

Balancing the Benefits and Risks of Inhaled Long-Acting Beta-Agonists — The Influence of Values

Judith M. Kramer, M.D., M.S.

In December 2008, the Food and Drug Administration (FDA) convened a joint meeting of the Pediatric Advisory Committee, the Pulmonary–Allergy Drugs Advisory Committee, and the Drug Safety and Risk Management Advisory Committee (of which I am a member) to review the risks and benefits of inhaled long-acting beta-agonists (LABAs) for the treatment of asthma in adults and children. Committee members were asked to weigh the public health implications of real and serious but relatively infrequent occurrences of severe asthma exacerbations and asthma-related death against the symptomatic benefits of bronchodilation and asthma control. The drugs in question included single-agent LABA products (salmeterol, or Serevent [GlaxoSmithKline], and formoterol, or Foradil [Novartis]) and LABAs available in combination with inhaled corticosteroids (fluticasone plus salmeterol, marketed as Advair [GlaxoSmithKline], and budesonide plus formoterol, marketed as Symbicort [AstraZeneca]). The FDA's continuing approval of an asthma indication for these agents was at stake.

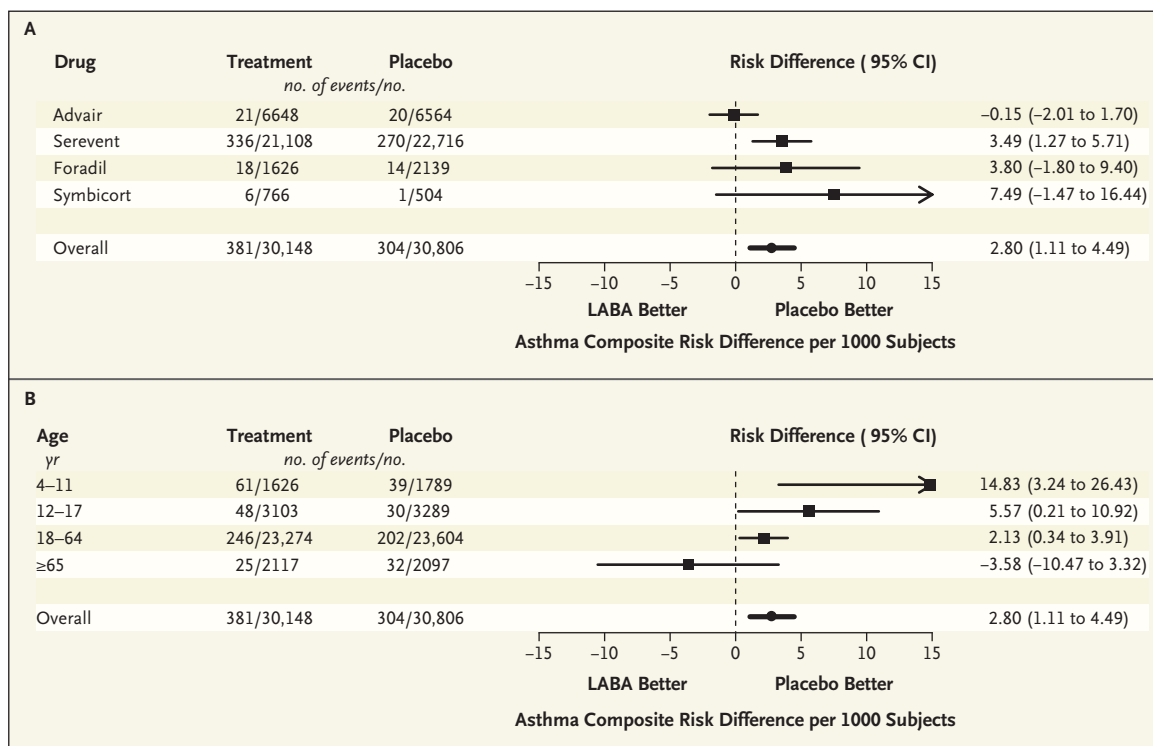
Decades before any LABA had reached the market, the inhaled short-acting beta-agonist isoproterenol was linked to an increase in asthma-related deaths. Although the mechanism remains uncertain, some have hypothesized that beta-agonists may increase patients' sensitivity to bronchocon-

stricting stimuli or mask symptoms of worsening asthma.

When salmeterol — the first LABA bronchodilator to reach the U.S. market — was approved in 1994, the FDA knew that a study had shown a not-quite-significant increase in the rate of asthma-related deaths associated with salmeterol as compared with short-acting albuterol. Asked by the FDA to conduct a postmarketing surveillance study, the drug's manufacturer initiated the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. The trial was prematurely terminated in 2003 because of adverse outcomes in black patients and difficulties with enrollment. But published results showed that the salmeterol group had a statistically significant relative risk of 4.37 for the secondary end point of asthma-related death.¹ The FDA responded by requiring a black-box warning on the Serevent and Advair labels, and in July 2005 the SMART results and those of a phase 4 study of formoterol convinced the Pulmonary–Allergy Drugs Advisory Committee that LABAs should not be used as monotherapy (without concomitant inhaled corticosteroids) and that the black-box warnings should be strengthened accordingly. But the committee voted unanimously that both salmeterol and formoterol should remain on the market for the treatment of asthma. The joint meeting in December 2008 was held in response to a recommendation from the Pedi-

atric Advisory Committee a year before that a more extensive discussion be held to consider salmeterol's benefits in the context of the risks for pediatric patients.

Before the meeting, the FDA statistical safety reviewer conducted a meta-analysis of patient-level data from 110 randomized, parallel, controlled trials of the use of LABAs for asthma.² The FDA specified the inclusion criteria for trials, post hoc adjudication of asthma-related events, data to be submitted, and quality-assurance requirements. Of the 60,954 patients in these trials, 11% were adolescents (12 to 17 years of age) and 6% were children (4 to 11 years of age). A composite end point of asthma-related death, intubation, or hospitalization was used, and there were 2.80 more such events per 1000 patients in the group that received LABAs than in the group that did not (see graph, Panel A). In the trials comparing LABA therapy without assigned inhaled corticosteroids with non-LABA therapy, there was a statistically significant difference in rates of 3.63 per 1000 subjects, whereas in the trials comparing LABAs plus assigned inhaled corticosteroids with inhaled corticosteroids alone, the difference was only 0.25 per 1000 subjects and was not significant. The results for individual drugs showed an increased risk with formoterol, salmeterol, and Symbicort, but not with Advair. For all products except Advair,



Estimated Differences in the Risk of Asthma-Related Death, Intubation, or Hospitalization According to Medication Used (Panel A) and Age Group (Panel B).

Data are from Levenson.² Reprinted with permission from the FDA. CI denotes confidence interval.

risk appeared to increase as age decreased (see graph, Panel B).

As for benefits, at the time of approval, all the agents had been shown to significantly improve bronchodilation as measured by pulmonary function tests. The pre-approval studies for adults included adolescent patients; separate small studies (200 to 350 patients) conducted in younger children had results consistent with those in adolescents. Although the correlates of improvement in pulmonary function included increases in symptom-free days and days without the need for rescue therapy, overall changes in quality-of-life scores often were not clinically important. None of the agents were shown to decrease asthma-

related mortality or asthma-related hospitalizations.

Although the various FDA reviewers who prepared materials for the December 2008 meeting agreed that LABAs pose a real, though small, risk of asthma-related exacerbations and death, their recommendations for regulatory actions varied. Reviewers in the agency's Office of Surveillance and Epidemiology unanimously recommended that for patients under 18 years of age the asthma indication should be removed from all LABAs, even those in combination products containing corticosteroids. They unanimously recommended removing the asthma indication from single-entity LABAs for patients of

all ages and contraindicating their use for asthma. Regarding the use of combination products in adults, their views were split: some recommended requiring a new trial comparing inhaled corticosteroids plus a LABA with both inhaled corticosteroids plus a short-acting beta-agonist and inhaled corticosteroids alone; others recommended removing the asthma indication for these combination products for adults. One reviewer in the latter group characterized the counterbalancing benefits of LABAs as "trivial."

In contrast, FDA reviewers from the Division of Pulmonary and Allergy Products (DPAP) thought that the risks were counterbalanced by clinically meaningful

symptomatic benefits, such as reduced nocturnal awakening from asthma symptoms and decreased use of rescue therapy. The DPAP reviewers argued that the risk could be managed by spelling it out on labeling that would also direct the use of LABAs to the appropriate patient population. They expressed concern that removing the asthma indication from single-agent LABAs would limit clinicians' options for treating asthma that cannot be controlled by inhaled corticosteroids alone — narrowing the choice of corticosteroids that could be used with a LABA, limiting flexibility in balancing the doses of corticosteroids and LABAs, and precluding the combined use of LABAs with long-term control medications other than corticosteroids. (Because salmeterol and formoterol are also indicated for chronic obstructive pulmonary disease, however, they would remain on the market even if the asthma indication were removed.)

Two fundamental issues confronted the joint advisory committee. First, the data were inadequate to address the important clinical and public health questions. Not much had changed since the 2005 meeting of the Pulmonary–Allergy Drugs Advisory Committee, when safety concerns about LABAs had been raised.³ Most patients in the FDA meta-analysis participated in studies years ago, when LABA monotherapy was common. The trials had not been designed to evaluate the effect of inhaled corticosteroids in mitigating the risk of asthma exacerbations or death or to assess the end points being evaluated in the meta-analysis, and many of the studies did not

document differences in baseline risk. None of the studies addressed patients' adherence to medication regimens. And there were minimal clinical trial data for children. Although more than a decade's worth of data from clinical asthma trials sponsored by the National Institutes of Health (NIH) were summarized at the meeting, this information was not distributed beforehand and there was little opportunity to reconcile results of these trials with those of the industry-sponsored studies.

The second issue was the apparent variation in the subjective values and import being assigned to benefits and risks by various FDA representatives, committee constituencies, and speakers in the public session. Though not articulated or debated, these value judgments were entangled in the scientific discussions attempting to quantitate benefit and risk. Clearly, drugs known to have life-threatening risks have been approved for their symptomatic benefits. Yet FDA advisory committees rarely have more than anecdotal data on the values patients assign to symptomatic benefits in the face of life-threatening adverse effects. Often, medical professionals act on the assumption that there is a hierarchy of benefit, at the top of which is avoidance of death. Many patients, however, may prioritize benefits differently. In the public session, for example, five of the six speakers pleaded for the retention of the asthma indication for LABAs despite the risks; one of these speakers was a 13-year-old boy with severe asthma who described the dramatic benefit of combination LABA–corticosteroid ther-

apy in reducing his hospitalizations and enabling him to attend more days of school and sleep through more nights without requiring rescue therapy. Without an explicit discussion of the importance of such benefits when weighed against life-threatening side effects, health care practitioners and regulators often bring their own value systems to bear on these decisions.

Ultimately, the committee unanimously agreed that for single-agent LABAs the benefits did not outweigh the risks in children 4 to 11 years of age. This view appeared to be driven primarily by the paucity of randomized data for this age group and the suggestion in one NIH-sponsored study that LABAs may not add much benefit to inhaled corticosteroids in children 5 to 11 years old. Most committee members also agreed that the benefits of single-agent LABAs did not outweigh the risks for adolescents and adults under the current labeling. However, many indicated that their concern could be addressed if labeling changes were made for adolescents and adults both to strengthen admonitions against using LABAs as monotherapy and to emphasize that LABAs should be added to corticosteroids only when corticosteroids alone proved inadequate for asthma control.

The committee voted (unanimously for Advair and with one abstention for Symbicort) that for adults the benefits of combination products outweighed the risks. For adolescents, a substantial majority voted that the benefits outweighed the risks for both products, and a slim majority thought the same applied to Ad-

vair for children 4 to 11 years of age. Two different FDA actions for adults would be consistent with committee sentiment: removing the asthma indication for single-agent salmeterol and formoterol, and retaining the indication but strengthening the labels.

Clearly, the challenge of protecting the public's health is heightened by variability in the values placed on benefits and risks. Opinion also differs on the virtue of leaving these choices to patients and their physicians — as opposed to withholding access to drugs with life-threatening adverse effects. Future deliberations

on drugs that carry serious risks yet also have counterbalancing symptomatic benefits should include explicit discussion of the range of values that patients, health care practitioners, and regulators assign to those risks and benefits.

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Dr. Kramer is an associate professor of medicine and executive director of the Clinical Trials Transformation Initiative at the Duke Translational Medicine Institute, Duke University Medical Center, Durham, NC,

and a voting member of the Drug Safety and Risk Management Advisory Committee of the FDA.

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