Meta-Analysis: Effect of Long-Acting β-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths

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Background: Long-acting β-agonists may increase the risk for fatal and nonfatal asthma exacerbations.

Purpose: To assess the risk for severe, life-threatening, or fatal asthma exacerbations associated with long-acting β-agonists.

Data Sources: English- and non–English-language searches of MEDLINE, EMBASE, and Cochrane databases; the U.S. Food and Drug Administration Web site; and references of selected reviews through December 2005.

Study Selection: Randomized, placebo-controlled trials that lasted at least 3 months and evaluated long-acting β-agonist use in patients with asthma. All trials allowed the use of as-needed short-acting β-agonists.

Data Extraction: Outcomes measured were Peto odds ratio (OR) and risk difference of severe exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma-related deaths. The OR for asthma-related deaths was obtained from the Salmeterol Multi-center Asthma Research Trial (SMART).

Data Synthesis: Pooled results from 19 trials with 33 826 participants found that long-acting β-agonists increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). The absolute increase in hospitalization was 0.7% (CI, 0.1% to 1.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%).

Limitations: The small number of deaths limited the reliability in assessing this risk, and 28 studies did not report information on the outcomes of interest.

Conclusions: Long-acting β-agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths.

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threatening asthma attacks, and asthma-related deaths. We used subgroup analyses to compare results for salmeterol and formoterol and for children and adults.

**Methods**

**Search Strategy**

We searched the MEDLINE, EMBASE, CINAHL, and Cochrane databases to identify randomized, controlled trials on long-acting β-agonist use in patients with asthma that were published between 1966 and December 2005. The search used the terms bronchodilator, sympathomimetic, adrenergic beta-agonist, formoterol, eformoterol or salmeterol and asthma, bronchial hyperreactivity, wheeze, respiratory hypersensitivity, obstructive lung disease, and obstructive airway disease or obstructive pulmonary disease. Trials were not excluded on the basis of language. The search was augmented by scanning references of identified reviews, as well as relevant files from the FDA Web site (www.fda.gov).

**Study Selection and Assessment of Validity**

We included studies if they were randomized, controlled trials of long-acting β-agonists compared with placebo and lasted at least 3 months. Two reviewers assessed the methodologic quality of each trial according to the following factors: 1) Was the randomization procedure adequate and was allocation concealment described? 2) Were patients and providers blinded to the interventions? 3) Were dropouts and withdrawals reported and was analysis performed by the intention-to-treat principle? Each of these quality domains was scored on a 3-point scale. Trials received an A score when all quality criteria for the domain were met, a B score when the criteria were partially met, and a C score when the criteria were not met. The quality assessment was used for a sensitivity analysis (27, 28).

**Data Extraction and Synthesis**

Two reviewers independently extracted data from the selected articles, reconciling differences by consensus. Outcomes assessed were severe asthma exacerbations requiring hospitalization, life-threatening asthma exacerbations requiring intubation and ventilation, and asthma-related deaths. Asthma deaths were those thought to be related to asthma as the underlying cause. Asthma deaths were also included as life-threatening exacerbations. We attempted to contact investigators to obtain additional information on asthma exacerbations and deaths.

The proportions of patients with severe exacerbations or asthma-related deaths to patients without those events from each trial were pooled by using the fixed-effects method expressed as a Peto odds ratio (OR) with corresponding 95% CIs (29, 30). We considered this method appropriate because we noted low event rates and minimal heterogeneity in the analyses. Evidence of interstudy heterogeneity was evaluated, with statistical significance set at an α value of 0.1. The analysis was performed by using Cochrane Review Manager 4.2 (Cochrane Library Software, Oxford, United Kingdom). Only trials that reported at least 1 event, such as hospitalization or death, could be used in the estimation of ORs. If more than 1 event occurred in the same patient, only the first event was counted.

Risk differences and exact 95% CIs were calculated for the difference between 2 independent binomial proportions (StatXact 7, Cytel Software, Cambridge, Massachusetts). The results for each trial were pooled by using the fixed-effects method (29). Trials that reported no events were included in the analysis of risk difference.

Subgroup analyses, chosen a priori, were performed to evaluate the difference in ORs between trials of salmeterol versus formoterol and trials in children (<12 years of age) versus adults. The results of the subgroups were compared with each other by using the test of interaction (31).

**Role of the Funding Source**

This analysis was funded by salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ornstein. The institution had no role in the design, conduct, or reporting of the study. All investigators had complete access to the data, and no sponsorship from the institution or the pharmaceutical industry was provided to conduct this analysis.

**Data Synthesis**

**Search Results**

Figure 1 shows the results of the search for articles. Through the MEDLINE search, we identified approximately 5000 articles, of which 133 were potentially relevant trials of long-acting β-agonist use in patients with asthma. After scanning references from selected articles and the FDA Web site, we identified an additional 6 trials. The
EMBASE and Cochrane databases provided no additional trials. Of these 139 trials, 47 met the inclusion criteria (4, 23, 32–76). Thirty of these trials did not report outcomes of interest. After we attempted to contact investigators, 2 responded with unpublished information on deaths (36, 39). The 28 trials that did not provide adequate information on exacerbations or asthma-related deaths (4, 50–76) were not included in the primary pooled analysis but were used in a sensitivity analysis to estimate the lower limit of risk difference by assuming that no deaths occurred in them.

Trials were excluded for the following reasons: One trial was not randomized, 1 trial was on asthma and chronic obstructive pulmonary disease (COPD), 30 trials did not compare a long-acting β-agonist with placebo, 51 trials lasted less than 3 months, and 9 trials provided duplicate data on participants from other trials.

**Trial Characteristics**

The primary analysis included 19 trials, with a total of 33,826 participants followed for 16,848 patient-years (Table). The mean trial duration was 6.0 months (range, 3 to 12 months), with a mean sample size of 1780 participants (range, 110 to 26,353 participants). The mean age of participants at baseline was 37.2 years (SD, 5.7) in the β-agonist group and 37.7 years (SD, 4.7) in the placebo group. The percentage of men in the 2 groups was 51.2% and 50.2%, respectively. Approximately 15% of the participants were African American. The dropout rate was 20.3% in the β-agonist group and 22.6% in the placebo group.

The long-acting β-agonists used in the studies were salmeterol, formoterol, and eformoterol. During the trials, concomitant inhaled corticosteroids were used in 53.9% of participants in the β-agonist group and 53.2% of those in the placebo group. Of note, all trials except 2 (36, 48) were sponsored by a pharmaceutical company that manufactures a long-acting β-agonist, and all allowed the use of as-needed short-acting β-agonists.

All trials were randomized, double-blind, placebo-controlled trials that performed analysis according to the intention-to-treat principle and described withdrawals. Nine trials described the method of randomization or allocation concealment, and 10 did not. No trial received the lowest quality score on any domain; therefore, no sensitivity analysis was performed.

**Quantitative Data Synthesis**

**Hospitalizations for Asthma Exacerbations**

The OR for hospitalization was 2.6 (CI, 1.6 to 4.3) (Figure 2) for long-acting β-agonists compared with placebo. The risk difference for hospitalization attributed to long-acting β-agonists was 0.7% (CI, 0.1% to 1.3%) over 6 months. We did not include SMART in this analysis because the investigators did not provide information on hospitalizations due to asthma, just life-threatening exacerbations. When we included the SMART data on life-threatening exacerbations, the OR was 2.1 (CI, 1.5 to 3.0).

Subgroup analyses evaluated results for children (33, 37, 46, 49) and adults (23, 34, 38, 40–45), and for salmeterol (23, 38, 40, 42, 46, 49) and formoterol (33, 34, 37, 41, 43–45). The risk for hospitalization was increased in children (OR, 3.9 [CI, 1.7 to 8.8]) and in adults (OR, 2.0 [CI, 1.0 to 3.9]). Results did not statistically significantly differ between the 2 groups (P = 0.22). The risk for hospitalization was also increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and with formoterol (OR, 3.2 [CI, 1.7 to 6.0]), without a statistically significant difference in results for the 2 agents (P = 0.109).
Life-Threatening Asthma Exacerbations

The OR for life-threatening asthma attacks attributed to long-acting \( \beta \)-agonists was 1.8 (CI, 1.1 to 2.9) (Figure 3), with a risk difference of 0.12% (CI, 0.01% to 0.3%) over 6 months. Results did not significantly differ between trials of children and adults or between salmeterol and formoterol.

Asthma-Related Deaths

Fourteen trials provided data on asthma-related deaths. Two trials reported 1 asthma death in the treatment group and 0 deaths in the placebo group. The SMART investigators reported 13 asthma-related deaths among 13 174 participants in the \( \beta \)-agonist group and 3 deaths among 13 179 participants in the placebo group. The OR for asthma-related deaths in SMART was 3.5 (CI, 1.3 to 9.3; \( P = 0.013 \)). The life-table estimate for relative risk for asthma-related deaths provided by SMART was 4.4 (CI, 1.3 to 15.3). When all trials with and without deaths were included in the analysis, the pooled risk difference was 0.07% (CI, 0.01% to 0.1%) over 6 months.

We did not include 28 trials in the primary analysis because they did not provide information on asthma-related deaths (2949 participants in the \( \beta \)-agonist group and 2795 in the placebo group). If we assume that no asthma-related deaths occurred in any of these trials and include them in the analysis, thus adding to the denominator, the absolute increase in risk is 0.06% over 6 months.

**DISCUSSION**

Pooled results from 19 trials with 33 826 participants followed for 16 848 patient-years showed that long-acting \( \beta \)-agonists increased the risk for hospitalization for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. Hospitalizations increased among adults and children and with salme-

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**Table. Studies Included in Primary Analysis**

<table>
<thead>
<tr>
<th>Study, Year (Reference), Duration</th>
<th>Study Group</th>
<th>Patients n</th>
<th>Mean Age, y</th>
<th>Men, %</th>
<th>Dropouts, %</th>
<th>Patients Receiving Inhaled Corticosteroids, %</th>
<th>Smokers, %</th>
<th>African-American Ethnicity, %</th>
<th>Quality Score†</th>
<th>Intervention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensch et al., 2001 (32), 12 wk</td>
<td>LABA</td>
<td>271</td>
<td>35.4</td>
<td>58.5</td>
<td>15.3</td>
<td>NS</td>
<td>NS</td>
<td>6</td>
<td>8</td>
<td>Formoterol, 12 ( \mu ) g and 24 ( \mu ) g BID</td>
<td>Albuterol also studied; sponsored by Novartis</td>
</tr>
<tr>
<td>Bensch et al., 2002 (33), 52 wk</td>
<td>LABA</td>
<td>342</td>
<td>9</td>
<td>60</td>
<td>20</td>
<td>&gt;75</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td>Formoterol, 12 ( \mu ) g and 24 ( \mu ) g BID</td>
<td>All patients received anti-inflammatory agents; trial 049; sponsored by Novartis</td>
</tr>
<tr>
<td>Russe et al., 2004 (34), 12 wk</td>
<td>LABA</td>
<td>80</td>
<td>39.1</td>
<td>38.5</td>
<td>12.5</td>
<td>81.3</td>
<td>0</td>
<td>NS</td>
<td>9</td>
<td>Formoterol, 10 ( \mu ) g BID</td>
<td>Albuterol also studied; sponsored by Novartis</td>
</tr>
<tr>
<td>D’Urzo et al., 2001 (35), 26 wk</td>
<td>LABA</td>
<td>455</td>
<td>46.5</td>
<td>47</td>
<td>19</td>
<td>93</td>
<td>NS</td>
<td>NS</td>
<td>8</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Sponsored by Glaxo Wellcome</td>
</tr>
<tr>
<td>Foradil 040 trial, 2001 (43), 12 wk</td>
<td>LABA</td>
<td>269</td>
<td>35.5</td>
<td>53</td>
<td>5.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>9</td>
<td>Formoterol, 12 ( \mu ) g and 24 ( \mu ) g BID</td>
<td>Phase III study; sponsored by Novartis</td>
</tr>
<tr>
<td>Foradil 041 trial, 2001 (44), 12 wk</td>
<td>LABA</td>
<td>275</td>
<td>32.6</td>
<td>53</td>
<td>6.2</td>
<td>45</td>
<td>NS</td>
<td>NS</td>
<td>9</td>
<td>Formoterol, 12 ( \mu ) g and 24 ( \mu ) g BID</td>
<td>Phase III study; sponsored by Novartis</td>
</tr>
<tr>
<td>Foradil 2307 trial, 2005 (45), 12 wk</td>
<td>LABA</td>
<td>1054</td>
<td>38.8</td>
<td>46</td>
<td>13.8</td>
<td>65</td>
<td>NS</td>
<td>12.7</td>
<td>9</td>
<td>Formoterol, 12 ( \mu ) g and 24 ( \mu ) g BID</td>
<td>Phase IV study; sponsored by Novartis</td>
</tr>
<tr>
<td>Lazarou et al., 2001 (36), 16 wk</td>
<td>LABA</td>
<td>54</td>
<td>31.6</td>
<td>38.9</td>
<td>24</td>
<td>53</td>
<td>0</td>
<td>12.9</td>
<td>9</td>
<td>Salmeterol, 42 ( \mu ) g BID</td>
<td>Triamicinolone also studied; unpublished information received‡</td>
</tr>
<tr>
<td>Levy et al., 2005 (37), 12 wk</td>
<td>LABA</td>
<td>127</td>
<td>9.4</td>
<td>74.8</td>
<td>8.7</td>
<td>74.8</td>
<td>0</td>
<td>NS</td>
<td>8</td>
<td>Formoterol, 10 ( \mu ) g BID</td>
<td>Sponsored by Novartis</td>
</tr>
<tr>
<td>Lockey et al., 1999 (38), 12 wk</td>
<td>LABA</td>
<td>234</td>
<td>40</td>
<td>41</td>
<td>15.0</td>
<td>67</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>Salmeterol, 42 ( \mu ) g BID</td>
<td>Sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>Price et al., 2002 (39), 26 wk</td>
<td>LABA</td>
<td>1054</td>
<td>38.3</td>
<td>42.4</td>
<td>21.9</td>
<td>100</td>
<td>NS</td>
<td>NS</td>
<td>8</td>
<td>Eformoterol, 9 ( \mu ) g BID</td>
<td>Sponsored by AstraZeneca; unpublished information received</td>
</tr>
<tr>
<td>Rosenbelt et al., 1999 (40), 24 wk</td>
<td>LABA</td>
<td>105</td>
<td>8.3</td>
<td>69</td>
<td>2.9</td>
<td>57</td>
<td>0</td>
<td>11</td>
<td>9</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>Salmeterol 5LD-390 trial, 2001 (47), 12 wk</td>
<td>LABA</td>
<td>1054</td>
<td>39.2</td>
<td>NS</td>
<td>22.5</td>
<td>49</td>
<td>NS</td>
<td>18</td>
<td>9</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Phase IV safety study; sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>SMART, 2006 (23), 28 wk</td>
<td>LABA</td>
<td>13 174</td>
<td>39.2</td>
<td>NS</td>
<td>22.5</td>
<td>49</td>
<td>NS</td>
<td>18</td>
<td>9</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Phase IV safety study; sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>Serevent 3041 trial, 2001 (46), 12 wk</td>
<td>LABA</td>
<td>229</td>
<td>8</td>
<td>14.8</td>
<td>47</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>Salmeterol, 25 ( \mu ) g and 50 ( \mu ) g BID</td>
<td>Phase III study; sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>Steffensen et al., 1995 (41), 12 wk</td>
<td>LABA</td>
<td>103</td>
<td>49</td>
<td>43.7</td>
<td>11.6</td>
<td>88</td>
<td>35.0</td>
<td>NS</td>
<td>8</td>
<td>Formoterol, 12 ( \mu ) g BID</td>
<td>Salbutamol also studied; sponsored by Ciba-Geigy</td>
</tr>
<tr>
<td>Taylor et al., 1998 (42), 24 wk</td>
<td>LABA</td>
<td>60</td>
<td>38</td>
<td>44.2</td>
<td>11.7</td>
<td>92</td>
<td>0</td>
<td>NS</td>
<td>9</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Salbutamol also studied; sponsored by GlaxoSmithKline</td>
</tr>
<tr>
<td>Von Berg et al., 2003 (48), 12 wk</td>
<td>LABA</td>
<td>164</td>
<td>11.4</td>
<td>66</td>
<td>6.1</td>
<td>82.1</td>
<td>0</td>
<td>NS</td>
<td>8</td>
<td>Formoterol, 4.5 ( \mu ) g and 9 ( \mu ) g BID</td>
<td>–‡</td>
</tr>
<tr>
<td>Weinstein et al., 1998 (49), 12 wk</td>
<td>LABA</td>
<td>102</td>
<td>8.5</td>
<td>68</td>
<td>9.8</td>
<td>57</td>
<td>0</td>
<td>14</td>
<td>8</td>
<td>Salmeterol, 50 ( \mu ) g BID</td>
<td>Sponsored by GlaxoSmithKline</td>
</tr>
</tbody>
</table>

* BID = 2 times per day; GSK = GlaxoSmithKline; LABA = long-acting \( \beta \)-agonist; NS = not stated; SMART = Salmeterol Multi-center Asthma Research Trial.
† Quality score was tabulated for each quality domain, with 3 points for an A score, 2 points for a B score, and 1 point for a C score, for a maximum total of 9 points.
‡ Not sponsored by a pharmaceutical company.
terol and formoterol. The results of SMART were similar to the pooled results from smaller studies.

In SMART, which followed 26,000 participants for 6 months, salmeterol compared with placebo was associated with a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma-related deaths (23). The trial did not provide data on asthma-related hospitalizations but reported an increase in all-cause hospitalization in the salmeterol group (4%) compared with the placebo group (3%) that approached statistical significance. One limitation of SMART is that patients with COPD were not excluded from the trial, and deaths from COPD were included as asthma-related deaths (23). Of note, 2 of the 3 asthma-related deaths in the placebo group were in patients older than 60 years of age, with 1 death listed as being due to COPD. In contrast, only 2 of the 13 asthma-related deaths in the salmeterol group were in patients older than 60 years of age, with 1 considered to be due to COPD. If

![Figure 2. Effect of long-acting β-agonists compared with placebo on odds ratio of hospitalizations for asthma exacerbation.](image)

![Figure 3. Effect of long-acting β-agonists compared with placebo on odds ratio of life-threatening asthma exacerbations.](image)
the reported COPD deaths were excluded from the analysis, salmeterol would be associated with a 6-fold increase in relative risk for asthma-related deaths.

To put these risks in perspective, it is necessary to understand the benefits that these agents provide. Unfortunately, all the trials evaluated allowed as-needed short-acting β-agonist use in both groups; thus, they were in effect comparing regular with as-needed β-agonist use. Some trials reported a reduction in asthma exacerbations associated with long-acting β-agonists (8, 9, 39, 42, 77). However, these trials used a definition of exacerbation that included clinical symptoms as well as a decrease in peak flows below a specified level in asymptomatic patients. The use of a short-acting β-agonist causes peak flows to regularly decrease below baseline levels as the effect of the medication wears off (77). Therefore, patients in the placebo group who are using intermittent short-acting β-agonists may be expected to have asymptomatic decreases in peak flow that would be called an exacerbation. This could explain why a reduction in exacerbations could be seen with long-acting β-agonists if this definition is used, even though the drug may actually increase true clinical exacerbations that are associated with hospitalization, intubation, or death.

Inhaled β-agonists are also widely used to treat COPD, although inhaled anticholinergics such as ipratropium and tiotropium have been shown to have equal or superior efficacy compared with β-agonists (78, 79). A recent meta-analysis pooled the results of 22 randomized trials, which followed more than 15 000 participants with COPD, and found that inhaled anticholinergics reduced respiratory deaths by 70% (relative risk, 0.3 [CI, 0.1 to 0.8]) while β-agonists increased respiratory deaths by more than 2-fold (relative risk, 2.5 [CI, 1.1 to 5.5]) compared with placebo (80).

Long-acting β-agonists may worsen asthma control by means of a negative feedback mechanism of the β-adrenergic system that is an adaptive response to stimulation of receptors (21). Stimulation results in uncoupling and internalization of receptors, which is known as desensitization, followed by a decrease in receptor density and receptor gene expression, which is known as downregulation (21). Regular use of β-agonists has been shown to increase bronchial hyperreactivity despite maintenance of some degree of bronchodilation (15, 65, 73, 81). These effects, along with a reduction in response to subsequent rescue β-agonist use, may worsen asthma control without giving any warning of increased symptoms (15, 51, 73, 82).

Inhaled corticosteroids have been shown to reduce bronchial inflammation and asthma exacerbations and to partially protect against the adverse effects seen with regular β-agonist use (9, 18, 83–86). Despite this protective effect, regular β-agonist use with concomitant inhaled corticosteroids still results in substantial tolerance over time (15, 87, 88). For example, in this meta-analysis, we separately evaluated trials in which more than 75% of partici-
and result in slightly more favorable symptom scores (81, 105).

Our analysis has several limitations. Standard metaanalytic results for ORs and risk differences can be uncertain when the numbers of events per study are small, as is the case with asthma-related deaths. The accurate assessment of asthma-related deaths in this analysis was further hindered by the fact that many trials did not provide this information, and also by the difficulty inherent in ascertaining the true cause of death. The OR for deaths in this analysis was obtained solely from SMART. However, the increased OR found in this trial was statistically significant. In addition, the absolute increase in risk was estimated by pooling all trials with and without deaths through the use of exact statistical methods; this finding was also statistically significant. Our analysis was based mainly on published literature and therefore may be subject to publication bias. However, we also included unpublished trials listed on the FDA Web site, and funnel plots of effect size versus standard error found no evidence for bias. Finally, it is unfortunate that no true placebo-controlled trials of long-acting β-agonist use in asthma have been published. Despite these limitations, we believe that this meta-analysis provides valuable information on the effect of long-acting β-agonist use on severe adverse clinical outcomes.

In summary, long-acting β-agonist use increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. Similar risks are found with salmeterol and formoterol and in children and adults. Concomitant inhaled corticosteroids do not adequately protect against the adverse effects. The use of long-acting β-agonists could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions, and deaths each year. Black box warnings on the labeling for these agents clearly outline the increased risk for asthma-related deaths associated with their use, but these warnings have not changed prescribing practices of physicians (25). This information could be used to reassess whether these agents should be withdrawn from the market.

From Santa Clara Valley Medical Center, San Jose, California, and Cornell University, Ithaca, New York.

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Potential Financial Conflicts of Interest: None of the authors have had any relationships with a pharmaceutical company that manufactures a β-agonist or other respiratory medications. Dr. Shelley Salpeter has consulted on legal cases involving β-agonists but has never given expert testimony and has no contracts with law firms.

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