

tween beneficial effects and harmful effects of acid suppression.

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for the Writing Committee of the American Lung Association Asthma Clinical Research Centers

Since publication of this article, Dr. Wise reports receiving consulting fees from Genentech. No further potential conflict of interest relevant to this letter was reported.

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## Long-Acting Beta-Agonists in Asthma

**TO THE EDITOR:** In her Perspective article, Kramer (April 16 issue)<sup>1</sup> succinctly summarizes the decisions of the Food and Drug Administration (FDA) regarding the continued availability of single-agent long-acting beta-agonist (LABA) inhalers for use in patients with asthma. She further clarifies that these drugs would remain on the market for patients with chronic obstructive pulmonary disease (COPD), even if the asthma indication were removed.

As a practicing pulmonary physician, I have a different perspective to offer for debate. A not insignificant number of patients that my colleagues and I see do not correctly differentiate between asthma and COPD, and therefore, it is quite possible that single-agent LABAs would end up being used in patients with asthma. Also, separate single-agent LABAs and corticosteroid prescriptions can often be used separately in real life, either because of a misunderstanding or because the inhaled corticosteroid runs out before the inhaled single-agent LABA does. Given the ready availability of two combined LABA-corticosteroid agents, the absence of evidence that single-agent LABAs are superior to single-agent corticosteroid inhalers in patients with asthma, and the well-defined risk of death from single-agent LABAs among patients with asthma, I submit that single-agent LABAs should be removed from the market as a public safety measure.

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1. Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists — the influence of values. *N Engl J Med* 2009;360:1592-5.

**TO THE EDITOR:** We respectfully disagree with the implication in the editorial by Drazen and O'Byrne<sup>1</sup> on the risks of LABAs in achieving asthma control that a large study on the safety of LABAs has not been performed because of financial considerations. GlaxoSmithKline has rigorously explored the conduct of a study of mortality associated with LABAs in patients with asthma. However, such a study is not feasible. Because of the low rate of asthma-related deaths, a study designed to rule out a 20% increase in mortality (relative risk, 1.2) would require approximately 700,000 subjects per group. If an appropriately powered mortality study had been feasible, we would have done it.

Recognizing that limitation, since the Salmeterol Multicenter Asthma Research Trial (SMART)<sup>2</sup> was completed, GlaxoSmithKline has sponsored important research on LABA safety, including a year-long study of asthma exacerbations in blacks,<sup>3</sup> the largest prospective study to date examining asthma genotype and response to salmeterol,<sup>4</sup> and epidemiologic studies of more than 80,000 patients receiving salmeterol. None of these varied approaches showed an increased risk of asthma-related death.<sup>5</sup> At GlaxoSmithKline, patient safety is our highest priority. We continue to conduct

studies with LABAs that are scientifically sound and feasible and that can provide information that has clinical and statistical significance.

Katharine Knobil, M.D.

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5. GlaxoSmithKline sponsor briefing information: Advair and Serevent. Silver Spring, MD: Food and Drug Administration, 2008. (Accessed June 18, 2009, at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-04-GSK.pdf>)

**THE AUTHOR REPLIES:** In response to Agarwal's letter: it is important to clarify that the December 2008 joint meeting of the Pulmonary–Allergy Drugs Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee was convened to consider the safety of LABAs for the asthma indication only, since that is where a safety signal had been detected. No concerns about the safety of LABAs in patients with COPD were raised. Briefing materials prepared by the FDA stated that if the asthma indication for single-agent LABAs is withdrawn, “the actual products will remain in the market [because of] the COPD indication these products carry.”<sup>1</sup> Thus, no scenario was described in which single-agent LABAs could be removed from the market completely.

It is also important to note that the “decisions” summarized in my Perspective article were not decisions of the FDA. They were recommendations by the advisory committee for FDA consideration.

The FDA's opinions referred to in the briefing materials for the December 2008 meeting were preliminary interpretations. To date, the FDA has not yet publicly issued any decisions based on the advice received at the December 2008 meeting.

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1. Long-acting beta-agonists and adverse asthma events meta-analysis: statistical briefing package for a joint meeting of the Pulmonary–Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee, December 10–11, 2008. (Accessed June 18, 2009, at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>.)

**THE EDITORIALISTS REPLY:** Knobil is correct that a study to prove the absence of a small increased risk of death among patients with asthma with the use of inhaled corticosteroid–LABA combinations would need to be large. However, she misses the point. The persisting concern is that the use of LABAs causes an increased mortality, which may be as high as 1 death in 700 patient-years of treatment; exclusion of a level of risk of this magnitude should be possible in a manageable study. We remain convinced that a study of similar scope to that of the original SMART study, but executed with a better design and comparing inhaled corticosteroid–LABA combinations with inhaled corticosteroids alone, would provide the data needed to establish the range of risk of death from asthma that exists with these combinations. Sometimes, in an effort to achieve perfection, we do nothing at all; we believe that this is unacceptable.

In our editorial, we said that the cost of executing these studies would be “about 2 weeks of gross profits.” This should have read “about 2 weeks of gross sales.”

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## Prescribing Records and the First Amendment

**TO THE EDITOR:** Two thoughtful Perspective articles by Post and by Grande and Asch (Feb. 19 issue)<sup>1,2</sup> address the potential consequences of restricting information transparency and the com-

plex policy and constitutional conundrums that can be created by this restriction.

Because variation in the availability and the utilization of health services contributes to con-