uncontrolled asthma symptoms despite otherwise optimal therapy, who also have evidence of allergic disease (e.g., positive skin prick testing, elevated serum IgE) (Hanci 2016). Allergists should work with eligible patients in selecting the best delivery system; options include sublingual tablets, which require daily dosing, and subcutaneous injections, which require travel to provider offices for administration. Pharmacists should ensure patient access to injectable epinephrine for possible anaphylactic reactions and educate patients on its proper use and administration.

Treatment of Asthma and COPD Exacerbations

Recommended treatment of acute asthma and COPD exacerbations is largely unchanged in recent years (GOLD 2017; GINA 2016). Bronchodilator therapy should be maximized by regular administration of larger doses (e.g., more puffs) every 4–6 hours. Delivery of inhaled medications can be optimized using holding chambers or nebulized therapy.

Brief courses of oral corticosteroids are usually indicated to limit severity and shorten the duration of exacerbations. For COPD, prednisone 40 mg orally for 5 days is recommended (GOLD 2017). For asthma, the recommended adult dose is 1 mg/kg (50 mg/day maximum) for 5–7 days. For children, the prednisone regimen is 1–2 mg/kg (40 mg/day maximum) for 3–5 days (GINA 2016).

Antibiotics are indicated for COPD exacerbations when all three cardinal symptoms (see Table 1-1) are present or when two cardinal signs are present, with one being increased sputum purulence (GOLD 2017). Specific antibiotics are based on local sensitivity of the common pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. More information on the treatment of exacerbations can be found in the GINA and GOLD guidelines.

MONITORING AND GOALS OF THERAPY

Patients with asthma and COPD should be monitored during frequent, regularly scheduled provider visits (Table 1-3). The most important clinical goals for patients with asthma include minimal daytime and nighttime symptoms, infrequent need for and use of quick-relief medications, and leading a normal life with the ability to perform all desired activities. Optimally, those with asthma should also have normal PFTs. It is important to note that use of 1 or more canisters of quick relief medication per month for treatment of asthma symptoms is a sign of poor asthma control and a risk factor for a fatal asthma attack. The most important clinical goals of COPD therapy include relieving/minimizing symptoms, improving exercise tolerance/activity level, and maintaining overall health. Other goals include preventing/slowing the rate of PFT decline (usually through tobacco cessation) as well as preventing future exacerbations with appropriate therapy, as previously discussed (GOLD 2017).

It is important to objectively measure the impact of either disease on the patient's QOL. For disease-specific questionnaires and desired cut points, see Table 1-3. Patients will want to minimize exacerbations and symptoms, but it is also important for providers to assess patients' perspective on and satisfaction with therapy because these factors affect adherence.

Because of clinical knowledge, medication expertise, and familiarity with pulmonary devices, pharmacists are well-suited to assist with smoking cessation counseling, selecting medications, ensuring appropriate vaccinations are up to date, providing patient education regarding device technique, and stressing the importance of adherence. Similarly, pharmacists can help ensure that comorbid disease states are appropriately being addressed and treated. In addition, pharmacists can assist with documenting and assessing performance indicators for both diseases to assess quality of care and maximize reimbursement in pay-for-performance models.

NEWER AND EMERGING THERAPIES FOR ASTHMA AND COPD

Newer Agents and Products for COPD

Newer LABA Agents

Several new LABAs have become available, including vilanterol, indacaterol, and olodaterol. Similar to older LABAs, their primary mechanism is activation of β_2-adrenergic receptors, increasing the production of cyclic adenosine monophosphate to relax airway smooth muscle and induce bronchodilation (Bjerg 2012; Malerba 2012; Cazzola 2010). Non-bronchodilatory effects, which are potentially significant in COPD, include decreasing airway obstruction by improving mucociliary clearance and decreasing adherence of bacteria to airway epithelial cells, which potentially lessens the frequency of COPD exacerbations (Barnes 2005). Although direct anti-inflammatory effects have not been documented, LABAs decrease neutrophil adhesion to airway epithelial cells and diminish airway microvascular leakage (Barnes 2005). Salmeterol and vilanterol have similar β_2-receptor affinity that is higher and more selective than that of formoterol or indacaterol (Slack 2013; Barnes 2005). In vitro and in vivo data show that vilanterol is equipotent to formoterol and salmeterol (Cazzola 2010).

Pharmacokinetically, vilanterol, formoterol, arformoterol, and indacaterol all have a similar onset (about 5 minutes) which is a quicker onset than salmeterol. Vilanterol, olodaterol, and indacaterol have longer half-lives, resulting in longer durations of action and allowing once-daily dosing. Comparatively, salmeterol and formoterol have significantly shorter durations of action requiring twice-daily dosing (Bjerg 2012; Malerba 2012; Cazzola 2010).

Table 1-3. Monitoring for Achievement of Goals and Key Outcome Indicators

Goal/Outcome	Asthma	COPD
Clinical goals and end points[a,b]	• No exacerbations • Daytime symptoms less than twice per week • Zero nighttime awakenings • SABA use for symptoms less than twice per week • No limitation of normal or desired activities • Normal PFTs	• Tobacco cessation • Decreased occupational/environmental exposures • Minimize frequency of exacerbations • Maintain normal daily function • Minimize/slow PFT decline • Manage comorbidities (e.g., osteoporosis, anxiety, cardiovascular disease)
Recommended frequency of PFTs[a,b]	• At diagnosis • 3–6 mo after initiating treatment • Periodically thereafter	• At diagnosis • Yearly thereafter
Monitoring questionnaires and cut points[c,d,e,f]	• ACT ≥ 20 (well controlled) • ATAQ = 0 (well controlled) • ACQ ≤ 0.75 (well controlled)	• CAT at every visit (< 10 symptoms; ≥ 10 more symptoms); significant change is ≥ 2 • mMRC < 2 less breathless; ≥ 2 more breathless
Patient end points[a,b]	• Choice of therapy is based (in part) on patient preference, cost, availability, and device skills of the patient • Patient acceptance of and satisfaction with therapy • Proper device technique by patient • Prevention of exacerbation, urgent care, hospitalization, missed work or school • Treatment of comorbid disease states that may affect disease control ◦ Asthma: Allergic rhinitis, obesity, GERD, sleep apnea ◦ COPD: Heart failure, anxiety and depression, arrhythmias, osteoporosis, lung cancer, and health maintenance needs addressed • Minimize symptoms that negatively affect QOL and ADL (e.g., fatigue, sleep disturbances, dyspnea, and activity limitation)	
Examples of performance indicators[g,h]	• Document ◦ Smoking status/counseling ◦ Exacerbation frequency ◦ Spirometry at diagnosis ◦ Device technique counseling and initial/continued competency • Vaccination rates • Use of emergency care (emergency/urgent care, same day provider appointments) • Hospital admission/ readmission rate • Adherence to controller medications (PDC > 80%) • ≥ 2 follow-up appointments per year with provider	• Document ◦ Smoking status/counseling ◦ Exacerbation frequency ◦ Spirometry at diagnosis ◦ Device technique counseling and initial/continued competency • Vaccination rates • Smoking cessation rates • Pulmonary rehabilitation referral/percent participation/completion • Use of emergency care • Hospital admission/readmission rates • Adherence to controller medications (PDC > 80%)

[a]Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2016.

[b]Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 Global Strategy for Diagnosis, Management, and Prevention of COPD.

[c]Asthma Control Test.

[d]Asthma Control Questionnaire (ACQ). Available at https://www.qoltech.co.uk/acq.html. Accessed December 7, 2016.

[e]Asthma Therapy Assessment Questionnaire (ATAQ).

[f]COPD Assessment Test (CAT). Available at www.catestonline.org/english/indexEN.htm. Accessed December 7, 2016.

[g]Agency for Healthcare Research and Quality (AHRQ). Asthma Care Quality Improvement.

[h]Heffner JE, Mularski RA, Calverley PMA. COPD performance measures. Missing opportunities for improving care. Chest 2010;137:1181-9.

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ADL = activities of daily living; ATAQ = Asthma Therapy Assessment Questionnaire; GERD = gastroesophageal reflux disease; PDC = proportion of days covered.

Table 1-4. Comparison of Inhaled LABAs

Generic (Brand)[a]	Device Available	Dose	Frequency
Arformoterol (Brovana)	Nebulizer solution	2 mL (15 mcg)	Twice daily
Indacaterol (Arcapta)	Neohaler (DPI)	1 capsule (75 mcg)	Daily
Olodaterol (Striverdi)	Respimat (spray)	2 puffs (5 mcg)	Daily
Salmeterol (Serevent)	Diskus (DPI)	50 mcg	Twice daily

[a]Vilanterol is only available in a combination product (see Table 1-6).
DPI = dry powder inhaler.

At this time, the currently available LABA agents appear to have no significant difference in the common adverse reactions or clinical efficacy. Choice of agent will likely be determined primarily on patient preference and competency with the device, formulary availability, and cost (Table 1-4).

Newer LAMA Agents

Tiotropium is the oldest LAMA agent; aclidinium, umeclidinium, and glycopyrrolate are newer to the market. Airway smooth muscle expresses muscarinic receptor M_2 and muscarinic receptor M_3. The M_3 receptor is responsible for bronchial and tracheal smooth muscle contraction and facilitates mucus secretion (Gosens 2006). Tiotropium blocks the effects of acetylcholine at the M_3 receptor located on bronchial smooth muscle (eFacts). Long-term trials have shown that tiotropium improves the lung function of patients with COPD and their health-related QOL (Braido 2013) and reduces exacerbations, including hospitalizations (Tashkin 2010). In combination with an ICS plus a LABA, tiotropium has benefit on all-cause mortality as well as mortality attributable to COPD (Short 2012).

As previously discussed, tiotropium and other LAMA agents are first-line maintenance options for COPD (GOLD 2016) (see Figure 1-2). A comparison of the available LAMA products is in Table 1-5. Limited comparison data from clinical trials are available. In a recent noninferiority trial, umeclidinium was superior to tiotropium for the primary outcome of trough FEV_1 at day 85 (Feldman 2016). The improvement was statistically significant; however, the difference was an FEV_1 of 59%. Because the minimal clinical important difference for FEV_1 is 100%, this change likely has minimal clinical significance. Similar to tiotropium, the newer agents in this class can lead to a worsening of narrow-angle glaucoma and urinary retention. Because the DPI LAMA products contain lactose, they should be avoided in patients with a severe milk protein allergy (eFacts). The tiotropium formulation in the Respimat device would be an option in this rare situation. Until more data analyses comparing the clinical outcomes of these agents are available, the choice of an individual LAMA or a LAMA in combination with other agents should be based on the patient's preference and ability to correctly use the delivery device, cost, desire for once- or twice-daily dosing, and agent availability.

Table 1-5. Comparison of Available LAMA Agents[a]

Generic (Brand)	Device Available	Dose	Frequency
Tiotropium (Spiriva)	HandiHaler (DPI) Respimat (spray)	18-mcg capsule 5 mcg	Once daily
Umeclidinium (Incruse)	Ellipta (DPI)	62.5 mcg	Once daily
Aclidinium (Tudorza)	Pressair (DPI)	400 mcg	Twice daily
Glycopyrrolate (Seebri)	Neohaler (DPI)	15.6-mcg capsule	Twice daily

[a]Ipratropium, a short-acting muscarinic agent, is also available in a Respimat device.

Table 1-6. Combination Inhaled Products for Asthma or COPD

Drugs (Trade Name)	Type of Device	Strength(s) mcg	Dose	Usual Dosing Frequency
ICS/LABA				
Budesonide/formoterol (Symbicort)	HFA MDI	80/4.5 160/4.5	2 puffs	Twice daily
Fluticasone furoate/vilanterol (Breo)	DPI (Ellipta)	100/25	1 puff	Once daily
Fluticasone propionate/ salmeterol (Advair)	DPI (Diskus)	100/50 250/50 500/50	1 puff	Twice daily
	HFA MDI	45/21 115/21 230/21		Twice daily
Mometasone/formoterol (Dulera)	HFA MDI	100/5 200/5	2 puffs	Twice daily
LAMA/LABA				
Umeclidinium/vilanterol (Anoro)	DPI (Ellipta)	62.5/25	1 puff	Once daily
Tiotropium/olodaterol (Stiolto)	Respimat	2.5/2.5	2 puffs	Once daily
Glycopyrrolate/formoterol (Bevespi)	MDI (Aerosphere[a])	9/4.8	2 puffs	Twice daily
Glycopyrrolate/indacaterol (Utibron)	DPI (Neohaler)	15.6/27.5	1 capsule	Twice daily
Aclidinium/formoterol[b]	DPI (Pressair)	400/12	One inhalation	Twice daily
ICS/LABA/LAMA[b]				
Budesonide/formoterol fumarate/ glycopyrronium	HFA MDI	TBD	N/A	TBD
Fluticasone furoate/vilanterol/ umeclidinium	DPI (Ellipta)	TBD	N/A	Once daily

[a]Aerosphere technology allows for uniform suspension of several drugs in the same device without the drugs interacting. Bevespi Aerosphere approved by the FDA for patients with COPD.

[b]In development.

HFA = hydrofluorocarbon; MDI = metered dose inhaler; TBD = to be determined.

Available Combination Products for COPD

As previously mentioned, double-drug therapy (LABA plus LAMA) or triple-drug therapy (ICS plus LABA plus LAMA) becomes increasingly necessary as lung function declines and symptoms increase. Combining agents from different classes, but with a similar dosing frequency, is logical to improve patient adherence (e.g., once vs. twice daily) and minimize the number of different inhaler products. This can also decrease the number of patient co-pays and save overall cost (Cazzola 2010).

Until recently, LABA plus LAMA therapy would have required two different devices, but now, several options are available. Available two-agent combination products are summarized in Table 1-6. For three-drug regimens, an ICS can be added to the LABA plus LAMA product or change to an ICS plus a LABA with a LAMA in a second device. Two triple-drug products are under development. Filing for FDA approval of the Ellipta formulation containing vilanterol/fluticasone furoate/umeclidinium occurred in November, 2016 (GSK 2016).

Newer Products and Agents for Asthma

Tiotropium for Asthma

Until recently, the use of tiotropium in patients with asthma was less well defined. Tiotropium is now FDA approved to treat patients 12 years and older with asthma (eFacts). Early studies showed that tiotropium can be beneficial to asthma still uncontrolled on medium- to high-dose ICS plus LABA

(Bollmeier 2013). Pharmacogenomic data (presence of Arg/Arg or 16 Arg/Gly polymorphism of the *ADRB2* gene) or sputum neutrophils, if known, can also help predict a positive response to tiotropium. Adding tiotropium to the regimen of adult patients receiving medium- to high-dose ICS plus LABA can reduce exacerbation frequency (Kerstjens 2012).

Adding tiotropium in adults receiving ICS monotherapy is less common. The effects of adding tiotropium in adults still symptomatic on a low- to medium-dose ICS (GINA step 2) was studied (Paggiaro 2016). Subjects (n=686) in 12 countries were enrolled, but only 465 were randomized to (1) tiotropium 2.5 mcg, (2) tiotropium 5 mcg, or (3) placebo by Respimat Soft Mist once daily. The primary end point was peak FEV_1 within 3 hours of dosing. Secondary end points included trough FEV_1, use of rescue medications, and QOL. Both tiotropium doses were superior to placebo for peak FEV_1 at week 12 (5 mcg: 128 mL; p<0.001; 2.5 mcg: 159 mL; p<0.001). Both tiotropium doses were also superior to placebo for the secondary end point of trough FEV_1 (5 mcg: 122 mL, p=0.001; 2.5 mcg: 110 mL, p=0.003), which is potentially clinically significant. Use of quick-relief medication decreased in all treatment groups; however, it did not reach statistical significance for either tiotropium dose at week 12. Both tiotropium doses improved QOL after 12 weeks; however, this did not reach statistical significance for either dose or placebo. The authors concluded that adding tiotropium to low- to medium-dose ICS monotherapy improved lung function after 12 weeks compared with placebo.

Use of tiotropium in pediatric patients is currently off-label, but similar studies are under way to determine its safety and efficacy in this population. One such study is a 48-week phase III randomized, placebo-controlled, parallel-group study of subjects 12–17 years old (Hammelmann 2016). At baseline, subjects were receiving ICS therapy (12–14 years of age: 200–800 mcg of budesonide or equivalent; 15–17 years of age: 400–800 mcg of budesonide or equivalent) with or without a leukotriene receptor antagonist. Two doses of tiotropium (2.5 mcg and 5 mcg daily) were compared with placebo. The authors found that both tiotropium doses improved peak FEV_1 after 24 weeks versus placebo (5 mcg: 174 mL [95% CI, 76–272 mL]; 2.5 mcg: 134 mL [95% CI, 34–234 mL]).

Another dose ranging (phase II) trial assessed peak FEV_1 3-hour post-tiotropium administration after three 4-week treatment periods in adolescents 12–17 years old (Vogelberg 2014). Subjects receiving a medium-dose ICS at baseline were then randomized to placebo or tiotropium 1.25 mcg, 2.5 mg, or 5 mcg daily. Overall, the mean FEV_1 at baseline was 2746 mL. The largest FEV_1 response was in the tiotropium 5-mcg group (602 mL), which was significant (p=0.004) compared with placebo (only 113 mL). These authors concluded that tiotropium is efficacious and well tolerated in adolescents.

The EPR-3 guidelines predate the results of tiotropium studies. However, updated international (GINA 2016) guidelines include tiotropium in the step-care approach (see Table 1-2).

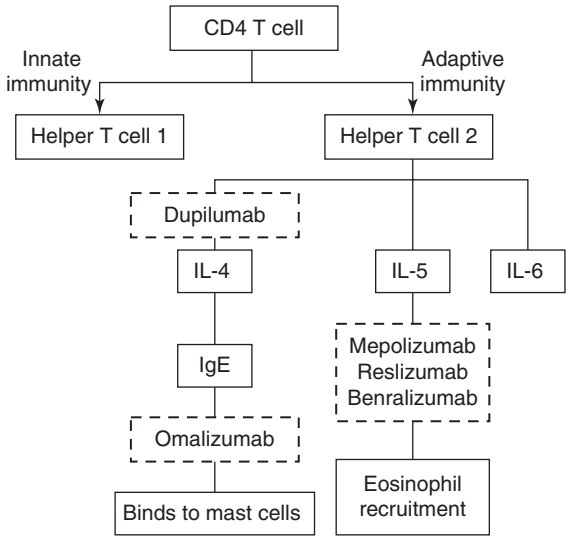

Figure 1-3. Mechanism of anti-IgE and anti-interleukin agents in the pathophysiology of asthma.

IL = interleukin.

Of importance, tiotropium dosing by the Respimat inhaler differs between asthma and COPD. For treating asthma, the dose is 2 puffs of the 1.25 mcg in a Respimat device once daily. For those with COPD, the dose is 2 puffs of the 2.5-mcg Respimat once daily (eFacts).

Monoclonal Antibodies

Mepolizumab, benralizumab, and reslizumab are new monoclonal antibodies; all are interleukin (IL)-5 (IL-5) antagonists that decrease the recruitment and circulating number of eosinophils (Figure 1-3). Mepolizumab and reslizumab are approved for patients with severe asthma of an eosinophilic phenotype. Mepolizumab is approved for those 12 years and older and reslizumab for those over 18 years old. (eFacts). AstraZeneca was expected to file for FDA approval for benralizumab in late 2016 (Murphy 2016), but the company has not announced filing as of March, 2017. Dupilumab is a first-in-class human anti–IL-4 receptor α antibody that interferes with IL-4 and IL-13 (Wenzel 2016, 2013). Dupilumab is in phase III studies for severe asthma (Chung 2016). The older monoclonal antibody, omalizumab, decreases the binding of IgE on mast cells, a slightly different mechanism from these newer agents (eFacts).

Similar to omalizumab, reslizumab is dosed monthly by intravenous injection. The reslizumab dose is 3 mg/kg over 20–50 minutes every 4 weeks. Mepolizumab can be given subcutaneously (upper arm, thigh, or abdomen) after reconstituting the 100-mcg vial (also every 4 weeks). Mepolizumab significantly reduces the number of asthma exacerbations in patients with a severe eosinophilic phenotype compared with placebo (Pavord 2012; Halder 2009) and significantly reduces eosinophil counts in the blood and sputum (Halder 2009)

Few data analyses compare the newer agents with omalizumab. A systematic literature review and meta-analysis included double-blind randomized controlled trials in those with severe asthma and a history of exacerbations receiving high-dose ICS plus another maintenance medication (Stynes 2016). Two populations were examined; subjects were potentially eligible for one or both monoclonal antibodies (omalizumab or mepolizumab). This indirect comparison showed that both treatments significantly reduced the rate of asthma exacerbations compared with placebo. Of interest, mepolizumab was associated with a reduction in clinically significant exacerbations compared with omalizumab in both study populations. The probability that mepolizumab had a greater treatment effect was over 90% in both populations. To further determine whether there was a preferential effect, a subanalysis compared the effect of mepolizumab on reducing exacerbations in those with severe eosinophilic asthma previously treated with omalizumab (Albers 2016). In the original study, 576 patients receiving a high-dose ICS plus another controller and having a history of frequent exacerbations received mepolizumab. Mepolizumab reduced exacerbations regardless of prior omalizumab treatment.

Prostaglandin D_2 Receptor Antagonists

Prostaglandin D_2 is released from activated mast cells and is thought to coordinate activity between mast cells, helper T cell 2, eosinophils, and dendritic cells (Arima 2011). Fevipiprant is a prostaglandin D_2 receptor antagonist agent being investigated for the treatment of moderate to severe asthma. Results of a clinical trial with 61 subjects with moderate to severe persistent asthma showed that 12 weeks of fevipiprant twice daily lowered the sputum eosinophil percentage by 4.5 times compared with 1.3 times in placebo ($p=0.0014$) (Gonem 2016). The secondary outcomes of QOL and FEV_1 were also significantly improved. Although three fevipiprant and four placebo subjects had asthma exacerbations, no serious adverse effects or withdrawals were attributed to fevipiprant. If data from ongoing clinical trials are also positive, fevipiprant's unique mechanism of action and twice-daily oral administration will make it an alternative in persistent asthma not well controlled by ICS-LABA combination therapy.

Re-release of OTC Epinephrine

Use of OTC racemic epinephrine as a quick-relief medicine is not new. The original MDI product was removed from the market because it contained a chlorofluorocarbon propellant. The manufacturer, Armstrong Pharmaceuticals, filed a new drug application with the FDA in 2013 with hopes of re-releasing this product in a hydrofluorocarbon form, but it was not approved (Brown 2014). According to the company's homepage, Nephron Pharmaceuticals Corporation released a version of racemic epinephrine for OTC use under the trade name Asthmanefrin; the product is administered by the EZ Breathe Atomizer. Patients buy a starter kit that contains the atomizer (similar to a portable handheld nebulizer device) and 10 single-use vials. The refill pack contains 30 single-use vials.

Patients with a diagnosis of asthma should see their health care provider regularly for appropriate controller and quick-relief prescriptions and monitoring. In addition, because albuterol is β_2-receptor selective, it generally produces fewer systemic adverse effects. Nonselective β-agonists such as epinephrine also act on α-receptors, which have the potential to constrict blood vessels and increase blood pressure. Moreover, by acting on β_1-receptors, epinephrine can potentially lead to tachycardia, nervousness, and palpitations. Epinephrine also has a shorter duration of action, requiring more frequent administration.

Frequent use of quick-relief drugs can signal escalation or chronic poor control of asthma. Asthma providers should be alerted when their patients use 1 or more canisters of quick-relief medicine per month because this indicates a risk of fatal asthma events (EPR-3). High or chronic use of OTC medication can go undetected by providers. Patients also need instruction on assembly of the EZ Breathe Atomizer and cleaning after each use. The initial assembly and maintenance required by the EZ Breathe Atomizer can be a challenge, especially for those with low health literacy. Partly used vials must be discarded. Inappropriate or lack of cleaning of the device can result in respiratory infections.

The use of OTC quick-relief medicines should be limited to short-term or unexpected situations until patients can access their medications or obtain a new prescription from their provider. When observing a purchase, pharmacists should intervene to assess the need for the product, facilitate/encourage follow-up with an asthma provider as necessary, and provide instruction regarding correct use of the product. In performing medication histories or reconciliation, pharmacists should specifically ask about epinephrine use.

Sublingual Immunotherapy

Sublingual immunotherapy can reduce allergy symptoms by delivering small, incremental doses of an allergen under the tongue. The goal is to induce tolerance to an allergen (e.g., house dust mites). Sublingual immunotherapy was recently FDA approved for the treatment of allergic rhinitis; however, less is known about its role in treating patients with an allergic component to their asthma. A recent Cochrane review analyzed the results of 52 trials treating over 5000 subjects (Normansell 2015). However, because of the lack of uniformity of outcomes reported among the trials, a conclusive recommendation could not be made. Future studies may help define the role of sublingual immunotherapy for patients with allergic asthma if positive outcomes such as lower ICS doses to control symptoms, less frequent SABA use, fewer exacerbations, and better QOL are reported.

EMERGING THERAPIES

Targets for Asthma Therapy

Further study of the pathophysiology of asthma has identified potential targets (in addition to those listed in Table 1-1.) Several emerging therapies for asthma target the inflammatory cascade and the immune system's response to allergens. Examples of disease-modifying agents for asthma include oligonucleotides (Senti 2009), toll-like receptors (Meng 2011), and chemoattractant receptor-homologous molecule (CRTH2) (Birkinshaw 2006). Tumor necrosis factor alpha-blockers (Wenzel 2009) have been studied in preclinical trials. Similarly, several cytokines have been targeted as potential targets for anti-asthma drugs. Other examples of potential targets include therapies affecting IL-9, IL-10, IL-12, IL-25, and IL-30; interferon-γ; CSFs; and T-lymphocyte-17 cells (Kim 2016a; Trivedi 2016; Darveaux 2015; Hansbro 2011; Desai 2009). As the understanding of the role of various cytokines and inflammatory cells continues to evolve, so too will the potential targets for anti-asthma therapy.

New Drug Targets for Treatment of COPD

The pathophysiology of COPD is complex, with cigarette smoking causing damage to both large and small airways, lung epithelium, and the pulmonary vasculature. As previously discussed, the role of ICS for patients with COPD is less clear than for patients with asthma. One hypothesis for the lower suppression of inflammation by ICS in COPD is reduced levels of a histone deacetylase enzyme (HDAC2) in COPD. This enzyme is involved with inactivation of proinflammatory genes; so lower HDAC2 activity could result in corticosteroid resistance. The reduction in HDAC2 is postulated to result from the activation of phosphoinositide-3-kinase δ (Ross 2014). Therefore, kinase inhibitors are currently being investigated as a potential new drug class for COPD (Onions 2016). Neutrophils are thought to play a large role in COPD inflammation. Chemokine receptors on neutrophils as well as neutrophil chemoattractant (leukotriene B_4) are also being investigated for their potential role in reducing COPD sputum neutrophils and improving lung function (Ross 2014).

The role of PDE continues to be investigated for its potential anti-inflammatory effects. An oral PDE4 inhibitor, roflumilast, was discussed earlier. So far, inhaled PDE4 inhibitors have been found ineffective. Other potential agents in the pipeline include retinoids to promote alveolar repair in the damaged lung (Ross 2014).

THERAPEUTIC CONTROVERSIES

Treatment of ACOS

If ACOS is suspected, a formal assessment should be made before treatment. The assessment should include the pattern of symptoms, triggers, and risk factors or exposures. In addition, PFTs (e.g., bronchodilator reversibility) should be done (see Table 1-1). A measure of airway eosinophils may also help predict corticosteroid responsiveness (Barnes 2016). If ACOS is likely (i.e., similar number of features of both asthma and COPD), the GINA 2016 guidelines recommend initially starting maintenance therapy with an ICS alone, similar to the step-care approach for asthma. The rationale is that if there is underlying asthma-type inflammation, ICS can lower morbidity. Typically, the next step in therapy is to add an inhaled long-acting bronchodilator, either a LABA applying evidence from asthma, or a LAMA similar to the COPD algorithm. However, a primary limitation to extrapolating current published evidence is that well-designed trials have inclusion criteria specific for asthma or COPD; these studies therefore exclude subjects who have the mixed picture of ACOS. As previously mentioned, a better understanding of the underlying ACOS pathophysiology and phenotypes and standardized criteria is needed to design the clinical trials necessary to determine the optimal treatment for ACOS. Neither the CAT nor the Asthma Control Test (ACT) questionnaires have been specifically validated in ACOS; hence, use of these symptom questionnaires cannot routinely be recommended. Similarly, adjunctive therapies for asthma and COPD have not specifically been evaluated in this population. However, vaccinations, trigger management (including treatment of allergic rhinitis), tobacco cessation, and pulmonary rehabilitation would seem to be reasonable interventions.

ICS and Risk of Height Reduction in Children

Controversy regarding the use of ICS in pediatric populations and the effect on ultimate adult height has been debated for decades. A follow-up to the well-known Childhood Management Asthma Program (CAMP) trial, which originally compared budesonide 200 mcg and 400 mcg daily with nedocromil and placebo, concluded in 2012. At the end of the CAMP trial, children were enrolled in an optional observational cohort. Adult height was determined at a mean age of 25 years for 943 of the original 1041 CAMP participants. This follow-up study showed that those treated with budesonide had a mean adult height that was 1.2 cm less than placebo (-0.5 to -1.9) at 24.9 years of age. This height deficit was observed 1–2 years after treatment initiation and persisted into adulthood, although the deficit was neither progressive nor cumulative (Kelly 2012).

A recent retrospective study compared 113 children with asthma (treated with budesonide, mometasone, or fluticasone) with 66 control children. Those receiving ICS therapy had decreases in prepubertal height gain and peak height velocity compared with controls, with a final height difference of about 2.5 cm, which is greater than that reported in the CAMP results (Leonibus 2016). In discussing parental concerns or effects of ICS treatment on growth, it is also important to include that uncontrolled asthma can delay and stunt growth.

Safety of LABA Therapy for Asthma

In 2006, publication of the results of the Salmeterol Multicenter Asthma Research Trial (i.e., SMART trial) raised concerns

about the safety of LABAs in asthma (Nelson 2006). At baseline, the subjects received standard asthma therapy for that time, including ICS, theophylline, leukotriene modifiers, or inhaled/oral β-agonists (excluding salmeterol). Subjects were randomized to either salmeterol twice daily or placebo. This landmark trial showed more respiratory- and asthma-related deaths in the salmeterol group (13 deaths of 13,176 patients) than in the placebo group (3 deaths of 13,179 patients) with an RR of 4.37 (95% CI, 1.25–15.34; p<0.05). A subgroup analysis suggested that this risk is greater in African American subjects than in white subjects.

The FDA conducted a meta-analysis to investigate these findings further; LABAs increased the risk of severe exacerbations that were driven by the number of asthma-related hospitalizations, especially in children age 4–11 years. The result was additional labeling changes of LABAs: LABAs should not be used for asthma without another controller drug (usually an ICS) and should only be used long term if patients are uncontrolled on ICS therapy alone. In addition, LABAs should be used for the shortest duration necessary and should only be prescribed in the form of a combination product in pediatric and adolescent patients (FDA 2010).

Randomized controlled trials, meta-analyses of randomized controlled trials, and other observational studies, although limited by low statistical power, have shown that use of combination therapy (LABAs plus an ICS) is not associated with serious asthma-related events (Rodrigo 2012). However, in 2010, the FDA requested that four manufacturers of LABA-containing medications further study this issue (FDA 2010). Five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to ICS with the use of ICS alone are being conducted in patients 12 years and older. These large-scale trials include about 12,000 subjects each, for a total of 47,000 patients, with a 6-month treatment period. The primary end point will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalization. The FDA expects to receive the results by 2017 (FDA 2016a).

Results of one of these studies have been published (Stempel 2016). The AUSTRI trial was a prospective, multicenter, randomized, double-blind trial for 26 weeks. Salmeterol plus fluticasone (fixed-dose ICS-LABA combination) was compared with fluticasone alone (ICS only). Subjects (age 4–11 years) were randomized in a 1:1 ratio within stratified groups (two arms: fluticasone/salmeterol (n~5800) at a dose of 100/50, 250/50, or 500/50 mcg; and fluticasone (n~5800) at a dose of 100, 250, or 500 mcg. Doses were administered twice daily by the Diskus. Among the 11,679 patients, 67 had 74 serious asthma-related events. The combination group had 36 events in 34 subjects compared with 38 events in 33 subjects in the ICS-only group. The HR was 1.03 for the ICS/LABA group (95% CI, 0.64–1.66). Fluticasone/salmeterol was noninferior to fluticasone alone (p=0.003). There were no asthma-related deaths in either group. Asthma-related hospitalizations occurred in 34 in the ICS/LABA group compared with 33 in the ICS-only group, which was not statistically significant. The authors concluded that asthma-related events occurred with similar frequency with combined and ICS monotherapy.

Hopefully, these results, together with those from other ongoing trials, will resolve the controversy regarding LABA use in patients with asthma. It is important that both patients and health care professionals be assured that adding LABAs with concurrent anti-inflammatory therapy (e.g., ICS) is appropriate and safe.

Treatment of Severe Asthma

Most asthma cases can readily be controlled with ICS with or without LABA therapy. A small, but significant and likely heterogeneous subset of patients with asthma is more difficult to treat. Severe asthma is defined as asthma that requires a high-dose ICS plus a second controller with or without systemic corticosteroids to maintain control, or remains uncontrolled despite this therapy (Chung 2014).

The American Thoracic Society and the European Respiratory Society recently published recommendations to address the treatment of severe asthma (Chung 2014). Additional diagnostic studies such as CT scans may be useful if asthma presentation is atypical. Assessment of sputum eosinophil counts may be useful to guide therapy in some adults, but this is not recommended in children. Assessment of IgE antibody may be useful in adults and children with severe allergic asthma in order to consider a trial of omalizumab. Measuring exhaled nitric oxide to guide therapy is not recommended because of the cost and uncertain benefit. Methotrexate therapy has a modest corticosteroid-sparing effect, which is offset by the potential for toxicity; thus, methotrexate is not recommended. Macrolide antibiotics are speculated to modulate the immune system and improve tissue repair in addition to their antibacterial effects. The lack of documented clinical benefit and concerns for bacterial resistance prevent recommending macrolide use beyond treatment of bacterial infections such as acute bronchitis and sinusitis. Antifungal therapy may be useful if a patient has had recurrent allergic bronchopulmonary aspergillosis. Antifungal therapy should not be used because of positive fungal skin prick testing alone. The BT discussed earlier is only recommended in the context of clinical studies of institutional review board registries. The recommendation regarding BT is strong; the other recommendations are conditional. The current level of evidence for these recommendations is low to very low. This report also provides definitions of high-dose ICS, discusses the pathophysiology and genetics potentially underlying corticosteroid resistance, and makes the case for conducting specific clinical trials in this asthma subtype to identify optimal therapy.

Pharmacists should provide an in-depth assessment of patients who appear to have severe asthma. The usual

reasons for poor control such as nonadherence, inadequate device technique, or lack of understanding of the asthma-action or environmental control plan should be ruled out or addressed. Patients with difficult-to-treat asthma should be referred to an asthma specialist or center for further evaluation so that additional therapies can be considered.

COPD Screening

Because of the significant burden of COPD on society, some advocate for screening at-risk patients for COPD (e.g., significant tobacco history) with PFTs, even if they are currently asymptomatic. This would mimic the successful screening approach of other chronic, costly, high-impact conditions such as hypertension, diabetes, and cardiovascular disease. However, in 2008, the U.S. Preventive Services Task Force recommended against screening, citing the cost of spirometry and the lack of documented benefit for this task. A recent systematic review set out to update the evidence and recommendation regarding screening asymptomatic patients at risk of COPD. These authors also found no direct evidence to determine the benefit and harms of screening patients for COPD using either screening questionnaires or spirometry. Of interest, screening those who smoke and then giving them their spirometry results did not increase cessation rates (Guirguis-Blake 2016). The GOLD 2017 guidelines also recommend doing spirometry only on symptomatic individuals with COPD risk factors.

OTHER ISSUES AFFECTING SELECTION OF OPTIMAL PHARMACOTHERAPY

Significance of Correct Device Technique to Optimal Patient Outcomes

To optimally aerosolize medication into the lungs, correct device technique is mandatory. Poor device technique is related to poor outcomes (Sanduzzi 2014). Historically, incorrect metered dose inhaler technique was as high as 89% with MDIs (Chapman 1993). Patients also struggle with the use of both DPIs and MDIs (Papi 2011). Not surprisingly, using several devices (Rootmensen 2010; van der Palen 1999), severe airway obstruction (Papi 2011), inadequate instruction (Chapman 1993), poor vision (Press 2011), and low health literacy are risk factors for improper device technique. Older age, lower lung function, comorbidities, and poor cognition have also been associated with poor device technique (Sulaimin 2016). On discharge, only 23% of patients with COPD in one study had appropriate adherence to DPI use (Sulaiman 2016).

To ensure that patients are aware of the proper way to use their device, providers should demonstrate correct inhaler device technique (GOLD 2017; GINA 2016). Although recommended by asthma guidelines, in one study, only about 5% of children received a demonstration, and even fewer children were even asked to show their provider how they used their inhaler (Sleath 2011). Initial and repeated assessments are necessary for patients to initially demonstrate and maintain correct device technique to optimize drug deposition in the lung (Broeders 2009). Knowledge of correct device technique by providers (physicians, nurses, and respiratory therapists) has been documented to be inadequate (Dolovich 2005). Brief office visits and lack of knowledge and/or confidence by providers regarding pulmonary device technique may contribute to the lack of patient education.

Both the GINA 2016 and the GOLD 2017 guidelines emphasize that device technique assessment and instruction should routinely be part of discharge counseling or follow-up visits for asthma and COPD-related events. Device technique and adherence should be assessed before step-ups or escalations in therapy. Pharmacists (inpatient, clinic setting, and outpatient) should personally be competent in device technique and have appropriate materials available (e.g., placebo devices, health literacy–friendly written instruction sheets). The importance of device technique in drug delivery and ultimate drug effectiveness should be emphasized. Provision of and results from such instruction should be documented clearly in the medical record to facilitate the next provider's follow-up. Facility fees can offset the cost of providing instruction. Some Medicaid and other insurance providers will directly compensate for such instruction, especially if the patient has had several urgent care events.

Changes in the Availability of Drug Delivery Devices

The Montreal Protocol prompted the discontinuation of chlorofluorocarbons in respiratory devices and led to the development of MDIs with newer propellants and delivery devices. Recent advances have resulted in smaller, easier-to-use devices; newer drugs may require less-frequent dosing. The downside has been the many devices, each with a seemingly similar, yet significantly different technique. Table 1-7 summarizes the differences in devices and medication availability by device type. Combination therapy often requires an individual to use two or more different devices (e.g., a common scenario is an MDI for a quick-relief medication, a multidose DPI for ICS-LABA therapy, and a capsule-based DPI device for a LAMA).

Because most patients with both asthma and COPD receive therapy involving more than one drug class, educating them about the different delivery systems can be challenging. One goal is to minimize the number and types of devices for an individual. As many drugs as possible should be combined into the same device. Double ICS-LABA products have been available; recently, LABA-LAMA products have been released. Soon, triple-drug (ICS-LABA-LAMA) products are expected (Hishler 2016). Using one type of device, when possible, can also decrease confusion (e.g., MDI devices can be used for quick-relief and controller medications). The same holding chamber may be used for all MDIs if timing of actuation to

Table 1-7. Available Controller Drugs and Respiratory Devices

Agent	Medications and available strengths (mcg)	Device Activation: Priming	Device Activation: Dose-loading Activation	Device Activation: Breath Holding (seconds)	Device Activation: Inspiratory Rate Required	Other Considerations
Diskus	FP 50, 100, 250 FP-S 100/50,[a] 250/50, 500/50 SAL 50	No	Click lever	Breath 10	Rapid	Hold level Small dose counter Contains lactose Secondary expiration: 4 wk Approved for age ≥ 6 yr
Ellipta	FF 100, 200 FF-V100/25[a] 200/25 U 62.5 U-V 62.5/25[b]	No	On opening	Breath 3–4	Rapid	Air vents Contains lactose Secondary expiration: 6 wk Approved for age ≥ 18 yr
Flexhaler	BUD 90	No	Twist base	Breath 10	Rapid	Has trainer device
MDI	BEC: 40,80 BUD-F: 80/4.5, 160/4.5 FL[c]: 80 FP: 44, 110, 220 FP-S: 45/21, 115/21, 230/21 GLY-F 9/4.8 IP 21 LEV 45 MOM 100, 200 MOM-F 100/5, 200/5	Yes	N/A	Manual 10	Slower	Holding chamber may be needed to assist with coordination Holding chamber with face mask may allow use in younger children Requires cleaning No lactose No secondary expiration
Neohaler	IND 75 IND-GLY 27.5/15.6	No	Insert capsule	Breath 10	Rapid	Contains lactose No secondary expiration Adults
Pressair	ACL 400	No	Click lever	Breath 10	Rapid	Signals that dose is released Locks out when empty No lactose Secondary expiration: 3 mo Approved for age ≥ 12 yr Caution: Narrow-angle glaucoma
Respimat	IP-A 20/120 OLD 2.5 TIO 1.25, 2.5 TIO-OLD 2.5/2.5	No	Twist base	Manual 10	Slower	Requires strength and dexterity to insert canister Secondary expiration: 3 mo
Twisthaler	MOM 110, 210	Yes	Twist base	Breath 10	Rapid	Air vents Approved for age 4 yr (110 mcg) and > 12 yr (220 mcg)

[a]Dose of ICS (mcg)/LABA (mcg).

[b]LAMA (mcg)/LABA (mcg).

[c]Has a built-in holding chamber; indicated for individuals ≥ 6 yr.

ACL = aclidinium; BEC = beclomethasone; BUD = budesonide; BUD-F = budesonide plus formoterol; F = formoterol; FL = flunisolide; FF-V = fluticasone furoate plus vilanterol; FP-S = fluticasone propionate plus salmeterol; GLY= glycopyrrolate; HFA-MDI = hydrofluorocarbon metered dose inhaler; IND = indacaterol; IP-A = ipratropium plus albuterol; LEV = levalbuterol; MOM = mometasone; MOM-F = mometasone/formoterol; N/A = not applicable; OLD = olodaterol; SAL = salmeterol; U = umeclidinium; U-V = umeclidinium plus vilanterol.

inhalation is a problem for a patient. With the release of an albuterol DPI (RespiClick), it will also be possible to consolidate quick-relief and controller therapy into DPI-type devices.

Because manufacturers spend billions of dollars in product development, testing, and marketing new pulmonary products, newer agents by those companies will most likely be released in the newer device (see Table 1-6). For example, newer GlaxoSmithKline medications were released in the Ellipta device. In designing this device, several improvements were made over the older Diskus device, including fewer steps, a larger dose counter, and a shorter required breath hold. Newer medications from Boehringer Ingelheim were released in Respimat rather than in a standard MDI or the HandiHaler capsule-based device. The capsule-based Aerolizer device was recently discontinued (MPR 2015). A generic form of salmeterol/fluticasone propionate in a RespiClick DPI is expected (Teva 2016).

Respiratory Device Selection Guidelines

According to the published guidelines (Dolovich 2005), there is no evidence to support improved efficacy (e.g., symptoms scores or PFT results) with one delivery device over another in asthma or COPD. The choice of device is often left to the provider or based on institutional formularies. With various devices now available, it is important to provide patients with available options. The authors of a small (n=287) COPD study sought to identify patient preferences between the Ellipta and Diskus DPIs. Patients preferred ($p<0.001$) the Ellipta DPI to the Diskus for larger-sized dose-counter numbers, fewer number of steps needed, smaller inhaler size, increased comfort of the mouthpiece and ease of opening, and overall preference. The once-daily dosing regimen was also preferred (Yun Kirby 2016).

Additional criteria are recommended when selecting appropriate devices for patients treated with inhalation therapies. Box 1-1 presents some questions to consider in selecting a device, according to the guidelines. Patients should play a role in device selection because dissatisfaction may negatively affect adherence (Darba 2016; Bereza 2015).

Box 1-1. Considerations in Choosing a Pulmonary Device

- What device is the desired medication or drug class available in?
- Can my patient use this device appropriately? (age and manual dexterity)
- Is this drug/device combination affordable or covered on insurance formulary?
- Can all drugs prescribed to the patient be delivered in the same type of device?
- Which device is most convenient for the patient or caregiver? (e.g., frequency, cleaning and maintenance, portability)
- How durable is the device? (can be especially important for pediatric populations)
- Does the patient prefer a specific device?

Importance of Adherence and Adherence Behaviors on Efficacy

Adherence to therapy can decrease with long-term therapy. In 2003, the WHO estimated that less than 50% of patients on chronic therapy were adherent (Restrepo 2008). Nonadherence results in poorly controlled symptoms, but it also worsens QOL, increases exacerbation rates, and increases the health care–related costs of COPD (Sanduzzi 2014). Nonadherence is linked to an increased risk of hospital admission and death (Vestbo 2009).

In those with COPD, the most common type of nonadherence is underuse, which can be either sporadic or chronic. The prescribed medication class, regimen complexity, delivery device, and design of the respiratory device can all play a role in whether the patient will be chronically adherent (Sanduzzi 2014; Agh 2011; Bourbeau 2008). Often, patients with low adherence lack sufficient understanding of their illness and options for management. Beliefs about ICS (e.g., concerns about adverse effects and necessity for a daily medication) also influence adherence (Menckeberg 2008; De Smet 2006). Comorbid depression and anxiety further complicate adherence rates, especially among patients with COPD (Sanduzzi 2014; Restrepo 2008).

Similarly, in asthma, the median adherence to controller medications has been reported to be only 46% of doses; hospitalizations can be prevented with optimal adherence (Boulet 2012). Some nonadherence is unintentional (e.g., misunderstood instructions). However, much of nonadherence is intentional (e.g., fear of adverse effects, cultural beliefs, practical lifestyle decisions, lack of perceived benefit).

As previously discussed, the lack of generic options and the many medications make the cost of therapy an adherence barrier, even for patients with insurance. Pharmacists should help patients identify options on the lowest-cost drug tier and facilitate applications for patient assistance programs for those who may be eligible.

Nonadherence is a multifactorial problem. Many of the underlying causes of nonadherence (e.g., poverty, lack of social support, family problems, unhealthy home and work environments) are not readily fixable. Therefore, it is especially important that pharmacists address as many resolvable adherence issues as possible.

Impact of Patient Preferences on Therapy Selection

Patient preference goes beyond device selection. Adherence rates in asthma and COPD can be improved by involving patients in their care. The burden of both asthma and COPD increases and QOL decreases with increasing disease severity. This highlights the need for patients to maintain autonomy, be involved in decision-making, and have a positive relationship with their provider. Pharmacists can play a key role in improving outcomes by explaining the importance of

adherence, discussing the role of each medication in symptom management or exacerbation prevention, addressing concerns regarding adverse reactions, and involving patients in decision-making.

Issues and Methods to Provide Effective Patient Education

Patients being prescribed, discharged with, or dispensed an inhalation therapy should be educated on both the medication and the delivery (proper device technique); a demonstration by providers should be part of that instruction (GOLD 2017; GINA 2016). Inhaler devices require many, sometimes complex, seemingly meaningless steps, rendering correct use difficult for some patients. Therefore, frequent assessment and reeducation is needed to attain and maintain correct technique. A patient's device technique should be assessed during each health care encounter (clinic follow-up appointments, dispensing of medication at pharmacy, and when hospitalized) (Press 2016). Verbal and written information should be age and health literacy appropriate for a particular individual. The topics and information should be comprehensive. Beyond the basic therapeutic plan (medication, regimen, onset, adverse reactions, expected effects, purpose of each medication), patients should have a basic understanding of the disease and options for adjunctive therapy. The management plan should include approaches to triggers, symptoms, and exacerbations. Individual concerns and health beliefs should be explored and realistic personal goals included.

Results of educational sessions should always be documented in the medical record, including the patient's ability to teach-back key information and demonstrate back his or her understanding and skills. Unresolved issues (e.g., technique problems, concerns) should also be documented to assist with the next provider's follow-up.

Patient Care Scenario

A 60-year-old man with a long history of tobacco use (70 pack-years starting at age 16) reports progressive dyspnea for the past 2 years and a productive early-morning cough. His provider reviews his PFT results with him: post-bronchodilator FEV_1/FVC less than 70% of predicted and post-bronchodilator FEV_1 of 59%. His baseline CAT score today was 8. He has never been hospitalized or been treated with antibiotics or with prednisone for his breathing. His COPD is assessed as moderate (given his post-bronchodilator FEV_1 of 50%–79% of predicted) and is classified as GOLD risk category B (see Figure 1-2). What is best to recommend for this patient?

ANSWER

The pharmacist provides brief advice to quit tobacco because his breathing will continue to worsen as long as he smokes. She assesses his current interest in quitting. He has tried to quit before, but he says he is too stressed with his job to quit now. The pharmacist offers assistance when he is interested and says she will follow up at his next appointment.

The pharmacist provides a brief overview of COPD. She instructs him on the proper use of the newly prescribed tiotropium by Respimat, including dose, frequency, correct insertion, expiration date of the canister, and reason for use. The pharmacist demonstrates the correct technique to him and uses the "show-me" technique to ask him to demonstrate back his understanding of the Respimat technique. After two attempts with feedback, he can correctly demonstrate the correct inhalation rate and breath holding. Using the teach-back method, the patient repeats back the correct dose and frequency. She gives him written instructions with pictures demonstrating correct technique. She asks about vaccinations; he reports receiving annual flu shots and a "pneumonia shot" when he was given a diagnosis of diabetes 2 years ago.

Initially, he did well; his CAT score decreased to 4, and he was sleeping better. His device technique was rechecked and found to be adequate. Over the next 2 years, his breathing continued to worsen. He can complete usual yard work with frequent stops to rest, but he is concerned that he may be forced to retire early because of his breathing. He continues to smoke, despite two assisted attempts with NRT, but he does smoke less than before. He has been to the urgent care center twice (but never hospitalized) in the past 12 months for COPD exacerbations and was treated with oral antibiotics and corticosteroids. His CAT score is now 9 with a post-bronchodilator FEV_1 of 45% of predicted. His new COPD status is group C. He has been adherent to tiotropium therapy with good device technique, so it is decided to initiate a double-drug regimen.

The preferred escalation option is a LABA plus a LAMA. Tiotropium plus olodaterol is available in the Respimat device he likes, and he uses it correctly. An ICS plus a LABA is an alternative, but it is not preferred because of the increased risk of pneumonia and other adverse effects. With the continued worsening of his breathing problems, he now agrees to attend pulmonary rehabilitation classes. His motivator is to be able to continue work with a steady income. He is also willing to try another quit attempt with dual NRT. The pharmacist helped him develop a specific cessation plan and provided ongoing support during the next quit attempt.

1. Dolovich MB, Ahrens TC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. Chest 2005;127:335-71.
2. Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 Global Strategy for Diagnosis, Management, and Prevention of COPD
3. Siu AL. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015;163:622-35.

Issues at Transitions of Care

Transitions of care can both create potential problems and provide opportunities for improvement. Medication reconciliation can uncover nonadherence and use of OTC medications. Changes in medications because of formulary issues (change in medication and device) and disease severity (nebulized medications) occur. Data analyses show that changing devices, especially without adequate instruction, can result in poor device technique and worsen outcomes (Braido 2015). Short-term changes that are not therapeutically necessary should be kept to a minimum. However, hospitalizations may provide time to explore and resolve issues causing the therapeutic failure or nonadherence resulting in the admission. Options include providing information and education, developing personalized action plans, exploring perceptions of medications, and providing intensive device instruction. Inpatient stays can also be a good time to make longer-term device changes, providing many opportunities for patients to be observed and provided feedback on their device technique. At discharge, instructions should be reviewed and understanding documented using the teach-back method. The "show-me" technique can be used to observe and then document patients' device skills. Patients' ability to afford and obtain discharge drugs should be verified, and a follow-up with their provider and pharmacist should be scheduled. Contacting patients within 2–3 days after discharge can double-check that they have completed any antibiotics and prednisone, are continuing to improve, have not developed adverse effects, and plan to keep the follow-up appointment with their provider. At the follow-up visit, medication reconciliation should again be done to update medications in the health record. Clinical improvement should be verified, and questions or concerns regarding the recent episode or new therapeutic plan should be addressed.

Documentation of Pharmacist Interventions

Good documentation has implications beyond improving follow-up by other providers. Documenting a comprehensive disease assessment, including status, severity, and presence of complications, is important for reimbursement. For example, stating that the problem is "severe, persistent asthma with an acute exacerbation" is a higher acuity level than "asthma." Similarly, "grade 3, GOLD group C COPD with complications of cor pulmonale" is more specific than "COPD, unspecified." It is important to document both the grade level and the group of COPD to support therapeutic recommendations. For example, two patients may both be in group B with a similar CAT score. But a patient whose lung function is grade 3 and who also has a history of frequent or more severe exacerbations will logically require more therapy than a patient with better lung function and rare, mild exacerbations. Electronic templates can make it fast and easy to document patient responses to and scores of CAT/ACT questionnaires. Assessments of therapy should be documented in the context of the guidelines. For example, "asthma uncontrolled (ACT score less than 20) on step 3 (GINA) therapy with a moderate-dose ICS and a LABA by Diskus device" is succinct and also helps familiarize other providers of the guidelines and questionnaire score interpretation. Education provided should be documented, as discussed earlier. Thorough documentation not only improves patient care, but also informs other providers of pharmacist contributions to the health care team.

CONCLUSION

Asthma and COPD offer a knowledgeable pharmacist a wealth of opportunities to select and implement optimal treatment to monitor for and maximize patient outcomes. With extensive knowledge of pharmacotherapy and device options, pharmacists can be pivotal in choosing and implementing the least expensive and most effective regimen with high patient satisfaction, adherence, and acceptance. A comprehensive plan includes adjunctive therapies such as

Practice Points

- **Clinical suspicion of asthma or COPD should be confirmed with PFTs to establish the correct diagnosis and to rule out other respiratory and non-respiratory conditions with similar symptoms.**
- **Although both asthma and COPD are inflammatory lung conditions with similar general symptomatology, the underlying pathophysiology of each is very different. As a result, the response to bronchodilators and corticosteroids and their respective place in the treatment algorithm are different.**
- **In patients with similar number of clinical features of both asthma and COPD, ACOS should be suspected and initially be treated with ICS therapy.**
- **The release of longer-acting agents in new respiratory devices now provides a range of therapeutic medication and device options. However, patients must be taught to use each device to optimize medication delivery. It is crucial to document that an individual patient can use the prescribed device correctly in order to optimize therapeutic effectiveness.**
- **In addition to inhaled medications, adjunctive therapies such as vaccines, treatment of comorbid conditions (e.g., allergic rhinitis, tobacco use, gastric reflux), and nondrug therapies (e.g., pulmonary rehabilitation) can provide benefit.**
- **Pharmacists should be aware of newer treatment modalities that can be beneficial in select patients (e.g., BT, monoclonal antibodies).**
- **Because adherence to medication therapy is significantly influenced by patient preferences and perceptions, these should be routinely assessed, respected, and incorporated into the therapeutic plan as possible and practical. Misperceptions should be addressed.**
- **Monitoring with disease-specific questionnaires (e.g., CAT, ACT) can help assess response to therapy.**
- **Attention to detail at transitions of care is important to prevent readmissions.**

preventive vaccinations, treatment of comorbidities, and non-drug therapy. Pharmacists should also model best practices in documenting medical records and in educating patients to increase active participation in their care.

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

K.G. is an active 56-year-old man who reports new onset of an early morning cough with white sputum. He can jog as far, but not as fast, as 6 months ago. His breathing is worse in the spring and fall months, but he has a stuffy nose year-round. K.G.'s medical history includes childhood breathing problems, but medications have been discontinued since adolescence; he has a 35 pack-year history of tobacco use. His family history includes a sibling with "hay fever" and another with eczema. Results of post-bronchodilator pulmonary functions tests are FEV_1 82% of predicted, FEV_1/forced vital capacity (FVC) 68% of predicted, and normal carbon monoxide diffusion in the lung (DLCO).

1. According to the GINA guidelines, which one of the following is most consistent with K.G.'s history and clinical findings?

   A. Persistent asthma
   B. Chronic bronchitis
   C. Emphysema
   D. Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS)

2. According to the available clinical data, which one of the following would be the best initial daily maintenance therapy to recommend for K.G. today?

   A. A long-acting β_2-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA)
   B. A LAMA plus an inhaled corticosteroid (ICS)
   C. An ICS alone
   D. A LAMA alone

3. Which one of the following adjunctive therapies is best to recommend for K.G.?

   A. Fluticasone nasal spray and pneumococcal polysaccharide vaccine (PPSV23)
   B. Sublingual immunotherapy and pneumococcal conjugate vaccine-13 (PCV13)
   C. Fluticasone nasal spray and sublingual immunotherapy
   D. PCV13 now and PPSV23 12 months later

4. A 62-year-old man has awakened with a productive cough most mornings for the past several months. He maintains normal activities but reports wheezing and shortness of breath with activity two or three times per week, with more frequent symptoms at the onset of cold weather in the late fall. His medical history includes over 40 years of tobacco use. Pulmonary function tests show pre-bronchodilator FEV_1 of 73% of predicted, post-bronchodilator FEV_1 of 76% of predicted, pre-bronchodilator FEV_1/FVC of 62% of predicted, and post-bronchodilator FEV_1/FVC of 69% of predicted; his DLCO is normal. Which one of the following experimental agents would be expected to have greatest clinical impact on this patient's breathing problem?

   A. Platelet-activating factor (PAF) antagonist
   B. Interleukin 8 (IL-8) antagonist`
   C. Histone deacetylase enzyme (HDAC2) antagonist
   D. Eosinophil chemotactic factor (ECF) antagonist

Questions 5 and 6 pertain to the following case.

J.M. is a 63-year-old man with a history of COPD (5 years). He reports increasing dyspnea for several days with a productive cough with more thick yellow sputum. His vital signs are heart rate 99 beats/minute, respiratory rate 28 breaths/minute, and temperature 99.4°F. His weight is 93 kg (91 kg 3 months ago). On physical examination, inspiratory and expiratory wheezes are noted bilaterally with rales and mild peripheral edema. No jugular venous distension or hepatojugular reflux is noted. J.M.'s laboratory findings from last month include Hct 50% and Hgb 16.7 g/dL. An echocardiogram reveals left ventricular hypertrophy with an ejection fraction of 37% and pulmonary artery pressures of 29/16 mm Hg.

5. Which of the following pairs of COPD complications is most likely present in J.M.?

   A. Pulmonary hypertension and an exacerbation
   B. Pulmonary hypertension and polycythemia
   C. Cor pulmonale and an exacerbation
   D. Cor pulmonale and a polycythemia

6. J.M.'s clinic visit is during the fall and he has had no vaccinations since his COPD diagnosis. Which one of the following would be best to recommend for J.M.?

   A. Influenza injection plus PPSV23
   B. Inhaled influenza plus PPSV23
   C. Inhaled influenza plus pneumococcal conjugate vaccine (PCV13)
   D. Influenza injection plus PCV13

7. An investigator wants to design a study comparing the clinical efficacy of ICS with that of LABAs as first-line therapy for ACOS. Which one of the following would be the most important barrier to focus on in designing an optimal study?

   A. Deciding on inclusion and exclusion criteria
   B. Selecting specific medications in the drug class
   C. Measuring the clinical outcomes of treatment
   D. Identifying an appropriate statistical analysis

8. A trial enrolled 200 patients to determine the effect of adding a long-acting muscarinic antagonist bronchodilator

to high-dose ICS plus LABA therapy on forced expiratory volume in 1 second (FEV_1). Of these subjects, 100 received double-drug therapy, and 100 received triple-drug therapy. Of the subjects in the triple-drug group, 15% showed significant improvement compared with 5% in the double-drug group. Which one of the following is the most accurate number of patients needed to treat with triple-drug therapy for one patient to show improvement in FEV_1?

A. 5
B. 10
C. 25
D. 30

9. A 43-year-old African American woman with asthma is concerned. "I have seen television commercials that my Advair medicine can cause bad asthma attacks. I want to breathe better, but am worried." Her Asthma Control Test (ACT) score is 15 today. Her prescription profile shows that her fluticasone propionate 250 mcg plus salmeterol 50 mcg Diskus has been filled on time for the past 3 months. During that time, she has used 1 canister of albuterol. Which one of the following is the best response to give this patient?

   A. The salmeterol in Advair is best avoided in African Americans; I will recommend an alternative to your physician.
   B. The salmeterol in Advair is OK for you because you are taking another controller medicine.
   C. The salmeterol in Advair is OK for you because your asthma is well controlled.
   D. The salmeterol in Advair should be discontinued now because your asthma is well controlled.

Questions 10–12 pertain to the following case.

Z.P. is a 65-year-old woman with a new diagnosis of COPD. She had one exacerbation in the past year; it did not require hospitalization. She can do usual household activities, but she cannot work as long in the garden as she would like. Z.P.'s post-bronchodilator FEV_1 is 73% of predicted with a DLCO of 62% of predicted. Her only medication is metformin. Z.P. did not quit tobacco using the nicotine patch and is precontemplative at this time. She received the PPSV23 at age 63 when she was given a diagnosis of diabetes and the PCV13 1 year later. Her COPD Assessment Test (CAT) score is 15.

10. Using the GOLD classification system, which one of the following would be the best classification of Z.P.'s COPD?

    A. Group A
    B. Group B
    C. Group C
    D. Group D

11. According to the GOLD 2017 guidelines, which one of the following would be the best recommendation for initial daily maintenance inhaled therapy for Z.P.?

    A. Vilanterol plus umeclidinium
    B. Fluticasone propionate plus salmeterol
    C. Budesonide alone
    D. Aclidinium alone

12. Which one of the following is the best adjunctive therapy to recommend for Z.P.'s COPD?

    A. PPSV23
    B. Pulmonary rehabilitation program
    C. Inhaled influenza vaccine
    D. Electronic nicotine delivery system

13. An older adult woman with asthma takes budesonide 80 mcg/formoterol 4.5 mcg metered dose inhaler (MDI) 2 puffs twice daily. During the past 6 months, her profile shows a proportion of days covered (PDC) of 96% for budesonide/formoterol and three albuterol refills. Her ACT scores for this time are 14–16. Although her technique has been good on several occasions, she says that it is painful to actuate the dose from the MDI because of arthritis in her fingers and wrist. Which one of the following is best to recommend for this patient?

    A. Change to budesonide 80 mcg plus formoterol 4.5 mcg inhaler with a holding chamber.
    B. Change to tiotropium/olodaterol in a Respimat.
    C. Change to fluticasone propionate 500 mcg plus salmeterol 50 mcg in a Diskus.
    D. Change to fluticasone furoate 100 mcg in an Ellipta.

14. A woman with asthma has received 6 months of high-dose ICS plus LABA therapy. She lives in a rural area, and transportation for medical visits is a problem. Her ACT scores range from 16 to 18. Skin prick test results show sensitivity to feather mix, cat hair, Bermuda grass, hickory/pecan mix, and fungus. Presuming she has good device technique, which one of the following is best to recommend for this patient?

    A. Add tiotropium.
    B. Try an antifungal agent.
    C. Add a macrolide antibiotic.
    D. Try methotrexate.

Questions 15 and 16 pertain to the following case.

M.V. is an 8-year-old girl with asthma; she has been receiving fluticasone propionate 44 mcg 2 puffs twice daily by MDI plus holding chamber. Her mother reports that M.V. awakens 1 or 2 nights per month because of asthma. She has missed 3 days of school this semester and has trouble participating in activities during gym class. A review of her pharmacy profile for the past few months shows monthly refills for fluticasone and albuterol.

15. Which one of the following is best to recommend for M.V.?

    A. Increase fluticasone strength to 110 mcg.
    B. Add montelukast 10 mg orally daily.
    C. Add salmeterol 25 mcg (combined inhaler).
    D. Change to nebulized budesonide.

16. Two years later, M.V. is 10 years old; she has been receiving fluticasone 115 mcg plus salmeterol 21 mcg in a combination MDI. M.V. has an average of one nocturnal episode per month and has missed 2 days of school this semester because of a GI virus. M.V. has received one albuterol refill in the past 6 months. She uses albuterol 4–6 puffs per week, primarily before gym class. Which one of the following is best to recommend for M.V.?

    A. Change to fluticasone propionate 45 mcg plus salmeterol 21 mcg in a combination MDI
    B. Change to fluticasone furoate 200 mcg plus vilanterol 25 mcg in a combination dry powder inhaler (DPI)
    C. Change MDI to salmeterol 50 mcg
    D. Change MDI to fluticasone propionate 110 mcg

17. An older adult woman (height 64 inches, weight 70 kg) was assessed as having GOLD grade 3, group C COPD at her last visit and was treated with fluticasone furoate 100 mcg plus vilanterol 25 mcg. Her CAT score is now 32, and she has had three exacerbations in the past 6 months, one requiring hospitalization. Her other medications include furosemide, lisinopril, fluoxetine, and ranitidine. Her physician asks for advice about prescribing roflumilast for her. Which one of the following responses best explains why roflumilast is not recommended for this patient?

    A. Her COPD is not severe enough for roflumilast to be indicated.
    B. A likely concurrent medical condition excludes roflumilast use.
    C. Weight loss caused by roflumilast would be a significant concern.
    D. There is an interaction between roflumilast and a concurrent medication.

18. An older adult man with GOLD grade 3, group D COPD has had several exacerbations in the past year, although none required hospitalization. He takes fluticasone propionate 115 mcg plus salmeterol 21 mcg MDI twice daily with a tiotropium HandiHaler once daily. The patient has had only one exacerbation in the past 6 months since he started using a holding chamber with his MDI. He takes both medications on awakening, but he forgets to take the medication in the evening twice weekly because his bedtimes are erratic. Because of poor vision, he has trouble placing the capsule in the HandiHaler and verifying that all the medication has been inhaled. Which one of the following regimens is best to recommend for this patient?

    A. Aclidinium Pressair plus fluticasone propionate 250 mcg with salmeterol 50 mcg Diskus
    B. Mometasone 100 mcg with formoterol 5 mcg MDI with holding chamber plus tiotropium Respimat
    C. Glycopyrrolate Neohaler plus budesonide 160 mcg with formoterol 4.5 mcg MDI with holding chamber
    D. Fluticasone furoate 100 mcg with vilanterol 25 mcg plus umeclidinium 62.5 mcg both in Ellipta

Questions 19 and 20 pertain to the following case.

L.L. is a 14-year-old female adolescent with severe persistent asthma with serum eosinophilia and elevated IgE. She is currently treated with mometasone 100 mcg plus formoterol 5 mcg using an MDI with a holding chamber. Her technique has been assessed as adequate on many occasions. L.L.'s prescription profile shows a PDC of 82% for mometasone/formoterol and four albuterol refills in the past 3 months. She reports two nocturnal awakenings per week and several missed schooldays because of asthma. Her teacher is concerned about her school performance, and she falls asleep in class at least once a week.

19. L.L.'s provider asks the pharmacist about the appropriateness of reslizumab or mepolizumab for L.L. Which one of the following is the most appropriate response to give L.L.'s provider?

    A. Mepolizumab is not indicated because she is too young.
    B. Mepolizumab is not indicated because she is unlikely to benefit.
    C. Mepolizumab may be preferred because it is administered less often.
    D. Mepolizumab may be preferred because it can be given subcutaneously.

20. L.L. starts monoclonal antibody therapy for her asthma. Which one of the following would best show achievement of clinical asthma control in L.L.?

    A. Decrease in sputum and serum eosinophil counts
    B. Increase in FEV_1 readings to above 70% of predicted
    C. Incidence of nocturnal awakenings is less than twice per month
    D. Use of 1 canister of quick-relief medication per month