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Over-the-Counter Epinephrine for Asthma Treatment: Too Much Risk for Too Little Benefit

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Asthma is a reactive airway disorder typified by wheezing, cough, and shortness of breath impacting ≈25 million people in the United States.[1] Putting the prevalence in perspective, ≈1 in 13 individuals in the United States carries a diagnosis of asthma with rates varying on the basis of patient age as well as racial and socioeconomic factors.[1] Historically, asthma treatment follows a step approach, starting with short-acting β agonists followed by escalation to a long-acting β agonist/steroid combination intermittently supplemented with oral corticosteroids as needed to attain disease remission. Before 2019, pharmacotherapy recommendations[2,3] suggested that patients with asthma have access to a short-acting $\beta 2$ agonist inhaler (commonly albuterol) for the treatment of acute symptoms, as this intervention alone was deemed appropriate for patients with intermittent asthma, defined as symptoms occurring less than twice weekly with (near) normal pulmonary function.[4] For patients with persistent asthma (defined as symptoms more than twice weekly or abnormal pulmonary function), daily maintenance with an inhaled corticosteroid (ICS) is generally appropriate.[4] The initial choice of medication was directed by severity of asthma classification (intermittent, mild, moderate, or severe persistent) at time of diagnosis.

However, updated 2022 guidelines promulgated by the Global Strategy for Asthma Management and Prevention Program (GINA) suggest a revised step therapy approach to asthma pharmacotherapy management. GINA 2022 recommends that patients with mild-intermittent asthma start therapy with an ICS-long acting β agonist combination (ICS-LABA).[5] Importantly, as-needed short-acting albuterol or its congeners as monotherapy is discouraged.[5,6] During periods of adequate asthma control, patients may be maintained with an ICS-LABA inhaler replacing albuterol as a rescue inhaler.[5] For patients with moderate or severe asthma, the ICS-LABA combination is considered both a maintenance (daily) and rescue treatment, with extra inhalations taken for breakthrough asthma symptoms as needed. Higher-dose ICS may be required in patients with more severe asthma with new therapy guidelines including use of anti–thymic stromal lymphopoietin biologics.[5] Guidelines recommend that albuterol inhalers are to be avoided entirely, although recommendations do not advise against albuterol as an add-on reliever therapy based on clinical discretion.[5,6]

Alarmingly, despite well intended GINA recommendations and ramifications of improper disease assessment and management, over-the-counter (OTC) asthma treatment options remain available for unrestricted and unsupervised public use. In November 2018, the US Food and Drug Administration (FDA) approved OTC Primatene Mist (Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, California), an epinephrine metered-dose inhaler (MDI), for the treatment of mild intermittent asthma in patients aged ≥12 years. This product reintroduction includes a hydrofluoroalkane-based MDI that replaces a chlorofluorocarbon-based MDI previously marketed with the same name, which was withdrawn due to the presence of a chlorofluorocarbon propellant. OTC

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epinephrine mist joins racepinephrine, a racemic mixture of epinephrine, as the only 2 OTC inhalers available for asthma treatment. Racepinephrine includes both the L (−) enantiomer, considered the biological active form of epinephrine and the D (+) form, which has relatively weak activity.[7] However as with epinephrine mist, examination of the effectiveness of racepinephrine for asthma treatment found the product to be far less effective than albuterol in treating asthma, even at 4 times the recommended OTC dose.[8] A similar sympathomimetic amine, ephedrine was banned in 2004 for use as a diet aid or in sports training; however, despite safety concerns resulting in removal of the drug for diet and sports use, the drug remains available as an OTC product for the treatment of asthma.[9] The Primatene brand is also marketed as a tablet dosage form that includes both ephedrine and guaifenesin for relief of chest tightness and wheezing due to asthma. Unfortunately, despite guidelines promulgated by GINA, it is suspected that the public wrongly perceives OTC inhaled epinephrine and its congener products as appropriate and effective pharmacotherapy for all forms of asthma, both chronic and acute, likely due in part to highly effective marketing by the manufacturer.[10] Compounding the danger of OTC inhaled epinephrine use, inhaled medications are rapidly absorbed systemically in a dose-dependent manner with all inherent and untoward risks associated with parenteral administration similar to topical ophthalmic dosage forms.[11,12] Therefore, toxicity risk with inhaled epinephrine mist may be significant, particularly in susceptible individuals such as the elderly or those with cardiac arrhythmia.[13]

Importantly, soon after approval of Primatene Mist in 2018, the American Lung Association responded to the FDA, stating that "the new version of the asthma inhaler Primatene Mist," recently approved by the FDA, will offer suboptimal care for the treatment of asthma.[14] The National Asthma Education and Prevention Program, an expert panel convened by the National Institutes of Health, recommends against the use of epinephrine for treatment of asthma exacerbations, recognizing "that it has the potential for undue cardiac stimulation."[15] Of further note, the American Thoracic Society has published statements of alarm regarding FDA approval of OTC epinephrine mist for asthma treatment.[16]

Despite pushback from the medical community, sales of Primatene Mist increased 186% in 2021 to $51.7 million according to industry analysis.[17] These impressive sales figures lend to the notion that Primatene Mist and similar OTC products are effective and important aspects of asthma management.[10] This is a dangerous view and signifies underlying roadblocks precluding appropriate management of asthmatics in part due to either lack of provider access, patient noncompliance, and/or lack of access to inappropriate prescription medications. Scenarios may arise in which patients who are not able to obtain refills for their prescription asthma medication may turn to OTC epinephrine in the belief the product is an appropriate asthma treatment. One reason for poor adherence with prescription inhaled asthma therapies may simply rest with the patients' inability to correctly gauge sufficient volume of drug on hand. Estimating the volume of medication remaining in an inhaler can be challenging, and when combined with circumstances in which a patient is experiencing an acute disease exacerbation in the setting of an empty inhaler with no medication refills, patients will resort to availability of subtherapeutic OTC alternatives with risk of toxicity due to inability to control symptoms with repeated inhalations.[18] Although epinephrine is a life-saving treatment option in conditions such as anaphylaxis, inhaled OTC epinephrine and its congeners have no rational place as a legitimate pharmacotherapeutic entity for asthma therapy.[15,19]

American College of Clinical Pharmacology Call to Action

As pharmacists become more involved in direct outpatient care and chronic disease management, it is time to discuss a greater role for pharmacists in the management of patients with noncomplicated asthma. Following initial diagnosis, drug treatment for asthma could be managed by accredited pharmacists who would oversee pharmaceutical care strategy for patients with asthma by providing required prescription medication refills. Pharmacists are widely accessible local health care providers with 24-hour availability to assist patients and providers in the guidance of appropriate pharmacotherapy. Being local to the patient and nearly always immediately available, pharmacists can provide prompt, effective drug therapy without undue delay. Alternatively, consideration should be given to replacing inhaled OTC epinephrine with inhaled OTC albuterol, a widely studied and effective pharmacotherapeutic agent well known for its benefit as a rescue medication.[10] The American College of Clinical Pharmacology joins with the following organizations in reexamining mechanisms for the delivery of asthma-related pharmacotherapy that precludes the use of inappropriate OTC products and maximizes pharmacist involvement for the optimization of patient outcomes.

Advocacy Council of the American College of Allergy, Asthma & Immunology; Allergy and Asthma Foundation of America; Allergy and Asthma Network; American Academy of Allergy, Asthma & Immunology; American Academy of Otolaryngic Allergy; American Academy of Pediatrics; American

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Association of Respiratory Care; American College of Allergy, Asthma and Immunology; American College of Chest Physicians (CHEST); American Lung Association; American Thoracic Society; and Society of Critical Care Medicine.

Conflicts of Interest

The opinions expressed in this article are those of the authors on behalf of the American College of Clinical Pharmacology and should not be interpreted as the position of the entities or institutions at which the authors are employed.

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All data and information are publicly available through the references.

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