

The long-acting β -adrenergic agonist controversy in asthma: Troublesome times!

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The quote from Shakespeare's *Macbeth*, "Double, double toil and trouble; / Fire burn, and cauldron bubble," captures the quagmire faced by many clinicians today when deciding on how to appropriately, effectively, and safely use long-acting β -agonists (LABAs) in the care of asthma. Should they be avoided altogether, used only in patients with the most severe disease, be the first or the last asthma medication withdrawn when control of asthma is achieved, or be continued as long as the patient's asthma is well controlled?

This commentary is written at the request of the Board of Directors for the American Academy of Allergy, Asthma & Immunology to briefly review the overall issues currently surrounding LABA use but, most specifically, to comment on a component of these discussions, the US Food and Drug Administration (FDA)'s recommendations to step down LABA use once asthma control has been achieved. In this regard we acknowledge our roles as members of the Expert Panel for the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program (NAEPP)'s "Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma"¹ and as respective Chairs of the Pediatrics and Joint Adult Steering Committees for the ongoing FDA-required

Long-Acting β -adrenergic Agonist Study.² However, the opinions rendered in this commentary represent our own thoughts and not those of any of the committees on which we currently serve nor of the NAEPP's EPR-3 or the American Academy of Allergy, Asthma & Immunology.

β -agonists are potent, effective, and, in short-acting formulation (short-acting β -agonists [SABAs]), an integral part of asthma care for the treatment and quick relief of acute symptoms. With the development of LABAs, clinicians have available potent β -adrenergic agonists with 12 hours of bronchodilation. Furthermore, when LABAs are added to ICSs, the additive benefits are striking, with improved bronchodilation, enhanced symptom control and prevention, and fewer asthma exacerbations.³ With β -adrenergic agonists and asthma, however, the story is often not always straightforward.

SABAs have been a mainstay of effective asthma symptom treatment for decades and continue to hold this position.^{1,4} In general, SABAs have been safe, but there have been bumps in the therapeutic road they traveled. Isoproterenol-forte was an extremely potent, broad-acting β -agonist. In fact, it was too potent; deaths, presumably cardiac in origin, led to its withdrawal, and consequently, asthma mortality rates returned to pre-isoproterenol-forte levels.⁵ Fenoterol appeared in the 1980s, and with its use on a regularly scheduled basis, asthma deaths mysteriously increased.⁶ Fenoterol is no longer available, and asthma morbidity and mortality decreased once it was withdrawn from use. Subsequent clinical trials with SABA formulations other than fenoterol revealed that regular use of SABAs neither produces harmful effects nor provides benefit.⁷ However, increasing use of SABAs, including albuterol, was associated with increased risk of asthma morbidity and mortality, perhaps as a marker of asthma severity or worsening long-term asthma control.⁸⁻¹⁰ These studies led to recommendations that SABAs should not be used on a regularly scheduled daily basis and that increasing use of SABAs should be considered an indication of poorly controlled asthma, requiring an initiation of or increase in anti-inflammatory therapy. The important role of SABAs in providing quick relief of symptoms, treating acute severe exacerbations, and preventing exercise-induced bronchospasm has not been changed.

LABAs joined the β -agonist family of bronchodilators and produced striking and consistent effects when used in combination with ICSs.¹¹ The use of combination LABA/ICS products in a single inhaler has enabled more convenient drug delivery and advanced the effective care for many patients with asthma. However, safety issues surfaced early in some trials with LABAs, particularly in patients with more severe disease and especially, or possibly exclusively, when LABAs were used in the absence of ICSs.¹² Differences in the interpretation of the safety data on LABAs have been at the center of a controversy in the United States for some time now. Both clinicians and patients are confused as to where and how to use LABAs safely in the treatment of asthma.

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For the past 20 years, concern has been raised by the FDA regarding the safety of LABAs in asthma management.^{2,13} This concern has been presented in previously published reviews, including those from the FDA, and is primarily based on 2 post-marketing studies of salmeterol conducted in the United Kingdom and the United States that were designed to evaluate safety in large populations of adults with asthma.^{12,14} A small but statistically significant increase in the number of deaths was noted in these early studies in the salmeterol treatment arms.^{12,14} This observation prompted an ongoing series of warnings from the FDA designed to reduce the use of LABAs to limit concern regarding the risk of LABA-associated deaths.^{2,13}

A recent publication by Chowdhury and Dal Pan¹³ provided recommendations for changes for LABAs in product information that has since been incorporated into product labeling. Although some of the recommendations have been accepted by clinicians, others are considered inconsistent with guideline recommendations and not readily adaptable in clinical practice.

In particular, the recommendation to step down LABA use when asthma control is achieved is controversial. This concern has been substantiated by the recent publication of a systematic evidence review that noted the adverse consequences of LABA step-down in patients with controlled asthma.¹⁵ The purpose of our editorial is to briefly summarize the major issues and, more importantly, to provide clinicians with approaches to consider when considering stepping down treatment once patients have achieved and maintained asthma control and are using combination ICS/LABA therapy.

CLINICAL PERSPECTIVE

Clinicians recognize that the safety concerns identified from early LABA studies were found in trials that were conducted primarily in adult participants and were likely based on LABA monotherapy without clear information on concomitant therapy. These studies were noted to have design limitations that raised concerns as to whether concomitant ICS therapy could be protective for the small, but statistically significant, increase in deaths noted in the salmeterol treatment arm. Clinicians have questioned the cause of the increased number of deaths noted in the 2 early LABA studies and queried whether deaths were due to inadequate control of airway inflammation. To date, most assessments have found no safety concerns in studies that have been conducted with ICS/LABA combinations, particularly when used in the same inhaler device, in asthmatic patients,¹⁶⁻¹⁹ but this conclusion has not been universal.^{20,21} Furthermore, an increase in respiratory-related deaths has not been seen in studies in participants with chronic obstructive pulmonary disease (COPD) who were treated with LABAs as either monotherapy or combined with an ICS. These observations raise doubt of an intrinsic toxicity of LABAs, especially because patients with COPD tend to be elderly and have a high incidence of cardiac disorders. Finally, asthma mortality has actually decreased and hospitalizations have not increased over the last 10 years during a period of increasing use of LABAs in asthma management.^{22,23} Consequently, clinicians have continued the use of LABAs in recognition of the scientific evidence of benefit in combination with ICS. They have, however, recognized the FDA's warnings and accepted the FDA's recommendation to avoid using LABAs as monotherapy for asthma in the absence of an ICS to minimize the potential risk of the medication. Clinicians have also accepted

the FDA's recommendation to use a fixed-dose combination product containing a LABA and an ICS to ensure adherence with concomitant therapy in asthmatic children and adults.

Where differences of opinion have occurred is in the principles of step-down therapy once asthma control is established in patients who are taking combination ICS/LABA therapy. Questions have emerged regarding the appropriate time to step down, which medication to step down, and the potential consequences that might result from stepping down therapy.

Clinicians often prefer not to step down either ICS or LABA therapy once control is established to avoid returning to a state of inadequate control, especially because patients are frequently seen only once or twice per year when their asthma has been previously established as well controlled. Furthermore, clinicians question whether it is wise to step down the LABA versus the ICS. This clinical concern was an impetus for the analysis reported in the recent publication by Brozek et al¹⁵ combined with a commentary by Chan and Shorr²⁴ that was critical of the FDA's black box warning and subsequent recommendations regarding LABA therapy for asthma. They believed that the FDA was placing too great an emphasis on the 2 past studies, in which LABA monotherapy was commonly used, rather than focusing on current studies and postmarketing surveillance of combination products.

CONSEQUENCES OF THE FDA'S LABA CONCERN

Based on the LABA concern, a study is in progress at the request of the FDA to examine the safety of LABAs in children and adults in a large randomized trial of ICSs and ICS/LABA combinations in approximately 50,000 participants, including 6,200 children aged 5 to 11 years.² The results of this study, assuming the proposed date of completion, will not be available until 2016. Data gathered from this large study will focus on severe outcomes: hospitalizations, intubations, and death. Hospitalizations and intubations will serve as surrogates for near-death events. At its best, evaluating these outcomes will resolve the concern regarding LABA safety when used in combination with an ICS, but the studies were not designed to address the step-down question.

There are, however, concerns from clinicians that this delay in resolving the issue will place a hold on the development and approval of newer asthma medications, including ICS/LABA combination products from additional pharmaceutical companies than those currently marketed, improved delivery devices, or the availability of new LABAs in the United States, such as longer-acting once-daily formulations. It appears that the use of ICS/LABA combinations for an as-needed strategy to supplement maintenance therapy, which is considered effective in many other countries,²⁵ will not be approved in the United States. Furthermore, it appears that new drugs in the β -adrenergic agonist class will be evaluated in patients with COPD first and therefore approved only in adults and perhaps limited for use in patients with COPD. Consequently, LABAs would not be evaluated in the United States for asthma and would therefore exclude children who are affected by asthma and not by COPD. This approach could either prompt the use of unlabeled medications for asthma or deny asthmatic patients a therapy potentially more effective than current therapy.

MOVING FORWARD

In a 2010 editorial, Lemanske and Busse²⁶ clearly outlined the dilemma created by the apparent inconsistencies noted in the

FDA's labeling and the national and global guidelines.^{1,4} The interpretation of the FDA's label is that LABAs should be discontinued entirely as soon as control is achieved. The EPR-3 guidelines recommend that clinicians consider stepping down therapy once asthma control is established for a period of time (eg, 3 months). There are few published studies that describe appropriate methods to step down therapy or the initial agent to select for step down (ie, ICS vs LABA).

The recent report by Brozek et al,¹⁵ based on a review of the available literature, concluded that discontinuing LABA therapy in adults and older children with asthma that is controlled with an ICS/LABA combination results in increased asthma-associated impairment. They recognized the limitations of the studies included in this review and called for further studies on approaches to step-down therapy. This remains a critical but unanswered question.

While awaiting the results of ongoing and future studies and an update of the NAEPP asthma guidelines, the clinician is left with the challenge of how to manage patients who have achieved asthma control with a combination LABA/ICS inhaler. Given the information available since the 2007 EPR-3 guidelines, we would like to provide a perspective on approaching step-down therapy in these patients and suggest the following issues be considered in asthma management:

1. Evaluate asthma as a variable disease that might have unpredictable episodes of loss of control that may be associated with seasonal exacerbations or a history of prior exacerbation. Therefore clinicians should evaluate the past history for a period longer than the past 3 months. Asthma control should also be evaluated in the perspective of both impairment and risk domains, and a review of medication requirements, perception of symptoms, pulmonary function, risks for seasonal exacerbations, medication adherence, and available indicators of airway inflammation (induced sputum cytology and exhaled nitric oxide) might have been performed in the past year, or even prior years, to assess variability both seasonally and overall.
2. Evaluate the benefits and risks of adjusting either the ICS dose or discontinuing the LABA. In addition to concerns over LABAs, there is ongoing awareness of the risk for potential dose-related effects of ICSs, such as a reduction in linear growth rates for children²⁷ or osteoporosis and cataracts for adults. Therefore, in patients who are receiving high-dose ICS/LABA combinations, the first consideration might be to reduce the ICS dose. In patients who are receiving low-dose ICS/LABA combinations, the decision would be to discontinue the LABA rather than to discontinue the ICS and always avoid LABA monotherapy.
3. There are certain times of the year when asthmatic patients are prone to exacerbations, such as the well-described "September epidemic." A reduction in maintenance controller therapy should be avoided before recognized seasonal periods of heightened risk.²⁸
4. Before stepping down therapy, patients should be educated on what symptoms and signs are associated with a loss of asthma control, such as an increased occurrence of nighttime symptoms, re-emergence of exercise-induced asthma, and increased use of SABAs for quick relief of symptoms. Peak flow measurements can also be useful as an indicator of loss of control after medication reduction. Office

measurements, including spirometry, are recommended to determine changes in pulmonary function. Measures of exhaled nitric oxide levels or induced sputum eosinophil numbers, if available, could be used to follow a medication reduction to determine an increase in airway inflammation, although the advantage of applying these measures in clinical settings has not been fully established.

5. For physicians who are concerned about risks of LABAs and ICSs, alternative strategies for medication reduction could be considered. For those patients with more severe asthma and existing allergic sensitization, omalizumab has proved beneficial,²⁹ as has allergen immunotherapy,¹ and, as suggested in 2 recent studies, tiotropium combined with an ICS³⁰⁻³² or, for mild asthma, an intermittent ICS combined with a SABA have proved useful.^{33,34} There have also been recent efforts to develop personalized approaches to asthma treatment based on the individual characteristics of patients. The effectiveness of this approach has been described in a recent report by Corren et al³⁵ and in ongoing studies correlating serum biomarker and periostin levels to the response to anti-IL-13. It would be of considerable benefit if clinicians could have biomarkers that direct treatment to specific characteristics of patients and not patient groups. The application of this approach has been tried in attempts to relate the genetic pattern of the adrenergic receptor to effectiveness of treatment. The results are variable.³⁶ Markers to alert the clinician and patient to whether the disease is susceptible to various treatment modalities are not available now, but efforts are moving forward.

In summary, the benefit/risk balance of LABA therapy is an ongoing controversy that has engendered vigorous debate among well-intentioned authorities. This debate has raised doubts and confusion in the minds of both clinicians and patients. The NAEPP EPR-3 carefully positioned LABAs in the treatment of asthma. First, there is no place for using LABAs as long-term control monotherapy. Second, advancing from step 2, where an ICS is the preferred step, to step 3, the clinician has the option of either a low-dose ICS plus LABA or a medium-dose ICS. Beyond step 4, ICS/LABA combinations are the preferred treatment. While we await information from current trials and a future expert panel review of studies available since the EPR-3's publication for an update of the NAEPP's asthma guidelines, our own review of current information leads us to conclude that there are no data to modify the EPR-3 approach. However, selecting which agent for step down remains an unresolved issue. Although arguments can be made for either approach, discontinuing a LABA versus decreasing the ICS dose, no comparative study has addressed this directly; however, current observations do not fully support withdrawing the LABA as the first step-down medication.¹⁵ The ongoing required FDA studies will provide information on LABA safety but not necessarily step-down approaches. If these ongoing FDA-required studies indicate LABAs are safe, the question on the effectiveness and safety of a LABA step down will remain largely unanswered. If there are safety concerns that arise in the FDA-required safety trials, the question on step down will require further thought.

The Scottish witches in *Macbeth* have an analogy to the LABA controversies, and we are, currently, in a "brew." Getting out of the boiling cauldron can serve to signal a resolution of a vexing

problem and point us in the right direction based on accurate and good data. Hopefully, emerging data on LABAs will remove the admonishment “double, double toil and trouble” and help settle the issue. In the meantime, recent data are reassuring regarding the use of combination products, and we must all strive to look forward. For those concerned with the use of LABAs, we offer our own thoughts for consideration in limiting the risk of LABAs, as well as ICS therapy.

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