**Goal:** The goal of this activity is to review the stepwise approach to the management of pediatric and adult asthma and the pharmacotherapies commonly used in asthma treatment.

After participating in this activity, the pharmacist should be able to:

- Explain the step-care approach to the management of asthma
- Discuss pharmacologic options for the management of asthma in adult and pediatric populations
- Discuss how pharmacists can identify and resolve adherence issues in patients with asthma
- Describe factors that contribute to health disparities in asthma care and ways to minimize these factors

**MtM essentials for asthma management: Part 2**

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**Abstract**

After asthma is diagnosed and the severity of asthma is determined, proper pharmacotherapy must be implemented to improve asthma control, reduce symptoms, and enhance the patient’s quality of life. Guidelines suggest the use of a stepwise approach to modify therapy as asthma control changes. The key maintenance therapy for patients of all ages with asthma is inhaled corticosteroids. All patients with asthma should also have access to a short-acting beta-agonist inhaler for quick relief of acute symptoms. Alternative therapies exist, although they are not generally preferred for the most optimal control. In addition to optimizing pharmacotherapy, pharmacists should work to promote adherence to medications and reduce health disparities in asthma management, which will lead to more widespread success of asthma control.
Managing asthma: A step-care approach

Initial pharmacotherapy selection is based on disease severity; modifications to therapy are based on disease control. Timely and ongoing assessment of control is important because current asthma control predicts future instability in asthma control and exacerbations. Therefore, the ultimate goal of asthma care is the achievement and maintenance of asthma control. This is accomplished by reducing both impairment and risk. Impairment is minimized by preventing chronic and troublesome symptoms, maintaining (near) normal pulmonary function, maintaining normal activity levels, using rescue medication no more than two days per week, and meeting the patient’s and family’s expectations and satisfaction with asthma care. Similarly, risk can be reduced by providing optimal pharmacotherapy with minimal adverse effects, preventing exacerbations that would require hospitalization, and preventing progressive loss of lung function. A patient’s level of asthma control (ie, well controlled, not well controlled, or poorly controlled) will help to guide adjustments to pharmacotherapy, so periodic assessment of disease control at one- to six-month intervals is critical. For a review of severity and control assessment, see “MTM essentials for asthma management: Part 1” in the April 2015 issue of Drug Topics.

National guidelines endorse a stepwise approach to the management of asthma (Figures 1-3). After asthma is diagnosed and the severity is assessed, the stepwise approach is used to determine which step of therapy should be initiated to correspond with the current level of asthma severity. The guidelines recommend starting with step 1, step 2, or step 3 in patients with intermittent asthma, mild persistent asthma, or moderate persistent asthma, respectively, regardless of patient age. Recommendations for treatment selection include both preferred and alternative therapies. Preferred medications refer to those that have consistent evidence from high-quality studies to support improvements in asthma control versus other therapies. Alternative therapies are usually reserved for those patients who have a contraindication to or cannot tolerate a preferred agent. The evidence supporting use of alternative therapies for asthma control is less robust. In patients aged five to 11 years, the medium-dose inhaled corticosteroid (ICS) option within step 3 is recommended over the other suggested preferred therapies within that step. The initial treatment of severe persistent asthma corresponds with step 3 in patients aged four years and younger and corresponds with step 3 or 4 in patients aged five to 11 years. In patients aged 12 years and older with severe persistent asthma, the guidelines suggest initiating treatment at step 4 or 5. For any patients beginning therapy for moderate or severe persistent asthma, clinicians should consider the addition of a short burst of oral corticosteroid therapy to help obtain prompt control of asthma symptoms.

For inadequately controlled asthma, a step-up approach is recommended to gain control. Conversely, a step-down approach is encouraged for patients with asthma that has been controlled for a sufficient period of time. For cases classified as well controlled, maintenance of the current treatment is advised, with routine follow-up occurring at one to six months. For cases that are not...
well controlled, the clinician should ensure that the patient has had good medication adherence, has used appropriate inhaler technique, and has maintained proper control of environmental triggers. In addition, if the patient is currently using an alternative therapy within the proper step, attempts should be made to change to the preferred therapy when possible. If the asthma is still not well controlled, pharmacotherapy should be adjusted by stepping up one step, with re-evaluation in two to six weeks. For very poorly controlled asthma, therapy should be stepped up by one or two steps. Treatment with a short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

A 25% to 50% ICS dose reduction every 3 months can be trialed as part of the step-down approach. To illustrate the use of the step-up approach, imagine you are a pharmacist conducting MTM for a 46-year-old woman with asthma. In speaking with your patient, you learn that she was recently diagnosed with mild persistent asthma. Two months ago, treatment with low-dose fluticasone was initiated (step 2), and your patient is also continuing to use the short-acting beta-2 agonist (SABA) rescue inhaler she was prescribed immediately after her diagnosis (step 1) (Figure 3). Today, she reports that she has had shortness of breath three times in the past week, causing nocturnal awakenings. Because of this, she has been using her SABA more regularly (estimated use, three times per week). She scores a 17 on the asthma control test (ACT). [Note: A score of 19 or less on the ACT indicates that asthma may not be as well controlled as it should be]. When asked, she denies any missed doses and is able to demonstrate proper inhaler technique. No other changes to her medication and/or health are noted, and she is currently on the preferred therapy within step 2 for a patient of her age. Based on her reported symptoms, the patient is showing evidence of impairment without risk. Her asthma is classified as not well-controlled, necessitating an adjustment in her therapy. Because her asthma is “not well-controlled” and not “very poorly controlled”, a one-step adjustment to step 3 is recommended. She should be re-evaluated within two to six weeks to reassess her asthma control.

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**STEPWISE APPROACH TO MANAGING ASTHMA IN CHILDREN AGED FOUR YEARS AND YOUNGER**

<table>
<thead>
<tr>
<th>Step 1 Preferred:</th>
<th>Step 2 Preferred: Low-dose ICS</th>
<th>Step 3 Preferred: Medium-dose ICS + either LABA or Montelukast</th>
<th>Step 4 Preferred: High-dose ICS + either LABA or Montelukast</th>
<th>Step 5 Preferred: High-dose ICS + either LABA or Montelukast</th>
<th>Step 6 Preferred: High-dose ICS + either LABA or Montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA PRN</td>
<td>Medium-dose ICS</td>
<td>step 2 care or higher is required.</td>
<td>Consider consultation at step 2.</td>
<td>Preferred:</td>
<td>Preferred:</td>
</tr>
<tr>
<td></td>
<td>Alternative: Cromolyn or Montelukast</td>
<td></td>
<td></td>
<td>Montelukast</td>
<td>High-dose ICS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral systemic corticosteroids</td>
<td>Oral systemic corticosteroids</td>
</tr>
</tbody>
</table>

**Patient Education and Environmental Control at Each Step**

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory infection: SABA q 4-6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
- Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term-control therapy.

**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; PRN, as needed; SABA, short-acting beta-agonist.

Notes available in the online version.

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Assessment of control can sometimes be challenging because of differences in patients’ and providers’ perceptions of control. A 2006 telephonic survey was designed to assess both asthma control among adult patients and knowledge and practices among providers actively involved in asthma management. For the purposes of this study, control was defined based on symptoms outlined in consensus guidelines. Of the 893 patients surveyed, 97% perceived their asthma to be well controlled, when in fact only 47% of cases were actually well controlled according to guideline criteria. Moreover, of the 463 providers studied, only 6% reported using clinical practice guidelines routinely, with an additional 33% reporting the use of these guidelines “most of the time.” These findings suggest a need to improve education regarding asthma control among patients with asthma and the providers who care for them.

**Treatment approaches for managing asthma in children and adults**

Treatment approaches for the management of asthma differ slightly among children and adults despite similar symptomatology. This is due in part to subtle and unique differences in the pathogenesis of asthma in children and adults. Asthma can develop at any phase of life, but the prevalence of asthma onset is highest among children of preschool age; approximately 50% to 80% of children with asthma will develop symptoms before age 5. Asthma is the leading cause of hospitalization among children. Children with asthma have more atopic disease with higher levels of serum IgE, whereas adult-onset asthma is commonly caused by genetic and environmental factors. Both patient populations, however, often present with comorbid allergic rhinitis. Classic asthma-related symptoms can be episodic in children yet persistent in adults. Additionally, asthma is often underdiagnosed in children, a problem that is further complicated by a lack of reliable objective measurements of lung function.

**Treatment in children.** The goal of asthma management in children is to maintain long-term control using the fewest medications possible at the lowest effective dose to minimize adverse drug events such as growth stunting. Daily long-term controller therapy can be initiated in infants and young children aged four years and younger who:

- Have experienced four or more wheezing episodes in the past year (lasting more than one day) that affected sleep AND have episodes in the past year (lasting more than two days per week for more than two days); OR
- Have required consistent symptomatic treatment more than two days per week for more than four weeks; OR
- Have had more than four weeks of symptoms per year; OR
- Have been hospitalized for asthma or had an asthma-related emergency department visit.

**Figure 2:** Stepwise approach to managing asthma in children aged five to eleven years.
■ Have experienced a second asthma exacerbation requiring systemic corticosteroids within the previous six months; OR
■ Have had periods of previously documented risk (eg, seasonal asthma).

For children aged five to 11 years, long-term daily controller therapy is recommended for those with documented persistent asthma.

Low-dose ICS remains the preferred initial treatment option for children of all age groups with persistent asthma (step 2). It is believed that the benefits of improved asthma control outweigh the potential (but small) risk of delayed growth seen with ICS. Clinical studies for the management of asthma in children aged four years and younger are limited; therefore, recommendations regarding medications other than low-dose ICS are based on expert opinion only. Similarly, many treatment recommendations for children aged five to 11 years are based on extrapolation from comparator trials in older children and adults. Full step-up recommendations for children are depicted in Figures 1 and 2.† Referral to an asthma specialist should be considered for children aged four years and younger who require step 3 or higher, as well as for patients aged five to 11 years who require step 4 or higher. To improve medication delivery, children are encouraged to use spacers and facemasks with inhaled therapy. Further information regarding inhalers and devices in asthma management will be presented in the August issue of this series.

**Treatment in adults.** As with asthma management in children, the goal of asthma treatment in patients aged 12 years and older is to achieve long-term control using the least amount of medications possible. Pharmacotherapy recommendations and preferences are shown in Figure 3.‡ Specific therapy needs to be tailored for individual patients. A long-term, daily controller medication with anti-inflammatory properties is the preferred therapy for the treatment of persistent asthma (step 2); ICS is preferred. Referral to an asthma specialist should be considered for patients requiring step 4 care or higher when the use of immunotherapy is being considered.† The guiding principles of stepping up or stepping down therapy apply across all age groups; however, several unique treatment issues must be considered when designing a care plan for older adults. Changes in physical dexterity and cognition can make use of an inhaler challenging, so more frequent assessment of adherence, environmental control, and comorbid conditions is needed. The initial recommendation for the treatment of persistent asthma (step 2) is ICS is preferred.
should be used and dose reductions may be necessary throughout treatment. Similarly, beta-agonists can precipitate cardiac effects such as tachycardia and tremor, and oral corticosteroids can cause changes in mental status or glucose metabolism. Pharmacists can help to identify, prevent, and resolve such medication-related problems.

All patients with asthma, regardless of age, should have a written asthma action plan as part of the management process. This allows patients to take an active role in self-management of asthma. The written plan should highlight information regarding the use of daily medications along with recognition and management of worsening asthma. Patients should be taught how to self-adjust their medications based on the presence of acute and/or alarming symptoms. Both peak-flow-based and symptom-based asthma action plans can be effective. The National Heart, Lung, and Blood Institute offers an asthma action plan template (available in both English and Spanish), which is available at http://www.nhlbi.nih.gov/health/resources/lung/asthma-action-plan. Asthma action plans should be re-evaluated and revised (if necessary) at each follow-up encounter.

Color-based “zones” are used in asthma action plans to categorize symptoms and offer treatment recommendations. A patient in the green zone is doing well and can perform usual activities without symptoms of asthma. Management for these patients includes the use of controller medications and SABAs as needed. For patients with exercise-induced bronchoconstriction (EIB), a SABA can be used five to 15 minutes before physical activity. Patients are in the yellow zone if they display symptoms of worsening asthma such as cough, wheeze, shortness of breath, nocturnal awakenings, or impairment in usual activities. These patients should be instructed to continue their green-zone medications and to use two to four puffs of a quick-acting SABA every 20 minutes for up to one hour during periods of worsening symptoms. Alternatively, one SABA treatment via nebulizer can be used in lieu of an inhaler. If the symptoms subside, patients should continue using their green-zone medications. If the symptoms do not improve and/or worsen after 1 hour of treatment, additional use of a SABA is recommended along with adding an oral steroid, usually for three to 10 days. Patients should call their healthcare professional shortly after taking the steroid. Patients in the red zone may exhibit severe symptoms including marked wheezing, shortness of breath, and an inability to speak or perform usual activities; these cases are medical emergencies. These patients should begin treatment immediately and call their healthcare provider. Treatment involves the use of rescue medications and an oral corticosteroid burst. If the treatment response is poor, the patient is advised to repeat the SABA treatment immediately and call 911.

Pharmacologic management of asthma

The NAEP EPR-3 suggests first-line preferred therapies for asthma control; these therapies should be used whenever possible. Within certain steps, there may be a suggested alternative, but clinicians should attempt to maintain the use of preferred therapies whenever possible.

**Beta-agonists.** Inhaled SABAs are the most effective therapy for reversing airway bronchoconstriction and are the drug of choice for rapid symptom relief in asthma, asthma exacerbations, and prevention of EIB. All patients with asthma should be prescribed an inhaled SABA to be used as needed for control of symptoms. As the drug of choice for the prevention of EIB, SABAs should be taken five minutes before the physical activity that causes asthma symptoms. Through the stimulation of beta-adrenergic receptors on the pulmonary smooth muscle, SABAs lead to bronchodilation in less than five minutes, with a duration of action of four to six hours.

Albuterol is the most common inhaled SABA used in asthma management and is available as a solution for nebulization and as a metered dose inhaler (MDI). The R-enantiomer of albuterol, levosalbutamol, is also available as a nebulizer solution and MDI; this formulation may be associated with fewer side effects (including tachycardia), although the data are inconclusive.

Patients who may benefit from levosalbutol over albuterol include those with asthma and concurrent cardiovascular disease, especially conditions that could potentially worsen with tachycardia such as decompensated heart failure or poorly controlled arrhythmias.

Both albuterol and levosalbutol MDIs, when used as rescue inhalers, are typically dosed at two puffs every four to six hours as needed, although levosalbutol is not indicated for children aged younger than five years. The dose of SABA used in acute exacerbations is higher and can reach four to eight puffs every 20 minutes for four hours in patients aged 12 years and older. Higher doses of SABA may be needed to relieve acute asthma symptoms if patients are also taking a nonselective beta-blocker (NSBB), although NSBBs should generally be avoided in asthmatics.

SABA side effects are dependent on dose and route of administration, with few systemic side effects when the usual doses are delivered through the inhaled route. The most common side effects of inhaled SABAs include skeletal muscle tremor, nervousness, cough, rhinitis, and dry mouth. Patients with cardiovascular disease, especially those of advanced age, may have cardiovascular adverse events with inhaled therapy.

The long-acting beta-agonists (LABAs) salmeterol and formoterol are adjunctive maintenance therapies used for asthma management in patients aged five years and older; there is a lack of clinical trial data regarding the use of LABAs in children aged younger than five years. LABAs improve lung function, reduce SABA requirements, and increase the number of symptom-free days. However, because of a risk of asthma-related deaths with these agents, LABAs are not indicated as monotherapy without an ICS in patients with asthma and carry a black-box warning for this reason. This warning is based on the results of the Salmeterol Multicenter Asthma Research Trial (SMART), which was terminated prematurely because of an interim analysis that found increased respiratory and asthma-related deaths in patients randomized to salmeterol versus those randomized to placebo. African American patients, especially those who were not taking ICSs at enrollment, were at the highest risk. Several hypotheses for this increased risk have been proposed, including direct car-

**Pause & Ponder**

In your daily practice, how can you help patients with asthma to achieve control of the condition?
dioxic effects of LABAs, genetic polymorphisms increasing the risk of adverse effects from LABAs, and the potential masking effect of LABAs on inflammation. As such, the Food and Drug Administration suggests that LABA use without an ICS is contraindicated in asthma patients. Once asthma control is achieved with the addition of a LABA to ICS, stepping down therapy to remove the LABA should be considered when possible. Clinicians should consider prescribing inhalers with combinations of a LABA and an ICS to avoid a scenario in which a patient may discontinue an ICS but continue taking a LABA. Examples of such inhalers include fluticasone and salmeterol Diskus or MDI, budesonide and formoterol MDI, and mometasone and formoterol MDI.

The onset of action of salmeterol is within 30 minutes, and the onset of action of formoterol is similar to that of albuterol. Despite their relatively quick onset of action, LABAs are not indicated for acute exacerbations. Both LABAs have a duration of action lasting 12 hours and are dosed twice daily. Because LABAs are more selective and lipophilic than albuterol, exposure outside of the lungs is reduced and systemic side effects are rare.

Corticosteroids. ICSs are the mainstay of therapy in the management of persistent asthma and are always preferred over other alternative therapies, for all age categories, because of the central role inflammation plays in the pathophysiology of asthma. ICSs improve symptom control and quality of life, improve measures of lung function, reduce airway hyperresponsiveness, and reduce the need for systemic steroids, emergency room care, hospitalizations, and asthma-related deaths. Currently, there are six ICSs marketed for asthma treatment: budesonide, beclomethasone, flunisolide, fluticasone, ciclesonide, and mometasone. These corticosteroids are equally efficacious when dosed at equipotent doses; ICSs are not equivalent on a puff-per-puff basis. Figure 18 in the NAEPP EPR-3 guideline specifies the doses for each marketed ICS that are considered “low,” “medium,” and “high” for each age category, corresponding to the stepwise approach for asthma management. Ciclesonide does not appear in Figure 18 of the NAEPP EPR-3 because its approval proceeded the latest guidelines. As it is approved for use in patients 12 years and older, based on clinical studies the suggested low, medium and high dose is 160-320 mcg, >320-640 mcg, >640 mcg, respectively. Pharmacists are encouraged to refer to the guidelines whenever checking ICS dosages to ensure that the prescribed dose is meeting the desired step and that when a change in dose is made, the change is sufficient to move along the stepwise approach. For example, in a patient aged five to 11 years, a low dose of fluticasone MDI is considered to be 88 to 176 mcg per day. Increasing to a medium dose would require achieving a total daily dose of greater than 176 to 352 mcg, and increasing to a high dose would require achieving a daily dose greater than 352 mcg. For a child currently at a low dose of fluticasone (using a 44-mcg inhaler and taking one puff twice daily [88 mcg per day]) who required a step up to a medium dose, simply increasing the regimen to two puffs twice daily (176 mcg per day) would increase the total daily dose but not to the amount required to be considered a medium dose. Two ICSs—budesonide and fluticasone—have doses recommended by the guidelines for children as young as one year of age, and budesonide is available as a nebulizer solution.

Patients should be advised to allow at least two weeks for the onset of ICSs to be noted, with upwards of four to six weeks of treatment required before full effects are seen. ICSs have a flat dose-response curve; therefore, less benefit is achieved when increasing the dose compared to the benefit seen when first initiating treatment. Common side effects of ICSs include cough, dysphonia, and oral candidiasis. The use of a valved holding chamber can reduce the deposition of ICS particles into the oropharynx and minimize these side effects. Sys stemic side effects are rare when low- and medium-dose ICSs are used, although high doses of ICSs may lead to systemic adverse events such as adrenal suppression, osteoporosis, skin thinning, and easy bruising. A decline in growth velocity has been noted in children using even low doses of ICSs, but the guidelines state that the clinical implications of such findings have not been established. More recent studies support the slower growth velocity observed in children using ICS. However, the greatest impact occurs within the first year of ICS use, is not cumulative, and expert opinion believes this risk to be small relative to the large benefit ICSs are known to have on overall asthma outcomes.

Fluticasone, budesonide, and mometasone are substrates of CYP3A4, so when these agents are used at high doses concurrently with a strong CYP3A4 inhibitor, systemic exposure may increase, and cases of Cushing syndrome and secondary adrenal insufficiency have been reported.

Systemic corticosteroids, including prednisone, methylprednisolone, and prednisolone, are primarily used during asthma exacerbations and for acute symptom control when a patient is unresponsive to LABAs. When short-term control is needed, the NAEP EPR-3 suggest a dose of 1 to 2 mg/kg/day with a maximum of 60 mg/ day for three to ten days in patients aged younger than 12 years and a dose of 40 to 60 mg/day as a single dose or two divided doses for three to ten days in older patients. Asthmatics with the most severe persistent category of disease may require daily steroid therapy for long-term control; in these cases, the daily dose should be the lowest dose possible to maintain control but also to minimize the long-term consequences of systemic steroid exposure. Systemic exposure in the short term can lead to glucose dysregulation, increased appetite, fluid retention, mood changes, and peptic ulcer disease. Long-term consequences include adrenal axis suppression, growth suppression, dermal thinning, hypertension, Cushing syndrome, cataracts, muscle wasting, and, rarely, impaired immune function.

Leukotriene receptor modifiers. Leukotriene receptor modifiers are orally dosed therapies represented by two classes: the 5-lipoxygenase inhibitor zileuton and the direct leukotriene antagonists montelukast and zafirlukast. Leukotriene receptor modifiers are significantly less effective than ICSs and for this reason are used as an alternative maintenance therapy (not preferred) or alternative adjunctive therapy in addition to ICS in place of LABA in asthma care. Montelukast is indicated for the treatment of asthma in patients aged as young as one year and has several advantages over other drugs in this class. Montelukast is available in multiple dosage forms; chewable tablets for children as young as 2 years, granules for children as young as 12 months, and film-coated tablets for patients 15 years of age.
and older. Montelukast is dosed once daily at bedtime without regard to food, is free from clinically significant drug interactions, and also has approval for use in EIB and seasonal allergic rhinitis. Zileuton and zafirlukast require monitoring of liver function tests because of a risk of hepatotoxicity; additionally, both of these medications are dosed twice daily, zafirlukast with food. Zafirlukast is also an inhibitor of CYP2C9. The guidelines state that zileuton is a less desirable choice in this class because of a lack of efficacy data and the aforementioned disadvantages. Pharmacists should be aware of the risk for neuropsychiatric events with this class of medications and should counsel patients who experience adverse effects to contact their prescribers. 

Mast cell stabilizers. Cromolyn is a mast cell stabilizer available as a nebulizer solution and as an MDI that can be used as an alternative maintenance therapy in cases of mild persistent asthma. This agent can be used in children aged as young as two years and is generally considered benign, aside from a risk of cough and mouth irritation, and free from drug interactions. The onset of action is at least two weeks; this delayed onset of action and a dosing regimen of four times per day are less convenient than other options and have led to the infrequent clinical use of this medication. Cromolyn is also indicated, although not preferred, for the prevention of EIB and can be used prophylactically upon unavoidable exposure to known allergens.

Anticholinergics. Ipratropium, available as an MDI and as a nebulizer solution, is indicated as an alternative rescue medication for patients with an intolerance to SABAs. Ipratropium causes bronchodilation through antagonism of muscarinic receptors in the bronchial smooth muscle. The onset of action is slower than albuterol (30 minutes), although the duration of action is longer (four to eight hours). In cases of moderate to severe asthma exacerbations requiring emergency room care, the addition of ipratropium to albuterol decreases hospitalization rates. The most common side effect of ipratropium is dry mouth, but patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction are at risk of symptom worsening. Additionally, in patients with chronic obstructive pulmonary disease, ipratropium may increase cardiovascular risk.

Methyloxanthines. Theophylline is a mild to moderate bronchodilator that may have mild anti-inflammatory properties. Sustained-release theophylline, an oral dosage form, is recommended by the guidelines as an alternative treatment in patients 5 years of age and older with mild persistent asthma (step 2) or as an alternative adjunctive therapy in addition to ICS (steps 3 and higher), although this medication is not preferred. The overall adverse effects profile, narrow therapeutic window, variety of potential drug interactions via CYP isoenzymes, and need for serum monitoring with this medication have led to the infrequent use of theophylline in contemporary asthma management. Theophylline’s half-life is also variable depending on various patient characteristics such as age, liver function, and smoking status, making proper dosing more complex. The guidelines suggest that serum theophylline concentrations (target of 5 to 15 mcg/mL) should be measured at least three to five days after therapy is initiated and should also be obtained in the middle of the dosing interval. If patients experience signs of theophylline toxicity (severe headache, tachycardia, nausea, and vomiting), the serum concentration should be assessed immediately.

Immunomodulators. Omalizumab is an anti-IgE monoclonal antibody that prevents the binding of IgE to receptors found on mast cells, dendritic cells, and basophils and subsequently interferes with the allergic response cascade that ultimately leads to asthma symptoms. Omalizumab is also implicated in the down-regulation of IgE receptors. Omalizumab is indicated for patients aged 12 years and older with moderate to severe persistent asthma inadequately controlled on corticosteroids and with a positive skin test or in vitro reaction to a perennial allergen. The NAEPP EPR-3 guidelines suggest the use of omalizumab as a maintenance therapy in steps 5 and 6 for patients aged 12 years and older. Omalizumab is a subcutaneous injection that is dosed at 150 to 375 mcg every two to four weeks according to patient weight and pretreatment IgE levels. The most common adverse reactions to this medication include arthralgia, general pain, leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatis, and earache. There is a 0.2% risk of anaphylaxis associated with this drug that can occur after the first dose or well into therapy, and therefore omalizumab should be administered in an environment that is able to handle such reactions safely. Patients should be observed for a reasonable period of time after injection, as cases of anaphylaxis have been seen as late as two hours after the dose.

Promoting adherence to asthma medications

Achieving and maintaining asthma control remain suboptimal despite advances in pharmacotherapy and inhaled delivery systems. One barrier is poor medication adherence, most notably to controller medications. Many patients may choose not to take their asthma medication because of their perception that it is not necessary and/or because of a fear of unwanted side effects. Other factors influencing medication adherence include disease severity, previous experiences with medication, health beliefs, understanding of the disease, and complexity of the regimen. Nonadherence to therapy is widespread; estimated adherence rates range from 30% to 70%, with most studies showing rates of less than 50%. Nonadherence has serious implications, including airway obstruction, impaired quality of life, and greater healthcare utilization leading to increased healthcare spending. Because of this, current practice guidelines state that efforts should be made to assess medication adherence at each point of patient contact. A multidisciplinary, team-based approach to care is recommended to address medication adherence. Pharmacists are highly accessible and adequately trained to assist with asthma care, and previous pharmacist-led initiatives regarding medication management have led to improvements in patients’ ACT scores, asthma-related quality of life, inhaler technique, and medication adherence.

Nonadherence to asthma medication varies and may present as a failure to fill
a prescription, overuse of rescue medications, underuse of controller medications, erratic use of medication, and/or premature discontinuation of therapy. Nonadherence is often further delineated as intentional or unintentional. Unintentional, or nondeliberate, adherence refers to failure to adhere to the treatment plan because of factors that are often beyond the patient’s control. These factors may include forgetfulness, poor inhaler technique, poor understanding of provider instructions, and inability to obtain the medication (because of either cost or availability). Intentional, or deliberate, nonadherence occurs when the patient makes a conscious decision not to take a medication or to alter the way in which a medication is taken despite receiving medical advice to the contrary. Being able to differentiate between these types of nonadherence is essential to best determine which interventional strategy is needed. Motivational interviewing is encouraged to address intentional nonadherence. For a full review of motivational interviewing techniques, please refer to the article “Motivational interviewing techniques for chronic disease management” in the October 2014 issue of *Drug Topics.* Unintentional nonadherence requires targeted interventions based on patient-specific factors. *Table 1* offers practical solutions for improving asthma medication adherence. Regardless of the strategy employed, pharmacists should focus on the positive benefits of adherence rather than the negative consequences of nonadherence. Pharmacists can also assist with preventing nonadherence by determining which patients are at high risk for nonadherence. Using software applications, pharmacists can scan dispensing and refill histories to generate a list of patients who have been overfilling rescue inhalers or underfilling controller medications. This can help to identify gaps in care and lead to care coordination with other healthcare professionals. Other methods to detect poor adherence include frequent assessment of inhaler technique and routine counseling about the medication regimen. Asthma disproportionately affects racial and ethnic minorities and low socioeconomic populations in the United States. The prevalence of asthma is 25% higher in children of American Indian or native Alaskan descent, 60% higher in African American children, and 140% higher in Puerto Rican children compared with asthma prevalence in white children. In these subgroups, quality of and access to care is often lower and the exposure to environmental triggers is higher than in the rest of the population. Mortality related to asthma is eight-fold higher in non-Hispanic black children compared to their white counterparts. The first step in addressing health disparities in asthma care is to recognize their existence. The Guideline Implementation Panel for the NAEP EPR-3 has made several recommendations as to how health disparities in asthma can be reduced. Pharmacists are well trained and positioned to implement many of these recommendations. Patient education to increase awareness of asthma and to improve asthma control, especially in low economic and racial/ethnic minority populations, is a central intervention to reduce health disparities in asthma. Patient education material should be available in the appropriate languages and should be sensitive to cultural practices. Clinicians are encouraged to undergo cultural competency training and to provide culturally and linguistically appropriate care through effective communication. Translator services should be available when needed to facilitate communication. Home visits and educational seminars open to the community can enhance self-management and awareness of asthma, and payors should reimburse clinicians to facilitate the provision of such services. Improvement in the coordination of care across providers and settings, such as the primary care provider, pulmonologist, and a child’s school, is encouraged. Additional recommendations include provision of home inspections and assistance to low-income or racial/ethnic minority households to minimize exposure to environmental triggers and to strategically place schools and residences away from major sources of air pollution. Last, quality improvement measures within healthcare facilities targeted toward asthma management are encouraged, as is surveillance of disparities within healthcare facilities.

### Conclusion

The burden of uncontrolled asthma is significant. Asthma-related hospitalizations and impairments in quality of life continue to affect those diagnosed with the disease and the healthcare system at large. Successful asthma management therefore centers on achieving and maintaining symptom control. Assessment of asthma control requires timely and frequent evaluation with appropriate modifications to pharmacotherapy as recommended in clinical practice guidelines. Medication adherence also

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**Table 1: Interventions to Improve Medication Adherence**

<table>
<thead>
<tr>
<th>Cause of nonadherence</th>
<th>Suggested interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgetfulness</td>
<td>• Encourage the use of memory aids, reminders, cues, and feedback</td>
</tr>
<tr>
<td></td>
<td>• Offer pharmacy refill programs</td>
</tr>
<tr>
<td>Complexity of medication regimen</td>
<td>• Simplify the medication regimen (eg, combination therapy)</td>
</tr>
<tr>
<td></td>
<td>• Tailor the regimen to the patient’s needs and/or situation</td>
</tr>
<tr>
<td>Cost of medication regimen</td>
<td>• Use generic medications</td>
</tr>
<tr>
<td></td>
<td>• Use prescription assistance programs</td>
</tr>
<tr>
<td></td>
<td>• Use drug discount coupons</td>
</tr>
<tr>
<td></td>
<td>• Simplify the medication regimen</td>
</tr>
<tr>
<td>Inappropriate technique</td>
<td>• Provide patient education</td>
</tr>
<tr>
<td></td>
<td>• Frequently assess inhaler technique</td>
</tr>
<tr>
<td></td>
<td>• Use a spacer</td>
</tr>
<tr>
<td>Other</td>
<td>• Use a shared decision process</td>
</tr>
<tr>
<td></td>
<td>• Monitor adherence</td>
</tr>
<tr>
<td></td>
<td>• Implement self-management programs with educational and behavioral components</td>
</tr>
<tr>
<td></td>
<td>• Offer multidisciplinary care with a common message</td>
</tr>
</tbody>
</table>

*Source: Ref 20, 27*
2. Which of the following illustrates an example of risk reduction as it relates to asthma control?
   a. Using a short-acting rescue inhaler < 2 days/week
   b. Preventing progressive loss of lung function
   c. Maintaining near-normal pulmonary function
   d. Minimizing chronic troublesome symptoms

3. When should a patient with poorly controlled asthma for whom therapy has been adjusted follow up for reassessment of asthma control?
   a. One month
   b. Six months
   c. Two weeks
   d. Two to six weeks

4. Which of the following statements regarding pediatric and adult asthma is TRUE?
   a. Objective measurement of lung function (eg, spirometry) is often unreliable in children.
   b. The prevalence of asthma is highest in adults aged 45 to 65 years.
   c. Asthma symptoms are chronic in children.
   d. Asthma is the leading cause of hospitalizations in adults.

5. What “zone” is a patient in if he or she can perform usual activities without exhibiting symptoms of asthma?
   a. White zone
   b. Green zone
   c. Yellow zone
   d. Red zone

6. How many months should asthma be controlled before therapy is stepped down?
   a. At last one month
   b. At least three months
   c. At least six months
   d. At least one year

7. Which of the following factors is least likely to contribute to nonadherence of asthma medications?
   a. Fear of unwanted side effects
   b. Regimen complexity
   c. Lack of understanding of disease severity
   d. Comorbid cardiovascular disease

8. Which of the following interventions would be best for a patient who does not take his or her asthma medication because he or she “doesn’t feel like it”?
   a. Simplifying the medication regimen
   b. Setting an alarm to alert when it is time for the next dose
   c. Using motivational interviewing techniques
   d. Referring the patient to a asthma specialist

9. Classify the level of asthma control for a 25-year-old patient with the following: ACT score of 12; rescue inhaler use four times/day; some limitation with usual activities.
   a. Well controlled
   b. Not well controlled
   c. Very poorly controlled
   d. Medical emergency

10. Which of the following statements is TRUE regarding asthma management?
    a. Initial pharmacotherapy selection is based on control; adjustments are based on severity.
    b. The preferred treatment option for persistent asthma is inhaled corticosteroids for adults and long-acting beta-agonists for children.
    c. Treatment recommendations for all age groups are based on randomized control trials.
    d. At minimum, asthma control should be assessed at one- to six-month intervals.

11. Which of the following therapies is the treatment of choice for exercise-induced bronchoconstriction?
    a. Albuterol
    b. Ciclesonide
    c. Ipratropium
    d. Fluticasone

12. Which of the following drug therapies is considered a preferred therapy for persistent asthma in patients aged 12 years and older?
    a. Budesonide
    b. Omalizumab
    c. Montelukast
    d. Trexophylline

13. A common side effect of albuterol is:
    a. Arrhythmias
    b. Chest pain
    c. Dry mouth
    d. Hyperglycemia

14. ________ carries a black-box warning advising patients not to use the drug as monotherapy in asthma without an inhaled corticosteroid.
    a. Ipratropium
    b. Salmeterol
    c. Levalbuterol
    d. Omalizumab

15. Omalizumab is best described as:
    a. A leukotriene receptor modifier
    b. An anti-IgE monoclonal antibody
    c. An anticholinergic
    d. A long-acting beta-agonist

16. Which of the following leukotriene receptor modifiers is least likely to be involved in clinically significant drug interactions?
    a. Zileuton
    b. Montelukast
    c. Zafirlukast
    d. None of the above

17. An alternative rescue inhaler in patients who cannot tolerate the first-line SABA therapy is:
    a. Albuterol
    b. Salmeterol
    c. Formoterol
    d. Ipratropium

18. A standard adult dose of prednisone for a short “burst” of therapy is:
    a. 40 mg by mouth daily for five days
    b. 80 mg by mouth daily for three days
    c. 10 mg by mouth daily for 15 days
    d. 30 mg by mouth daily for seven days

19. Health disparities in asthma are found in which of the following populations?
    a. Caucasians
    b. Pregnant women
    c. African Americans
    d. High-income societies

20. Which intervention(s) could be implemented to help reduce health disparities in asthma?
    a. Improve community awareness of asthma
    b. Provide translator services during clinician visits
    c. Conduct surveillance of health disparities
    d. All of the above
References


