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Supplement to
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Long-Acting Beta-Agonists Role in Asthma Management

Key Points and Recommendations

- The inhaled long-acting β -adrenergic agonists are associated with an increase in asthma-related deaths and life-threatening experiences. (SOR: B)
- The results of the Salmeterol Multicenter Asthma Research Trial (SMART) suggest that patients receiving salmeterol were at increased risk for fatal asthma events. In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo. (SOR: B)
- The results of SMART are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, or other asthma-controller therapy modified the risk of asthma-related death with salmeterol. (SOR: B)
- Long-acting β -agonists (LABAs) and combination products containing a LABA such as Advair Diskus[®] are not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled short-acting β -agonists. (SOR: B)
- The goal of asthma treatment is to titrate to the lowest effective dose after achieving stable asthma. (SOR: B)

This supplement is intended as a short review of the current uses of long-acting β -agonists, with an emphasis on the 2005 US Food and Drug Administration advisory and the March 2006 revised labeling changes for salmeterol xinafoate (Serevent[®] Diskus[®]) and fluticasone propionate and salmeterol xinafoate (Advair Diskus[®]); the labeling for formoterol fumarate (Foradil Aerolizer[®]) at the time of this publication remains unchanged. As such, the goal is to guide clinicians regarding effective use of these non-first-line treatments. It is not intended to be a review of asthma management.

In November 2005, the US Food and Drug Administration (FDA) issued a public health advisory regarding the inhaled long-acting β_2 -agonists (LABAs) salmeterol xinafoate (Serevent[®] Diskus[®]), fluticasone propionate and salmeterol xinafoate (Advair Diskus[®]), and formoterol fumarate (Foradil Aerolizer[®]).¹ The advisory stated that the FDA had requested that the manufacturers of these products “update their existing product labels with new warnings and a medication guide for patients to alert health care professionals and patients that these medicines may increase the chance of severe asthma episodes and death when those episodes occur.” The advisory reinforced that LABAs are not first-line drugs to treat asthma and should be added only if other medicines do not control asthma, that is, a low- or medium-dose corticosteroid, as stated in the guidelines issued by the National Asthma Education and Prevention Program (NAEPP) of the



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National Heart, Lung, and Blood Institute (NHLBI). This publication summarizes the history and recent clinical trials that contributed to the FDA advisory and the subsequent FDA actions taken in March 2006. The implications of this advisory and the FDA actions in the primary care setting are discussed.

Putting inhaled β_2 -agonists in perspective

Evidence for the role of long-acting β_2 -agonists

The inhaled LABA class was introduced in the United States in 1994. Both salmeterol and formoterol were shown to produce greater improvement in pulmonary function and a greater decrease in symptoms and use of rescue bronchodilators compared with regularly administered short-acting inhaled β_2 -agonists or placebo.^{2,7} The beneficial effects of LABAs have been found to be additive when combined with an inhaled corticosteroid. The combination has been shown to improve lung function and increase the number of days and nights without symptoms or the need for rescue medication, with no increase in exacerbations of any severity, compared with administering twice as much of the inhaled corticosteroid as monotherapy.^{8,9} The LABAs, however, have been shown to have no clinically significant effect on airway inflammation, which is the key cause of asthma, either as monotherapy or as add-on therapy to an inhaled corticosteroid.¹⁰⁻¹⁵ Nonetheless, the benefits of LABAs as bronchodilators have been demonstrated clearly. For this reason, the LABAs were included in the revised guidelines issued by the NAEPP in 1997.¹⁶

Concerns about the LABAs began shortly after the commercial availability of salmeterol. Most of these concerns stemmed from experience with the short-acting β_2 -agonists, particularly their association with an increase in deaths due to asthma.¹⁷ A case-controlled study showed that for each additional canister administered each month, the odds ratio of death from asthma increased by 2.6.¹⁸

This association was uncertain, however, since other data suggested that the high use of β_2 -agonists probably directly correlated with the severity of asthma and that those with more severe asthma are at greater risk of death.¹⁹ Given these concerns regarding the regular use

of a β_2 -agonist, the Salmeterol Nationwide Surveillance (SNS) study was initiated in 1990 to compare the safety of the regular use of salmeterol and albuterol.

Salmeterol Nationwide Surveillance study

The SNS study, conducted in the United Kingdom in 1990-1991, randomized 25,180 patients with asthma considered to require regular treatment with bronchodilators.²⁰ Patients received salmeterol, 50 mcg twice daily (N=16,787), or albuterol, 200 mcg 4 times daily (N=8,393), in combination with previously prescribed asthma drugs for 16 weeks. Approximately three quarters of patients were taking an oral or inhaled corticosteroid. The incidence of drug-related serious events was similar in both groups (1.19% vs 1.15%, respectively), although a significantly lower rate of severe, nonfatal asthma-related events was observed in the salmeterol group compared with the albuterol group (9.9% vs 11.6%, respectively). The incidence of the combined endpoint of respiratory and asthma-related deaths was higher but not statistically significantly so in the salmeterol group compared with the albuterol group (0.07% vs 0.02%, respectively).

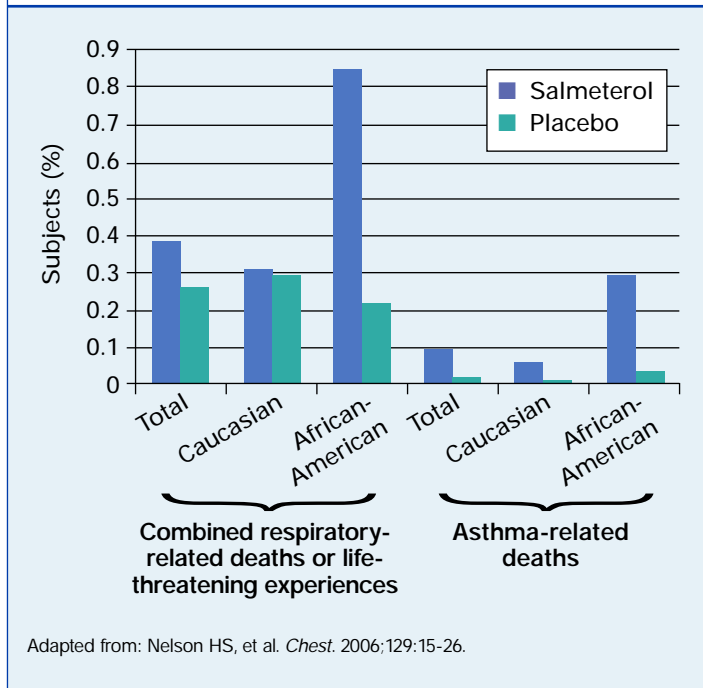
Salmeterol Multicenter Asthma Research Trial

A multicenter, randomized, placebo-controlled study was launched in 1996 to compare the safety of usual asthma therapy with and without salmeterol.²¹ The Salmeterol Multicenter Asthma Research Trial (SMART) enrolled subjects 12 years or older with asthma. Subjects received either salmeterol, 42 mcg twice daily, via metered-dose inhaler (MDI) or placebo twice daily via MDI for 28 weeks. A planned interim analysis was conducted after 26,355 subjects had been randomized. At that time, the study was terminated because the overall rate of death was higher in patients treated with salmeterol than placebo.

The interim analysis showed that the occurrence of the primary outcome, combined respiratory-related deaths or life-threatening experiences, was low and not statistically different between groups (**FIGURE**). Similarly, asthma overall did not appear to worsen in those receiving salmeterol. There was, however, a small but statistically significant increase in respiratory-related deaths (24 vs 11) and asthma-related deaths (13 vs 3) in subjects receiving salmeterol vs placebo, respectively. Post hoc analysis showed that

FIGURE

Effects of salmeterol on selected end points at 28 weeks of treatment



compared with placebo, a higher rate of asthma-related deaths occurred in the salmeterol group in both whites (0.01% vs 0.07%) and African Americans (0.04% vs 0.31%), respectively. While the relative risks of asthma-related deaths were similar in both groups, estimates of excess deaths attributable to salmeterol were greater in African Americans, primarily because they demonstrated a higher rate of these events. Also observed was that the occurrence of asthma-related deaths and life-threatening experiences occurred nearly equally in the salmeterol and placebo cohorts in those using inhaled corticosteroids at baseline (16 vs 13, respectively). However, the study design does not allow for conclusions about whether inhaled corticosteroids significantly change the asthma death risk profile of salmeterol or any LABA.

Combined formoterol trials

The FDA staff analyzed data from 3 clinical trials^{7,22} submitted by Novartis Pharmaceuticals Corporation in support of the approval of Foradil Aerolizer for marketing in the United States.²³ The prospective, randomized, placebo-

controlled, and double-blind trials compared formoterol, 12 mcg twice daily or 24 mcg twice daily, with albuterol, 180 mcg 4 times daily, or placebo. [The 24 mcg twice daily dose of formoterol is not within the currently approved product labeling for Foradil Aerolizer.] Both formoterol doses were statistically significantly superior to placebo for the primary endpoint of improvement in FEV₁ at 12 weeks. The studies did not show a statistically significant benefit for formoterol, 24 mcg twice daily, compared with formoterol, 12 mcg twice daily. Serious asthma exacerbations occurred more frequently in the formoterol, 24 mcg twice daily, group compared with placebo, albuterol, or formoterol, 12 mcg twice daily, groups (TABLE 1). In the 2 12-week studies in adults/adolescents, 9 patients in the formoterol, 24 mcg twice daily, groups experienced a serious asthma exacerbation; all required hospitalization. One patient died because of a cardiorespiratory arrest. Two placebo-group patients experienced a serious but nonfatal asthma exacerbation; both were hospitalized. In the 1-year pediatric study, 11 patients had serious nonfatal asthma exacerbations in the formoterol, 24 mcg twice daily, group.²²

16-week phase IV formoterol trial

In a 16-week, randomized, double-blind, placebo-controlled phase 4 study,²⁴ the occurrence of asthma exacerbation was evaluated in 2085 adolescent and adult subjects with a mean FEV₁ of 69% of predicted. Subjects received formoterol, 12 mcg twice daily or 24 mcg twice daily; formoterol 12, mcg twice daily combined with up to 2 additional as-needed doses; or placebo. A serious respiratory-related adverse event requiring hospitalization occurred in 0.9%, 0.4%, 0.2%, and 0.2% of the subjects, respectively (TABLE 2).

Summary of prospective study results

Investigations have identified an increased risk of asthma-related death or life-threatening experience but not an overall worsening of asthma control in those treated with salmeterol. This risk appears to be especially high in African Americans. Formoterol use is associated with more frequent serious asthma exacerbations compared with placebo.

TABLE 1

Occurrence of serious asthma exacerbations in 3 asthma studies with formoterol

	Formoterol 12 mcg BID	Formoterol 24 mcg BID*	Albuterol 180 mcg QID	Placebo
12-wk trial in adults/adolescents	0/136 (0)	4/135 (3)	2/134 (1.5)	0/136 (0)
12-wk trial in adults/adolescents	1/139 (0.7)	5/136 (3.7)	0/138 (0)	2/141 (1.4)
1-y trial in pediatric patients	8/171 (4.7)	11/171 (6.4)		0/176 (0)

Data reported as n (%)

*Not within currently approved product labeling for Foradil Aerolizer®

TABLE 2

Formoterol-associated respiratory-related serious adverse events requiring hospitalization

Formoterol 12 mcg BID (n=527)	Formoterol 24 mcg BID* (n=527)	Formoterol 12 mcg BID+ on demand† (n=517)	Placebo (n=514)
5 (0.9%)‡	2 (0.4%)	1 (0.2%)	1 (0.2%)

*Not within currently approved product labeling for Foradil Aerolizer®; †Up to 2 doses/day; ‡2 were not asthma-related

Wolfe J, et al. *Chest*. 2006;129:27-38.

FDA actions

On March 2, 2006, the FDA approved new safety labeling for fluticasone propionate/salmeterol xinafoate (Advair Diskus) and salmeterol xinafoate (Serevent Diskus). For Advair Diskus, this labeling contains a black box warning stating that: Long acting β_2 -adrenergic agonists, such as salmeterol, one of the active ingredients in Advair Diskus, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe Advair Diskus for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

A similar warning has been included in the prescribing information for salmeterol xinafoate. The labeling for formoterol fumarate (Foradil Aerolizer®) remains unchanged.

Implications for primary care

Given the evidence now available, the following should be considered^{1,25} (TABLE 3).

- The recent evidence and the FDA actions pertain to asthma only.
- It is unknown whether or not similar concerns exist with LABA use for exercise-induced bronchospasm or

chronic obstructive pulmonary disease.

- The revised labeling pertains to salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus); the labeling for formoterol fumarate (Foradil Aerolizer) remains unchanged.

- No studies with objectives similar to SMART have been conducted for formoterol fumarate. However, the FDA believes there is a potential for a class effect.

- LABAs and LABA combination products are not indicated for first-line treatment in asthma. They should be used according to the NAEPP guidelines revised in 2002²⁶ (TABLE 4) and should not be used for patients with mild intermittent or mild persistent symptoms; they should be used only for patients with moderate or severe persistent asthma in combination with an inhaled corticosteroid. Salmeterol, formoterol, and salmeterol and fluticasone should be administered twice daily in doses listed in the approved product labeling.

- LABAs and LABA combination products should not be used to treat worsening wheezing, which indicates an increase in airway inflammation requiring the initiation of or increased dosage of an anti-inflammatory medication, generally an inhaled corticosteroid.

- An inhaled short-acting β_2 -agonist not a LABA should be used to manage acute asthma symptoms.

TABLE 3

Implications of clinical trials and
FDA actions for primary care

- Clinical trial results and FDA advisory pertain to asthma only
- Revised labeling pertains to salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus)
- LABAs are not first-line for asthma
- Add LABA only if other medicines, including low- to medium-dose corticosteroids, do not control asthma
- Do not use LABA to treat wheezing that is getting worse
- A short-acting bronchodilator—not a LABA—should be used to relieve sudden wheezing
- Ensure that airway inflammation is adequately controlled with anti-inflammatory therapy
- Communicate with the patient

FDA, US Food and Drug Administration; LABA, long-acting β -agonists
US Food and Drug Administration website. Available at: <http://www.fda.gov/cder/drug/advisory/labla.htm>. Accessed January 20, 2006.

TABLE 4

Role of inhaled long-acting β_2 -agonists as a controller in asthma*

Asthma severity	Infants and young children (age \leq 5 y)	Adults and older Children (age > 5 y)
Mild intermittent	No role for inhaled LABA	No role for inhaled LABA
Mild persistent	No role for inhaled LABA	No role for inhaled LABA
Moderate persistent	<p><i>Preferred treatments:</i></p> <ul style="list-style-type: none"> • Low-dose ICS + inhaled LABA or • Medium-dose ICS <p><i>Alternative treatments:</i></p> <ul style="list-style-type: none"> • Low-dose ICS + LRA or • Low-dose ICS + theophylline <p>If needed (recurring severe exacerbations) <i>Preferred treatment:</i></p> <ul style="list-style-type: none"> • Medium-dose ICS + inhaled LABA <p><i>Alternative treatments:</i></p> <ul style="list-style-type: none"> • Medium-dose ICS + LRA or • Medium-dose ICS + theophylline 	<p><i>Preferred treatment:</i></p> <ul style="list-style-type: none"> • Low- to medium-dose ICS + inhaled LABA <p><i>Alternative treatments:</i></p> <ul style="list-style-type: none"> • Medium-dose ICS or • Low- to medium-dose ICS + LRA or • Low- to medium-dose ICS + theophylline <p>If needed (recurring severe exacerbations) <i>Preferred treatment:</i></p> <ul style="list-style-type: none"> • Medium-dose ICS + inhaled LABA <p><i>Alternative treatments:</i></p> <ul style="list-style-type: none"> • Medium-dose ICS + LRA or • Medium-dose ICS + theophylline
Severe persistent	<p><i>Preferred treatment:</i></p> <ul style="list-style-type: none"> • High-dose ICS + inhaled LABA <p>AND, if needed:</p> <ul style="list-style-type: none"> • Oral corticosteroid 2 mg/kg/d (NMT 60 mg/d) 	<p><i>Preferred treatment:</i></p> <ul style="list-style-type: none"> • High-dose ICS + inhaled LABA <p>AND, if needed:</p> <ul style="list-style-type: none"> • Oral corticosteroid 2 mg/kg/d (NMT 60 mg/d)

*In addition to an inhaled short-acting β_2 -agonist
ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LRA, leukotriene receptor antagonist; NMT, not more than
US National Institutes of Health. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/astsumm.htm>. Accessed January 30, 2006.

Physician/patient communication and asthma management

The importance of patient communication remains a critical aspect of asthma management. Patients should be made aware of the benefits and risks of treatment, and steps to take in the event of destabilizing symptoms. Symptom and lung-function monitoring ensure that appropriate therapy, particularly anti-inflammatory therapy, is being provided. Bronchodilators, including short-acting and long-acting β_2 -agonists, must not be overused as this may temporarily mask an increase in airway inflammation.

Summary

The LABAs have played an important role in the management of asthma over the past decade. They are of clear benefit in reducing asthma-related symptoms and improving lung function when used in combination with an anti-inflammatory agent. Studies have shown, however, that their use has been associated with various negative outcomes, which has led to a restricted indication for salmeterol xinafoate (Serevent Diskus) and fluticasone propionate and salmeterol xinafoate (Advair Diskus), along with medication guides that will be given to patients with every new and refill prescription. Convincing data now exist that show an association of salmeterol with an increase in asthma-related deaths and life-threatening experiences, while formoterol is associated with more frequent serious asthma exacerbations. Nonetheless, LABAs remain an important component of asthma therapy. Further clarification about their role may occur with the release of additional analyses from SMART, as well as updated guidelines from the NAEPP Expert Panel, both expected later in 2006. In the meantime, LABAs and LABA-containing products are to be used only for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. The NHLBI/NAEPP guidelines recommend inhaled corticosteroids as the first step in controller therapy, with LABAs as an option if low- to medium-dose inhaled corticosteroids do not adequately control the patient's asthma."¹

REFERENCES

1. US Food and Drug Administration website. FDA Public Health Advisory. Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol xinafoate powder), Foradil Aerolizer (formoterol fumarate inhalation powder). Available at: <http://www.fda.gov/cder/drug/advisory/lababa.htm>. Accessed January 20, 2006.
2. D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA*. 1994;271:1412-1416.
3. Pearlman DS, Chervinsky P, Laforce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med*. 1992;327:1420-1425.
4. Johnson M, Butchers PR, Coleman RA, et al. The pharmacology of salmeterol. *Life Sci*. 1993;52:2131-2143.
5. Anderson GP. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective beta 2-adrenoceptor agonist bronchodilator. *Life Sci*. 1993;52:2145-2160.
6. FitzGerald JM, Chapman KR, Della CG, et al. Sustained bronchoprotection, bronchodilation, and symptom control during regular formoterol use in asthma of moderate or greater severity. The Canadian FO/OD1 Study Group. *J Allergy Clin Immunol*. 1999;103(3 Pt 1):427-435.
7. Bensch G, Lapidus RJ, Levine BE, et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. *Ann Allergy Asthma Immunol*. 2001;86:19-27.
8. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ*. 2000;320:1368-1373.
9. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med*. 2001;164(8 Pt 1):1392-1397.
10. Kraft M, Wenzel SE, Bettinger CM, Martin RJ. The effect of salmeterol on nocturnal symptoms, airway function, and inflammation in asthma. *Chest*. 1997;111:1249-1254.
11. Roberts JA, Bradding P, Britten KM, et al. The long-acting beta2-agonist salmeterol xinafoate: effects on airway inflammation in asthma. *Eur Respir J*. 1999;14:275-282.
12. Wallin A, Sandstrom T, Soderberg M, et al. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Respir Crit Care Med*. 1999;159:79-86.
13. Wallin A, Sue-Chu M, Bjermer L, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol*. 2003;112:72-78.
14. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *Am J Respir Crit Care Med*. 2000;161(3 Pt 1):996-1001.
15. Li X, Ward C, Thien F, et al. An antiinflammatory effect of salmeterol, a long-acting beta(2) agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1493-1499.
16. US National Institutes of Health. National Heart, Lung, and Blood Institute website. National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. Available at: <http://www.nhlbi.nih.gov/health/prof/lung/index.htm#asthma>. Accessed January 27, 2006.
17. Pearce N, Crane J, Burgess C, Jackson R, Beasley R. Beta agonists and asthma mortality: deja vu. *Clin Exp Allergy*. 1991;21:401-410.
18. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992;326:501-506.
19. Zach MS, Karner U. Sudden death in asthma. *Arch Dis Child*. 1989;64:1446-1450.
20. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ*. 1993;306:1034-1037.
21. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15-26.
22. Bensch G, Berger WE, Blokhin BM, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. *Ann Allergy Asthma Immunol*. 2002;89:180-190.
23. Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest*. 2003;124:70-74.
24. Wolfe J, Laforce C, Friedman B, et al. Formoterol, 24 µg bid, and serious asthma exacerbations: Similar rates compared with formoterol, 12 µg bid, with and without extra doses taken on demand, and placebo. *Chest*. 2006;129:27-38.
25. Nelson HS. Is there a problem with inhaled long-acting beta-adrenergic agonists? *J Allergy Clin Immunol*. 2006;117:3-16.
26. US National Institutes of Health. National Heart, Lung, and Blood Web site. Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. Available at: www.nhlbi.nih.gov/guidelines/asthma/astsumm.htm. Accessed January 30, 2006.