

## EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Describe the pathophysiology and severity classifications of asthma
- Identify the class, mechanism of action, place in therapy, and potential side effects of asthma therapies
- Recall updates in the 2020 NHLBI Guideline Update
- State what SMART Therapy is, why it was added to the asthma guidelines, and how to apply it to patient cases

After completing the continuing education activity, pharmacy technicians will be able to

- List the basic symptoms and pathophysiology of asthma
- Recall how patients are diagnosed with asthma and what the severities are
- Recognize common medications used for asthma
- Explain SMART and the pharmacy technician's role



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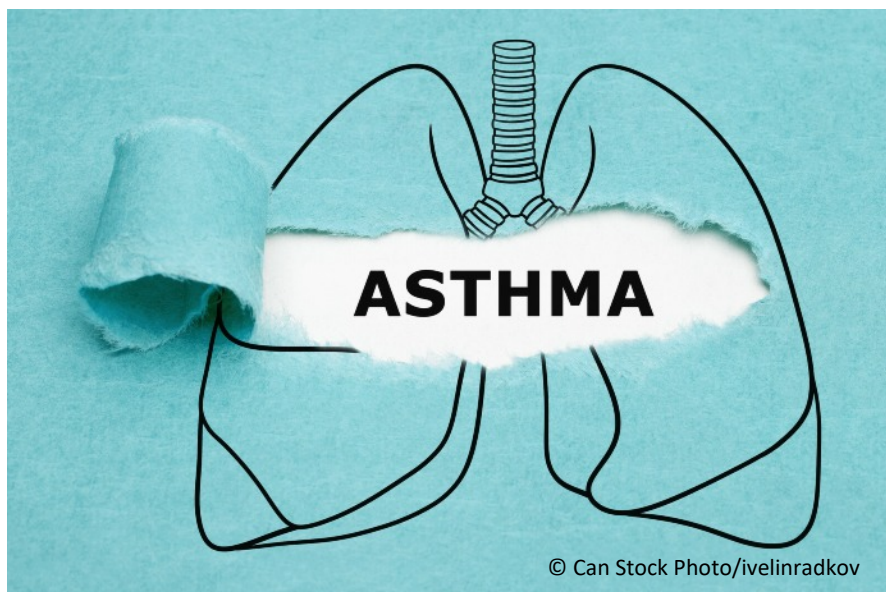
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## SMARTen Up: Asthma Management Guidelines

**ABSTRACT:** Asthma is one of the most common chronic diseases. Patients with asthma may have respiratory symptoms that affect their ability to breathe, daily activities, and quality of life. Understanding asthma and its pathophysiology, diagnosis, severities, and medications are pertinent to managing the disease.

This continuing education activity describes the 2020 update to the Asthma Management Guidelines by the National Heart, Lung, and Blood Institute (NHLBI) expert panel recommendations. Single Maintenance and Reliever Therapy (SMART) is a guideline revision that impacts clinical practice significantly. Pharmacy personnel need to familiarize themselves with the guideline updates to navigate transformations in prescribing that will follow.

**FACULTY:** Lindsey Sawtelle, PharmD Candidate 2022, University of Connecticut School of Pharmacy, Storrs, CT. Melanie Collins, MD, and Jessica Hollenbach, PhD, AE-C, are Co-Directors, Asthma Center, Connecticut Children's Medical Center, Hartford, CT.

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## INTRODUCTION

Let's start this continuing education (CE) course with a story. A 13-year-old adolescent, Emily, had asthma exacerbations that were impacting her life. In addition to sitting out at her soccer games, she was having difficulty waking for school because her asthma exacerbations kept her up a few nights a week. Her physician prescribed a budesonide/formoterol (Symbicort) prescription for maintenance and reliever. When she and her mom went to pick up the prescription, their pharmacist told them this prescription was "inappropriate" and "dangerous" at the pick-up counter. This pharmacist likely frightened the patient and her mother. The patient would have been rightfully hesitant to take the prescription as the physician prescribed.

Although the guidelines did not recommend using this combination for reliever and maintenance before 2020, the pharmacist was mistaken. This pharmacist didn't know about new NHLBI guidelines for SMART therapy. This continuing education activity will explore a recent change to the asthma guidelines that helps aspiring soccer players like our Emily score a goal with their asthma. Staying up to date on guidelines is the only way pharmacists will keep their place as trusted health-care professionals.

## BACKGROUND

All pharmacy team members need to know about asthma because it is a common chronic disease in both children and adults. The Center for Disease Control (CDC) estimates that around 8% of the population has asthma. As a chronic disease affecting the airway and lungs, asthma is characterized by airway inflammation, bronchospasm, and mucus hypersecretion. These findings cause symptoms of difficulty breathing, wheezing, coughing, and chest tightness.<sup>1</sup> Asthma's symptoms can range from mild to severe and they fluctuate. Symptom worsening is called an asthma attack, flare, or exacerbation.<sup>2</sup>

Asthma is often diagnosed in childhood but affects people of all ages. It is diagnosed more commonly in males during childhood, but its prevalence is equal in males and females by adulthood.<sup>1</sup> Asthma seems to have a hereditary component, although many genes probably contribute to asthma.<sup>3</sup> Family history and the presence of eczema are both risk factors for asthma.<sup>1</sup> Other risk factors include exposure to environmental tobacco smoke, air pollutants, or allergens, such as pollen, dust, or workplace chemicals (see SIDEBAR, page 3, for discussion of household pests).<sup>1</sup> Risk factors for asthma are often present in childhood. For example, exposure to cigarette smoke in the womb increases the probability infants will develop asthma. Young children with allergies or who have respiratory infections are also more likely to develop asthma.<sup>1</sup>

## Asthma Pathophysiology

The bronchial tree is the branched system of cartilaginous tubes responsible for conducting gas to alveoli, the small air sacs that allow gas exchange, in the lungs. The word "tree" is an apt description because the lungs look like an upside-down tree, where the trachea is the trunk, and the bronchioles are the smallest terminal twigs. The bronchioles are the smallest bronchi and they facilitate gas exchange with alveoli, the air sacs in the lungs that exchange gas with the blood.<sup>4</sup> Each layer of the bronchi has a smaller diameter than the one it stems from and has more smooth muscle fibers, just like the branches of a tree.<sup>5</sup> Asthma primarily affects airways including the smooth muscle of the bronchi, where inflammation decreases the airway's size, in turn increasing the work it takes to breathe.<sup>3</sup>

In allergic asthma, an asthma exacerbation consists of an early phase and a late phase. IgE antibodies are responsible for the

first phase.<sup>3</sup> Environmental triggers cause plasma cells to release IgE antibodies, which bind to mast cells and basophils. Mast cells release cytokines, histamine, prostaglandins, and leukotrienes.<sup>3</sup> Ultimately, smooth muscle contracts and the airway tightens, causing bronchoconstriction.<sup>6</sup> Th2 lymphocytes sustain the inflammation by producing additional cytokines and maintaining the communication between cells.<sup>3</sup> The late phase occurs over the next hours as inflammatory cells localize to the lungs and cause bronchoconstriction and inflammation. The cells involved in this second phase include basophils, eosinophils, helper and memory T-cells, and neutrophils.<sup>3</sup> These cells cause inflammation and further edema. Mucous worsens airway obstruction and difficulty breathing. Successful management of an asthma exacerbation requires recognition of both phases.

Hyperresponsiveness of the bronchi is another mechanism of asthma's pathophysiology. Hyperresponsiveness is excessive bronchoconstriction after inhalation of or exposure to triggers.<sup>7</sup> Triggers can include smoke, exercise, emotion, cold temperatures, humidity, animals with fur, infections, and non-steroidal anti-inflammatory drugs.<sup>8-11</sup> This mechanism of excessive inflammation involves histamine and increased free intracellular calcium that increases smooth muscle contractility.<sup>12</sup> Disease severity and therapeutic intervention are related to bronchial hyperresponsiveness.

Structural changes occur in the airway due to chronic inflammation and airway muscle hyperreactivity. This is known as airway remodeling. An asthmatic bronchiole is narrower than a normal bronchiole. Increased swelling, chronic inflammation, and mucus buildup from persistent airflow obstruction cause the narrowing.<sup>3</sup> The narrowing of the lumen disrupts the normal replication of epithelial cells, compromising the layer's structure and function.<sup>16</sup> The hyperresponsiveness of the bronchioles leads to hypertrophied smooth muscle, disrupting the basement membrane. Irreversible obstruction of airflow is a consequence of airway remodeling.<sup>12</sup> Effective treatment of asthma can prevent or delay airway remodeling.

## ASTHMA DIAGNOSIS

The first step in diagnosing asthma is a focused medical history and physical examination. Symptoms consistent with asthma include episodes of cough, wheezing, difficulty breathing, and chest tightness. It is also notable if these symptoms worsen at night and awaken the patient, as they did for our patient Emily.<sup>17</sup> The physical exam may show use of accessory muscles when breathing, sounds of wheezing during normal breathing, increased nasal secretion with mucosal swelling, or atopic dermatitis/eczema.<sup>17</sup> Noting patient allergies or a family history of asthma helps establish a diagnosis.

Spirometry can be used to evaluate asthma and monitor disease severity; it can also be used to monitor response to therapy in patients aged 5 and older. Of note, it is not common to find many five-year-olds who are capable of reliably performing the



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test.<sup>17</sup> Spirometry measures the air a patient breathes in and out. Specifically, spirometry measures the forced expiratory volume in 1 second (FEV<sub>1</sub>) and the forced vital capacity (FVC).<sup>18</sup>

- FEV<sub>1</sub>: maximum amount of air a patient exhales in one second.
- FVC: maximum amount of air exhaled when blowing out as fast as possible

Comparing results against values normalized by age, height, weight, gender, and race is the only way to interpret them. An easy way to interpret results is based on the percent predicted; however, most pulmonologists now use z-scores to interpret spirometry.<sup>19</sup> Physicians may have the patient repeat spirometry after taking a bronchodilator to evaluate for airway reversibility.

Clinicians also use spirometry to evaluate if current therapy is controlling asthma effectively. The results of patients' spirometry tests while on treatment guides doctors to increase or decrease the dose of asthma medications.<sup>18</sup>

Airway hyperresponsiveness is measured using a methacholine test. The clinician uses spirometry to find the patient's FEV<sub>1</sub>. The patient then uses a nebulizer and inhales increasingly larger doses of methacholine. The physician takes the FEV<sub>1</sub> before and after each dose. The test is positive if the FEV<sub>1</sub> drops 20% or more from the baseline FEV<sub>1</sub>. The test is negative if the maximum methacholine dose does not decrease the FEV<sub>1</sub> by at least 20%.<sup>20</sup> Regardless of asthma control and response to therapy, most people with asthma would have a positive methacholine challenge test.

The 2020 NHLBI guideline update includes the conditional recommendation to use fractional exhaled nitrous oxide (FeNO) as a test to diagnose asthma.<sup>21</sup> Nitric oxide (NO) is a gas produced by cells involved in inflammation. The higher the NO level, the more inflammation in the body. This test is plausible to use as an adjunct for patients aged 5 and older whose asthma diagnosis is uncertain using history, clinical course, and spirometry. Our patient in this CE case would not be a candidate for a FeNO test, as

### **SIDEBAR: Rodent and Cockroaches<sup>13,14,15</sup>**

The prevalence of asthma is highest in developed countries, especially in urban areas. In urban areas, up to 1 in 4 children may have asthma. Urban areas increase the risk of exposure to cockroaches and rodents, increasing allergen sensitization in these areas, ultimately leading to asthma. Mouse Mus m 1, mouse urinary protein (MUP), rat N 1, and cockroach (Bla g 1 and Bla g 2) are the responsible allergen proteins. Tests have confirmed high levels of these proteins in houses, schools, and daycares in urban locations.

Multifamily homes, high population density, lower socioeconomic status, and poor physical condition of buildings are all settings that foster cockroach and rodent infestation. Sensitization to cockroaches and rodents is associated with wheezing and severe asthma morbidity. Most research done to date has been in children.

Like people, pests need food, water, and shelter to live. They prefer to live in dark and damp areas. Pest mitigation strategies can decrease the likelihood of exposure to rodent and cockroach proteins:

- Do not leave food containers open or dirty dishes out in the open.
- Do not leave pet food and water out overnight.
- Clean regularly. Pick up garbage, crumbs, and clean liquid spills.
- Use trash cans with lids, bags that resist breaking, and do not allow them to overflow.
- Check for plumbing leaks and moisture problems and fix any issues right away.
- Seal cracks and openings around doors, windows, and foundations.
- Use bait gel in cracks and traps rather than pesticides.



her asthma diagnoses are apparent without one. One should also note that most commercial insurances no longer cover this test.

## Asthma Severities

The NHLBI classifies asthma as intermittent, mild persistent, moderate persistent, or severe persistent. Asthma symptoms before treatment determine the classification, but the patient's classification may change over time. Patients are diagnosed with the asthma classification in which their most severe symptom falls.<sup>17</sup> As you look at these classifications, think about Emily and decide where her asthma would fall.

- Intermittent Asthma
  - Symptoms occur fewer than two days a week and do not interfere with normal activities
  - Nighttime symptoms occur fewer than two days a month
  - Lung function tests are normal when the patient is not having symptoms
- Mild Persistent
  - Symptoms occur more than two days a week, but not every day. Attacks interfere with daily activities
  - Nighttime symptoms occur three to four times a month
  - Lung function tests are normal when the patient is not having symptoms
- Moderate Persistent
  - Symptoms occur daily and interfere with daily activities
  - Nighttime symptoms occur more than once a week, but not daily
  - Lung function tests are abnormal
- Severe Persistent
  - Symptoms occur daily and severely limit daily activities
  - Nighttime symptoms occur multiple times weekly
  - Lung function tests are abnormal

The severity of asthma drives the treatment recommendations. Asthma classification can change over time. From our case, Emily likely has moderate persistent asthma. She is kept up a few times weekly by nighttime symptoms, interfering with her sleep. She also needs to sit out of soccer games and was having trouble in school due to her lack of sleep. Her symptoms limit her daily activities.

## TREATMENT

With the revision to the guidelines in 2020, several things have changed, and pharmacy staff need to be aware of the changes.

**PAUSE AND PONDER:** How would asthma attacks occurring nightly affect a patient's quality of life?



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## Medications

People can manage asthma with appropriate medications. **Table 1**<sup>22-26</sup> (next page) provides additional detail on the mechanism of action, pharmacology, and adverse events associated with preferred medications used to treat asthma. Inhaled corticosteroids (ICS) are the cornerstone of asthma therapy, and this has not changed with the updated guidelines, although use of biologic agents to control asthma is more prominent.<sup>23</sup> ICS may be dosed once or twice daily but more often during symptomatic periods.<sup>24</sup> Beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, and mometasone are all commonly used ICS.<sup>22</sup> When dosed at equipotent doses, all corticosteroids are equally effective, but some individuals respond better to certain ICS than others.<sup>24</sup> The dose of ICS can be titrated for symptom relief and spirometry response, but the dose-response is relatively flat after moderate doses.<sup>25</sup> A flat dose-response is like continuing to eat when you are already full. When you are full, you likely have gotten all the calories you need from a meal, and now you are just increasing your chances of bellyache. Increasing the dose of ICS past moderate strengths does not continue to provide additional relief of asthma symptoms as before, and the risk of side effects increases. Some patients with severe asthma do escalate to high dose ICS.

**Table 1. Preferred Medications for Asthma Therapy<sup>22-26</sup>**

Medication Class	Mechanism of Action	Pharmacology	Adverse Events
ICS	Inhibit production and release of signals allowing extravasation of immune cells into the airway. Decrease inflammatory response and airway hyperresponsiveness	<ul style="list-style-type: none"> <li>● 1-2 Weeks of treatment for full effect</li> <li>● Goal is high pulmonary affinity with low systemic absorption</li> <li>● MDI vs. DPI may affect absorption</li> <li>● Metabolism and active metabolites may contribute to systemic effects</li> </ul>	Nasopharyngitis, headache, bronchitis, sinusitis, influenza, respiratory tract infection, back pain, toothache, abdominal pain, cough, oral candidiasis, rhinitis, and throat irritation
Inhaled SABA		<ul style="list-style-type: none"> <li>● Onset: Within minutes</li> <li>● Peak: 30 minutes</li> <li>● Bronchodilation: 4-6 hours</li> </ul>	Tremor, nervousness and insomnia in children, nausea, fever, bronchospasm, vomiting, headache, pain, dizziness, cough, dry mouth, sweating, chills, dyspepsia
Inhaled LABA		<ul style="list-style-type: none"> <li>● Onset: 5-30 minutes</li> <li>● Peak: 15 minutes- 3 hours</li> <li>● Bronchodilation &gt;12 hours</li> </ul>	Adverse events are same as short acting, but less likely. LABAs are more B2 selective and lipophilic, concentrating their effects in the lungs
Inhaled SAMA	Antagonize acetylcholine at muscarinic (M3) receptors, leading to decreased bronchoconstriction, mucus secretion and edema	<ul style="list-style-type: none"> <li>● Onset: Within 15 minutes</li> <li>● Peak: 1-2 hours</li> <li>● Bronchodilation: 6-8 hours</li> </ul>	Adverse events are related to systemic anticholinergic activity at all muscarinic receptors including urinary retention, dry mouth, headache, dizziness, sinusitis, dyspnea, back pain, cough
Inhaled LAMA		<ul style="list-style-type: none"> <li>● Onset: 30 minutes</li> <li>● Peak: 3-4 hours</li> <li>● Bronchodilation: 12 to &gt;24 hours</li> </ul>	

B2: Beta-2 receptor, ICS: inhaled corticosteroid, DPI: dry powdered inhaler, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonist, MDI: metered dose inhaler, SABA: short-acting beta agonist, SAMA: short-acting muscarinic antagonist

Patients use oral systemic corticosteroids for severe exacerbations or if they have a history of severe exacerbations or difficult-to-control asthma.<sup>21</sup> Oral corticosteroids have many unfavorable adverse events that need to be considered by prescribers.<sup>27</sup> An increase in the release of cortisol from the adrenal glands through a negative feedback loop on the hypothalamus-pituitary-adrenal (HPA) axis causes many of these the adverse effects.<sup>27</sup> Systemic corticosteroid adverse events differ by duration of therapy<sup>27</sup>:

- Short-term: hyperglycemia, leukocytosis, mood alteration, sodium and fluid retention, increased weight gain, nocturnal enuresis
- Long-term: growth retardation, osteoporosis, skin thinning, impaired wound healing, bruising, cataracts, glaucoma, Cushingoid feature, increased weight gain, and immunosuppression

ICS have little systemic absorption and are preferred for asthma control over oral corticosteroids. Patients taking higher doses of ICS have increased risk of systemic absorption and adrenal sup-

pression. It is important to titrate to the lowest effective dose of ICS to avoid systemic absorption and adverse events. Corticosteroids have a dose-response relationship to adverse events.<sup>27</sup> Clinicians must monitor for systemic side effects to determine the risk and benefit balance of both oral corticosteroids and ICS.

While corticosteroids treat the inflammatory component of asthma, additional medications are needed to address airway hyperresponsiveness and can be either short or long-acting medications. "Quick-relief" and "relief" medications are common ways to refer to short-acting medications.<sup>22</sup> Short-acting beta-agonists (SABAs) and inhaled short-acting muscarinic antagonists (SAMAs) are the two classes of relief medications. Patients use SABAs and SAMAs when experiencing symptoms or before exposure to triggers.

SABAs are highly effective bronchodilators but have short durations of action.<sup>22</sup> Typically, all patients with asthma are prescribed a SABA as a "relief" inhaler.<sup>22</sup> Albuterol metered-dose

**Table 2. Asthma Inhalers**<sup>28,30-46</sup>

<b>ICS</b>	Beclomethasone dipropionate	QVAR Redihaler	MDI
	Budesonide	Pulmicort Flexhaler Generic	DPI Nebulizer
	Ciclesonide	Alvesco	MDI
	Fluticasone propionate	Flovent HFA Flovent Diskus Arnuity Ellipta Armon Air Digihaler	MDI DPI DPI DPI
	Mometasone	Asmanex HFA Asmanex	MDI DPI
<b>SABA</b>	Albuterol	ProAir Ventolin Proventil Generic	DPI, MDI MDI MDI DPI, MDI
	Levalbuterol	Xopenex HFA	MDI
<b>LABA</b>	Formoterol	Perforomist	Nebulizer
	Salmeterol	Serevent	DPI
<b>SAMA</b>	Ipratropium	Atrovent HFA Generic	MDI Nebulizer
<b>LAMA</b>	Tiotropium	Spiriva Respimat	DPI

inhalers (MDI) are the most used relief inhaler. Albuterol is dosed at one to two puffs every four to six hours as needed to control an asthma exacerbation.<sup>28</sup> SABA use is changing in clinical practice. Newer research shows that SABAs are more effective when followed by an ICS.<sup>29</sup> Even in patients with infrequent symptoms, a prescription for daily low-dose ICS reduces asthma symptoms and risk. Increased SABA use is associated with worse outcomes. A patient is at risk of severe asthma exacerbations and asthma mortality if they pick up three or more albuterol inhalers a year from the pharmacy, the equivalent of 1.6 puffs per day.<sup>29</sup>

SAMAs can be used in place of SABAs but are less effective. SAMAs will be used if SABAs are not tolerated as relief therapy. Ipratropium is a commonly used SAMA. Emily, our patient in the CE case, does not have a SAMA prescription because she receives symptom relief when using albuterol. Technicians can emphasize many points (including cleaning) when patients pick up refills—see the [Appendix](#) on pages 11 and 12).

Long-acting medications include long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). LABAs are never used alone in asthma therapy but are companions to inhaled corticosteroids (ICS).<sup>22</sup> Patients should take these medications even when asthma symptoms are not present because they are maintenance therapy. All LABA medications have a boxed warning cautioning about the potential for severe asthma exacerbations. Some severe exacerbations, when using LABA monotherapy, have led to death.<sup>22</sup> LABAs do not have the same association with severe exacerbations and death when used in a combination with ICS. Salmeterol and formoterol are

the most frequently used LABAs.<sup>22</sup> The two LABAs differ in their time of onset. Formoterol and salmeterol have an onset of 15 minutes and 45 minutes, respectively. Patients aged 6 and older can use tiotropium as an add-on LAMA in maintenance therapy.<sup>30</sup> [Table 2](#)<sup>28,30-46</sup> gives an overview of the current inhaled therapies available in the U.S. to treat asthma. You will find details about Emily's long-acting therapy in the section where SMART is explained.

Many patients require multiple medications for asthma management. Clinicians prescribe combination inhalers—inhalers that have two medications—to increase efficacy, patient adherence and ease of inhaler use. Patients experience less confusion about when and how to use their inhalers when using fewer products. Clinicians can assess patient adherence and correct use of medications when a patient is on combination products. With this information, clinicians can determine if the patient needs education or an increased medication dose. [Table 3](#)<sup>47-52</sup> (next page) shows the many combination products on the market.

Think back to our case. This patient's prescription was for budesonide/formoterol. This therapy is an ICS and LABA combined therapy. The patient previously used a fluticasone inhaler once daily and albuterol as a relief inhaler. This new therapy would give the patient only one inhaler to control her asthma, avoiding inhaler confusion. Also, as patients cannot exactly “feel” the inhaled corticosteroid inhaler making a “difference,” but patients can always feel a change with SABA/LABA therapy—the combination inhalers help patients to experience a positive effect while taking chronic medications.

**Table 3 Combination Products<sup>47-52</sup>**

Budesonide/formoterol	Symbicort	MDI
Fluticasone/salmeterol	Advair	DPI, MDI
Fluticasone/vilanterol	Breo Ellipta	DPI
Mometasone/formoterol	Dulera	MDI
Budesonide/umeclidinium/vilanterol	Trelegy Ellipta	MDI

The 2020 NHLBI Guidelines for Asthma Management list the following medications as alternatives to the preferred therapies: leukotriene receptor antagonists (LTRA), cromolyn (Intal), theophylline, and immunotherapies. The guidelines list nedocromil (Tilade) as an alternative therapy, although the FDA has discontinued this medication.<sup>21,53</sup>

LTRAs include montelukast and zafirlukast. These medications antagonize the effects of pro-inflammatory chemicals called leukotrienes. LTRAs work to decrease the inflammatory component of asthma.<sup>22</sup> Montelukast is indicated in patients aged 1 and older, is only dosed once a day, and does not have many drug interactions.<sup>54</sup> Montelukast use is discouraged because of side effects and limited efficacy. Montelukast's labeling includes a boxed warning because of potential neuropsychiatric adverse events.<sup>54</sup>

Cromolyn is a nebulized solution approved for asthma prophylaxis. The approval is for patients aged 2 and older. It inhibits release of histamine and leukotrienes from mast cells.<sup>55</sup>

Theophylline is an oral medication rarely used as maintenance therapy for asthma. It has many side effects and requires titration via blood tests. It is a phosphodiesterase inhibitor and adenosine antagonist. Theophylline ultimately relaxes smooth muscles in the bronchial airway.<sup>22</sup>

Immunotherapies are injectable monoclonal antibodies reserved for patients with severe and treatment-resistant asthma. Currently, omalizumab (Xolair) is the only biologic approved for asthma in patients as young as 4-years-old.<sup>21</sup> The NHLBI 2020 guideline update does not contain specific recommendations for the use of biologics. The systematic reviews the panel examined to update the guidelines did not include the use of biologics. Anti-IgE (omalizumab), anti-IL5 (mepolizumab [Nucala], reslizumab [Cinqair]), anti IL5-R (benralizumab [Fasenra]), and anti-IL4 (dupilumab [Dupixent]) are other biologic treatments for asthma. Insurers typically require prescribers to document the patient's allergen sensitization and phenotyping before approving immunotherapies. Patients will have to try other therapies and either be unresponsive or intolerant of them before trying biologics. Specialist supervision is needed.<sup>22</sup>

### Step Therapy Rationale

The NHLBI Guidelines recommend a stepwise approach to the treatment of asthma. The recommendation guides initial asthma treatment based on the asthma severity and subsequent therapy if symptoms persist despite changes in asthma therapy.<sup>21</sup> **Table 4** represents a combination of the stepwise therapy recommendations across all age groups in the NHLBI Guidelines.<sup>21</sup> For simplicity, the figure only shows the preferred medication recommendations. The full step therapy recommendations can be found in the full version of the NHLBI 2020 Update to the Asthma Management Guidelines.

In Step 1—which addressed patients with intermittent asthma—patients only use a reliever inhaler to control intermittent asthma symptoms, meaning the patients will only use an inhaler when experiencing symptoms or for pre-treatment before exercise. A clinician would initiate ICS therapy in a patient with mild asthma on Step 2.<sup>17</sup> A patient with moderate asthma would start

**Table 4. Stepwise Approach to the Preferred Treatment of the Management of Asthma<sup>21</sup>**

Intermittent Asthma	Management of Persistent Asthma				
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Individuals Ages 0-4 years					
PRN SABA Short daily course of ICS at the start of respiratory tract infection	Daily low-dose ICS  PRN SABA	Daily medium-dose ICS  PRN SABA	Daily medium dose ICS-LABA  PRN SABA	Daily high-dose ICS-LABA  PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid  PRN SABA
Individuals Ages 5-11 Years					
SABA	Daily low-dose ICS  PRN SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination	Daily high dose ICS-LABA  PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid  PRN SABA
Individuals Ages 12+					
SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS & SABA	Daily and PRN combination low-dose ICS-formoterol	Daily and PRN combination medium-dose ICS-formoterol	Daily high dose ICS-LABA  PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid  PRN SABA



therapy on Step 3 or Step 4.<sup>17</sup> A patient with severe asthma would start therapy on Step 5 or Step 6.<sup>17</sup>

Once treatment has started, a clinician should reassess the patient every two to six weeks to ensure control of asthma symptoms.<sup>21</sup> If symptoms persist and asthma is uncontrolled, this would be an appropriate time to step-up therapy. Questioning patients about how frequently they use their reliever inhalers, or how many times they forgot to take their inhaler in the past week may help guide clinicians.<sup>17</sup> More frequent use of the SABA, including using a reliever inhaler more than two days a week, would favor stepping up therapy. Appropriate use of asthma inhalers is critical to achieving control. Adherence to the regimen and proper technique are required to determine if the patient is using the medication correctly.<sup>21</sup> Pharmacists can play an integral role in educating patients in proper inhaler technique.

Objective measures, like spirometry, can also be used to assess control. Improvements in spirometry readings indicate better control of a patient's asthma.<sup>21</sup> Increased healthcare utilization, like emergency room visits for an exacerbation, is another way to determine if a patient's asthma is under control.<sup>17</sup> An increase in patients' healthcare utilization suggests poorly controlled asthma. Mitigating the risk of severe exacerbations is another goal of achieving good asthma control.<sup>17</sup> Any patient on step 3 or higher should consult with an asthma specialist for treatment.<sup>21</sup>

If a patient has well-controlled asthma after three consecutive months on a medication, the patient also may step down on therapy.<sup>21</sup> A patient would always only go down one step of treatment. A clinician would schedule follow-up in the same two-to-six-week timeframe to ensure a patient still has asthma control.<sup>17</sup> The benefit of stepping down therapy is to lower the patient's systemic ICS and LABA dose exposure, decreasing the risk of potential adverse events.

## 2020 Asthma Management Guideline Updates

The 2020 NHLBI Guideline update focused on six select topics: intermittent ICS (e.g. SMART), LAMAs, indoor allergen mitigation, immunotherapy in the treatment of allergic asthma, FeNO testing, and bronchial thermoplasty (BT). A major update to the guideline that is changing clinical practice is SMART.

### Time to be SMART

The 2020 NHLBI Asthma Management Guidelines recommend SMART in patients with moderate persistent asthma ages 4 and older. Keeping a patient's current regimen would be appropriate if asthma symptoms are well controlled. SMART employs a single ICS+formoterol combination inhaler product dosed daily and as needed for asthma exacerbations. This is a significant change, and all pharmacy staff need to be aware of it! SMART medications are FDA-approved in patients 12 and older. SMART is recommended off label in children aged 4 through 11.

### Pause and Ponder: Who makes the ideal candidate for SMART therapy?

Before the 2020 update, patients with moderate persistent asthma would be on Step 3 or Step 4 therapy. Therapy consisted of a daily ICS inhaler for maintenance and a SABA inhaler for relief—two separate inhalers. If a patient was uncontrolled on ICS, a physician added a LABA to the regimen. SMART potentially transitions patients from three inhalers to one inhaler. An ICS+LABA combination has never been a reliever option before; the only option was SABA. The drastic change in recommendations is why the pharmacist in the CE case, unaware of this change, was hesitant to fill the prescription. It is an extreme change in therapy and based on outdated information, and he was understandably uncomfortable.

It would be reasonable to switch patients who are uncontrolled on their current regimens or have had an exacerbation in the past year.<sup>21</sup> It is also reasonable to discuss with patients or families who want to streamline their treatment regimens or those with difficulty adhering to their current regimens. Patients with uncontrolled moderate asthma should switch to SMART on the same treatment step they are currently on before moving up. For example, Emily in the CE case was on Step 4 of the 2007 guidelines, a medium-dose ICS and a LABA.<sup>17</sup> After being transferred to SMART, her regimen includes a medium-dose ICS-formoterol. This is Step 4 of therapy in the 2020 guidelines.

Along with an ICS, formoterol, a LABA, is being used as the reliever component of the regimen. Using formoterol is entirely different than our previous approaches where SABAs and SAMAs were the reliever medications. Formoterol's onset is two to three minutes.<sup>56</sup> Its duration of action is up to 12 hours, creating quick and durable smooth muscle relaxation.<sup>56</sup> Formoterol is also an ideal drug because patients can use it more than twice daily. The maximum dosage of formoterol varies by age. Each inhalation of SMART will deliver 4.5 mcg of formoterol. Patients aged 4 to 11 can use eight puffs of formoterol daily (36 mcg).<sup>21</sup> Patients aged 12 and older can use twelve puffs of their inhaler per day (54 mcg).<sup>21</sup>

The two ICS currently used in SMART inhalers are budesonide and mometasone.<sup>57</sup> A patient using a SMART inhaler as needed will also receive the long-term anti-inflammatory effects of an ICS with each use. SMART therapy aims to provide enough long-acting preventive medicine when symptoms occur to prevent them from recurring.<sup>57</sup>

This treatment will be prescribed as one to two puffs once or twice daily for maintenance with one to two puffs as needed every five to 10 minutes for asthma symptoms. Age, asthma severity, and ICS dose in the inhaler determine the dosage and



frequency a clinician prescribes.<sup>21</sup> Pharmacists should ensure the maximum puffs on a patient's prescription do not exceed the limit for their age.

SMART reduces asthma exacerbations and decreases healthcare utilization while increasing quality of life and asthma control.<sup>21</sup> SMART therapy also decreases patients' systemic corticosteroid use. Patients who decrease their use of oral corticosteroids and maintain lower doses of ICS reduce the risk of corticosteroid-associated adverse events.<sup>57</sup>

SMART may make asthma treatment easier for patients and families. Patients appreciate this one inhaler approach with a single prescription to refill and pickup.<sup>57</sup> Having a single inhaler decreases confusion about which inhaler is responsible for maintenance and reliever. It also ensures the patients always have the correct inhaler in their possession. SMART may be especially beneficial for patients who regularly skip their maintenance inhaler when they do not have symptoms.<sup>57</sup> These patients rely on their reliever inhalers. With SMART, if patients only take their reliever inhaler, they still receive anti-inflammatory medication.

Costs, insurance formulary considerations, and intolerance are all reasons SMART may not be appropriate for some patients.<sup>21</sup> Patients who overuse their SABA reliever inhalers may not be good candidates for SMART. Some patients use their reliever inhalers when they are anxious or feel short of breath, even when this is not asthma related.<sup>57</sup> These patients are at risk of receiving ICS doses that are too high. Patients who use ICS-salmeterol as their maintenance should not use it as SMART.<sup>21</sup> Patients using both inhalers will expose themselves to higher and potentially dangerous LABA & ICS doses.

Pharmacists are responsible for reminding patients to use only their maximum daily puffs and to contact a physician if their asthma symptoms require them to exceed this maximum. The pharmacist should also consider the supply a patient will need using the medication for both maintenance and relief doses. Patients may need to pick up multiple inhalers monthly for adequate supply.<sup>21</sup>

Pharmacy technicians will prevent errors if they can recognize SMART. These prescriptions will contain directions for daily use and as-needed use in the same inhaler. An example prescription is budesonide/formoterol 80/4.5, inhale 2 puffs twice daily and 1-2 puffs every 4 hours as needed for asthma exacerbations (maximum 12 puffs daily). Current evidence only recommends formoterol as the LABA in SMART. Knowing this, a technician can be on the lookout for the look-alike sound-alike medication salmeterol in combination inhalers which are not safe to use for SMART. A patient on SMART therapy will likely need all other prescriptions for asthma therapy put on hold. Let's emphasize this point: Patients with automatic refills of a SABA or other maintenance medication will be at risk of over-treatment if they continue to take their old inhalers with SMART. **If a patient with**



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**a SMART prescription comes into the pharmacy, it is important for the technician to recognize this to help prevent medication errors.**

## Additional Guideline Updates

### Intermittent ICS<sup>21</sup>

The NHLBI organized the recommendations for the use of intermittent ICS by age. This update includes SMART.

The guidelines recommend that from birth to age 4, children with recurrent wheezing related to respiratory tract infections (RTI), not currently on asthma therapy and with no symptoms between infections should use a seven-to-ten-day course of daily ICS when the RTI begins.<sup>21</sup> It recommends combining ICS with as-needed quick-relief SABA therapy. This recommendation aims to decrease exacerbations, systemic corticosteroid use, and healthcare utilization.<sup>21</sup> Healthcare utilization declines when caregivers have clear instructions for initiating ICS.

Individuals aged 4 to 12 with mild to moderate persistent asthma who are currently taking daily ICS should not increase their regular daily ICS dose for short periods.<sup>21</sup>

Individuals aged 12 and older with mild persistent asthma have two preferred treatments recommended as Step 2 of therapy<sup>21</sup>: either a daily low-dose ICS and as-needed SABA or an as-needed SABA and ICS delivered concomitantly, one after the other.<sup>21</sup> SMART therapy is the preferred treatment in patients with moderate to severe asthma in patients 4 and older.<sup>21</sup>

### LAMAs

The 2020 NHLBI guideline update changed the recommendation for LAMA use in patients 12 years and older with asthma not controlled by ICS therapy. The next appropriate step is to add a LABA to ICS rather than a LAMA, unless the patient is unable to

tolerate, has a contraindication, or has an adherence barrier to a LABA.<sup>21</sup> A prescriber may still add a LAMA onto the ICS+LABA combination for improved symptom control and increased quality of life.<sup>21</sup> A patient on ICS+LABA and LAMA will require the use of multiple inhalers.

### Indoor Allergen Mitigation

Some patients have an identified allergen component of their asthma. Patients may use mitigation strategies like air purifiers, impermeable pillows, mattress covers, and HEPA filters to reduce their risk of allergen exposure.<sup>21</sup> The 2020 NHLBI guideline update recommends patients use multiple mitigation strategies, as one strategy alone likely will not improve outcomes.<sup>21</sup> The guideline recommends integrated pest management in patients' homes who are allergic and exposed to rodents and cockroaches.<sup>21</sup> If an individual does not have an allergy to indoor substances, the 2020 Update does not recommend home mitigation strategies.<sup>21</sup>

### Immunotherapy for Allergic Asthma

Immunotherapy includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The 2020 NHLBI guideline update recommends SCIT as an adjunct treatment in patients with demonstrated sensitization to allergens, but not when patients are experiencing asthma symptoms or have severe asthma.<sup>21</sup>

### FeNO Testing

The 2020 NHLBI guideline update recommends FeNO measurement in patients older than 4 years with an uncertain asthma diagnosis after a medical examination, complete history, and spirometry testing.<sup>21</sup>

### Bronchial Thermoplasty

BT is a procedure that removes muscle tissue from the airway using heat. The benefits in this procedure are small, the risks are moderate, and long-term outcomes are uncertain.<sup>21</sup> The 2020 NHLBI guideline update conditionally recommends against this procedure.<sup>21</sup> Patients who may consider BT must have a risk-benefits conversation with their provider.

### CONCLUSION

The update to the 2020 NHLBI Asthma Management Guidelines offers new guidance to clinicians treating patients with asthma. Patients need to go to the pharmacy and pick up their evidence-based treatment without unnecessary intervention—or incorrect and possibly frightening information—from the pharmacist. Pharmacists should expect to see prescriptions of ICS-formoterol written for SMART. The patient case in this CE is an avoidable situation. Staying up to date with the current guidelines is a pharmacists' responsibility. Technicians should work with patients and pharmacists to put outdated medication prescriptions on hold to avoid further medication errors.

Figure 1 summarizes key points.

## Figure 1. Summing Up Key Points about Asthma and SMART Approaches

### Best

- 1 **BE COMMUNITY CHAMPIONS.** Spread the word about guideline changes to other clinicians.
- 2 **Always ask prescribers when you see a drug used in a different way.** Don't assume it's a mistake.
- 3 **Check autofill when patients start SMART therapy!** Discontinue older, unnecessary, and potentially dangerous inhalers.

### Better

- 1 **Check guidelines for common disease** annually or more often so you will know when they change.
- 2 **Memorize the lingo!** SABA, LABA, SAMA, LAMA! Confusing!
- 3 **Ask patients if they know their specific diagnosis;** it can help you counsel appropriately and make sure they have the medications recommended in the guidelines.

### Good

- 1 **Know the different inhaler types** and how they must be used.
- 2 **Remind** your patients who have asthma that adherence is life-saving.
- 3 **Involve parents and minors in counseling** beginning at an early age.

## APPENDIX: Basics of Inhalers

Proper inhaler technique is an essential aspect of asthma control. It may seem like a silly statement, but there are different kinds of inhalers and devices. Each inhaler requires patients to use specific inhalation techniques that deliver medications effectively. Some patients may have multiple inhalers, complicating their regimen and increasing the chance for error. Understanding the different types of inhalers highlights the importance of pharmacist counseling for patients who use inhalers. Below are explanations of the differences between using, cleaning, and storing a metered-dose inhaler (MDI), a dry powder inhaler (DPI), and a nebulizer. Pharmacy technicians can point out that every inhaler has an information sheet that a patient can find specific additional instructions. Technicians should encourage patients to read them.

### DPI<sup>58</sup>

The DPI contains pre-set doses of medications in powder form. The medicine is released into the airways with deep, fast breaths. The DPI may be easier than the MDI for patient use. However, patients with really low lung function or small children may not be able to generate enough inspiratory flow to effectively get the medications. Patients do not need to coordinate breathing and using the inhaler with a DPI.

- Instructions for use:
  - Open the cover. Hold the inhaler as shown on instructions.
  - Load a dose of medicine as shown in your instructions. Do not tip or shake the inhaler.
  - Stand or sit up straight.
  - Holding the inhaler away from your mouth, breathe out completely to empty your lungs.
  - Place the mouthpiece of the inhaler in your mouth. Close your lips around it to form a tight seal.
  - Take a fast, deep, forceful breath in through your mouth. Take as big of a breath as possible.
  - Hold your breath and count to 10.
  - Take the inhaler out of your mouth. Breathe out slowly.
  - If you need more than one puff, wait 1 minute between puffs. Repeat steps 2-8 for each puff.
  - When you finish close the cover. Store in a cool, dry place.
  - If the medicine is an inhaled corticosteroid, rinse your mouth with water and spit it out. This helps prevent infection.
  - Some multi-dose DPI have a built-in counter to tell you how many doses are left. When the counter gets to “0,” throw it away. Arrange your refill pick-up before it gets to 0.
- Instructions to clean the DPI
  - Wipe the mouthpiece at least once a week with a dry cloth
  - Do not use water to clean to DPI

### MDI<sup>59</sup>

The MDI is a canister of medication placed into an actuator inhalation mouthpiece. Every use of the MDI delivers the correct amount of medication.

- Instructions for use:
  - Take off the cap, shake the inhaler. Prime the inhaler (if needed)
  - If a spacer\* is used, place the inhaler in the rubber ring on the end of a spacer
  - Stand or sit up straight
  - Breathe out completely to empty your lungs
  - Place the mouthpiece in your mouth and close your lips around it to form a tight seal
  - While breathing in, press down firmly on the top of the canister to release one “puff,” or dose of medication. Take as big of a breath as possible, breathing in slowly for 3-5 seconds.
  - Hold your breath and count to 10.
  - Take the mouthpiece out of your mouth. Release your breath.
  - If you need more than one puff, wait 1 minute between puffs. Repeat steps 3-8 for each puff.
  - Put the cap back on the inhaler.
  - If the medicine is an inhaled corticosteroid, rinse your mouth with water and spit it out. This helps prevent infection.
- Important cleaning instructions:
  - Do not put the medicine canister in water
  - Do not brush or wipe the inside of the inhaler



A “spacer” is a tube or chamber that adds distance between the mouth and the canister of medication. The device increases the ease of administering medication.

## Nebulizers<sup>60</sup>

Nebulizers change liquid medication into an aerosol. Nebulizers come in both home and portable sizes. Nebulizers need a power source. They plug into a wall, have chargers, or need batteries replaced. Nebulizers take longer to use than MDI or DPI. They are also more laborious to use and store.

- Instructions for use:
  - Wash hands well.
  - Put together the nebulizer machine, tubing, medicine cup, and mouthpiece or mask as shown in instructions.
  - Put the prescribed amount of medicine into the nebulizer cup.
  - Place the mouthpiece in your mouth and close your lips around it to form a tight seal. If a child wears a mask, make sure it fits in snugly around the child’s face and covers their mouth and nose.
  - Turn on the nebulizer machine. You will be able to see a light mist coming from the back of the tube or from the mask.
  - Take normal breaths through the mouth until the medicine cup is empty or the mist stops. This should take about 10 minutes.
  - Take the mouthpiece out of your mouth (or the child’s mouth) and turn off the machine.
  - If the medicine is an inhaled corticosteroid, rinse your mouth with water and spit it out. This helps prevent infection. If a child uses a mask, wash the face as well.
- How to clean and store:
  - After each treatment
    - Wash hands well.
    - Wash the medicine cup and mouthpiece/ mask with warm water and mild soap.
    - Do not wash tubing.
    - Rinse well and shake off excess water.
    - Air dry parts on a paper towel.
  - Once a week:
    - Disinfect nebulizer parts to help kill any germs. Use the instructions that come with your device.
    - Do not wash or boil the tubing.
    - Air dry parts on a paper towel.
  - Between uses:
    - Store nebulizer parts in a dry, clean plastic storage bag.
    - If the same machine is used by more than one person, keep each person’s medicine cup, mouthpiece or mask, and tubing in a separate, labeled bag to prevent the spread of germs and medication errors.
    - Wipe surface with a clean, damp cloth as needed.
    - Replace parts as stated in the instructions or when they appear damaged.

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