

## The Role of Long-Acting $\beta$ -Agonists in the Management of Asthma: Analysis, Meta-Analysis, and More Analysis

We teach that medical decisions, including prescription of treatments, should be informed by the available data addressing the problem in question. Practicing in accord with evidence-based medicine precepts assumes that the practitioner can become familiar with which studies and expert guidelines are relevant to a particular patient and which studies best control for important confounding variables. It assumes, in other words, identification of the “best” evidence. While this process may be straightforward for some conditions or treatment alternatives, it is often quite a challenge.

The place of long-acting  $\beta$ -agonists (LABAs) in the management of asthma exemplifies that reality. Although these agents have been widely prescribed for the management of asthma for some years, their use has been controversial for much of that time. Thus, while several studies have supported the efficacy and safety of LABAs for treating asthma (1–4) (as has 1 recent summary of several Cochrane database reviews [5]), other studies (6–8) have reported very worrisome rates of serious asthma morbidity and death with the use of these drugs. Indeed, some of these latter studies prompted the U.S. Food and Drug Administration to issue a warning about the increased risk for adverse outcomes associated with LABAs.

This issue introduces a new participant in this debate. The report by Salpeter and colleagues (9) details a meta-analysis of 19 randomized, controlled clinical trials involving 33 826 asthmatic patients. The purpose of the study was to estimate the rate of and risk for serious adverse effects from LABAs. The investigators found that use of LABAs was associated with increased asthma exacerbations and increased asthma-related deaths. Moreover, statistically significant increases in hospitalizations occurred in both adults and children and across the class of LABAs (i.e., salmeterol and formoterol) compared with placebo. The results seem clear-cut. Do they settle the LABA controversy once and for all?

To answer that question, it is useful to consider some of the explanations for the discrepancies between previous studies of LABAs. Clearly, some previous studies involved too few participants or followed them for an insufficient period to reliably address these issues. A particular advantage of meta-analysis is that it pools results and study samples and thereby increases the number of patients for analysis. However, meta-analyses may not be able to address other explanations for differing study results because some studies fail to report the data that might explain why they had discrepant results. For example, asthma severity varies greatly, and outcomes are related to severity or level of control at the time of study entry, concomitant treatments prescribed (particularly inhaled or systemic corticoste-

roids), and degree of adherence to treatment. One or more of these factors could increase the risk for a serious adverse outcome while taking LABAs. Studies may differ considerably in these important features or, worse, provide no information about them. The study by Salpeter and colleagues does not completely address the possible roles of disease severity, co-treatments, and adherence in causing serious adverse outcomes, presumably because too few studies reported this information. This reflects the reality that a meta-analysis for 1 research question (e.g., hospitalization rates in patients taking LABAs) might reasonably include a study that has pertinent data on that variable even though it did not address other variables of importance (e.g., the effect of adherence on hospitalization rates while taking LABAs).

As our understanding of the biology of asthma has increased, other possible explanations for contradictory results between seemingly well-performed studies have emerged. Recently, polymorphisms at several positions within the human  $\beta_2$ -adrenergic receptor gene have been identified. Asthmatic patients homozygous for the variant resulting in an arginine at the 16th amino acid position of the  $\beta_2$ -adrenergic receptor (the so-called Arg/Arg genotype) have received considerable attention. Some studies suggest that these patients may actually experience declines in airflow and worsening asthma control when using  $\beta$ -agonists to treat their asthma (10). This genotype occurs in approximately one sixth of the U.S. population and may be disproportionately present in some racial or ethnic groups, such as African-American persons (11). Failure to control for and report this genotype or at least the racial distribution of study participants may account for discrepant study results. This source of variability between studies would also naturally carry over into any pooling of data in a meta-analysis. In fact, half of the studies analyzed by Salpeter and colleagues did not describe the racial composition of the study participants. One study that did (8) accounted fully for 78% of all asthmatic patients in the Salpeter meta-analysis. Enrolling 18% African-American participants, this 1 study also included all but 2 of the asthma deaths analyzed by Salpeter and colleagues.

Considering all of the available data, what should physicians do? First, it is important to follow current guidelines that emphasize the use of inhaled corticosteroids as the first line of treatment for patients with mild to moderate persistent asthma symptoms (12). Physicians should not use LABAs as initial therapy for any asthmatic patient. Second, physicians caring for patients who do not achieve at least good control (defined by recent guidelines [13] as minimal daily or nocturnal symptoms and infrequent exacerbations requiring systemic corticosteroids or emergency

department visits) should use an approach based on the recent Gaining Optimum Asthma control (GOAL) study (3). This randomized, double-blind clinical trial of more than 3000 patients with uncontrolled mild to moderate asthma stratified by corticosteroid use sought to achieve asthma control by escalating the dose of inhaled corticosteroids alone or combined with salmeterol. The GOAL investigators found that the combination of inhaled corticosteroids plus a LABA resulted in a greater rate and level of control and a lower dose of inhaled corticosteroids than did inhaled corticosteroids alone. However, on the basis of all available data, including the analysis by Salpeter and colleagues, it seems prudent to first escalate the dose of inhaled corticosteroids to achieve asthma control. If satisfactory control is not attained at maximal doses of inhaled corticosteroids, then a LABA should be added. The report by Salpeter and colleagues reminds us of the critical importance of careful monitoring to identify patients who are not responsive or whose condition deteriorates in response to LABA therapy. If LABA therapy fails, the physician should withdraw the drug, either abruptly or by tapering it over a period of days or weeks, a point of some uncertainty (14). As suggested by Salpeter and colleagues, physicians should be prepared to provide an alternative medication for patients in whom LABA therapy fails. Adding an inhaled anticholinergic agent has theoretical appeal, based on limited data suggesting that patients with the Arg/Arg genotype, who may constitute a substantial proportion of LABA-unresponsive patients, have a particularly favorable response to anticholinergics (14). An especially vexing problem is the African-American patient whose asthma is not adequately controlled by inhaled corticosteroids alone, even with maximal doses. On the basis of available information (8, 11), it appears reasonable to add an inhaled anticholinergic agent (since African-American persons have a higher prevalence of the Arg/Arg genotype) and to avoid LABAs if possible.

Although asthma treatment options have expanded, all of them have some risks, including the risk of not controlling asthma in a particular patient. With respect to LABAs, Salpeter and colleagues were not able to completely address the potential contribution of disease severity, co-treatments, adherence, and race to serious adverse outcomes. The report does, however, underscore the fact that LABAs are powerful and complex medications that we must use with care even as we await additional information to help us refine the decision to use them. Physicians must be alert to factors (for example, race) that may predict an unfavorable reaction to LABAs, carefully monitor patients receiving these drugs, and act promptly when patients do not respond favorably. Therapeutic decisions increasingly require tailoring therapy to individual needs and, some day perhaps, to pharmacogenomic profiles.

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