Are There Any Detrimental Effects of the Use of Inhaled Long-Acting \( \beta_2 \)-Agonists in the Treatment of Asthma?*

Michael A.B. Devoy, MD; Richard W. Fuller, MD; and James B.D. Palmer, MD

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BDP=beclomethasone dipropionate

Key words: asthma; \( \beta \)-agonist; formoterol; long-acting; morbidity; mortality; safety; salmeterol

It is widely accepted that short-acting inhaled \( \beta_2 \)-agonists, such as albuterol, represent the most appropriate bronchodilator therapy in the treatment of asthma. Indeed, all international and national treatment guidelines agree that they are the agents of choice to relieve bronchoconstriction in acute asthma.\(^1\)\(^2\) There has been considerable debate, however, as to the therapeutic value of regular inhaled short-acting \( \beta_2 \)-agonists long term.\(^3\)\(^4\) Particularly at issue is the concern that they may have the potential to worsen asthma control, thereby contributing to an increase in asthma mortality observed in certain countries.

Salmeterol and formoterol are two long-acting inhaled \( \beta_2 \)-agonists that have been developed for use as maintenance treatment in asthma.\(^5\) To obtain maximum benefit from these long-acting drugs they have to be taken regularly to prevent symptoms rather than on an "as required basis" to treat symptoms; it is under these circumstances that the longer duration of action gives advantages over shorter-acting drugs. It is appropriate, therefore, to review available data to see whether the concern surrounding the use of short-acting \( \beta_2 \)-agonists should apply equally in the case of long-acting inhaled \( \beta_2 \)-agonists. It might be reasonable to expect that any potential adverse effects of regular \( \beta_2 \)-agonist use would be more obvious with more potent, selective, long-acting agents.

The present article will review the effects of long-acting inhaled \( \beta_2 \)-agonists focusing on the major areas of debate with respect to \( \beta_2 \)-agonist safety and efficacy. We will concentrate on the effects of salmeterol and formoterol rather than on the potential adverse effects associated with the regular use of short-acting \( \beta_2 \)-agonists, about which so much has been written already.\(^6\)\(^7\)\(^8\)

The data presented herein are the product of a comprehensive literature search that was extended to include an on-line search of all relevant databases as of July 1994.

Does Regular Drug Therapy With Inhaled Long-Acting \( \beta_2 \)-Agonists Improve Overall Control of Bronchial Asthma?

In a study by Sears et al,\(^6\) an apparent deterioration in asthma control was related to regular use of inhaled fenoterol, a short-acting \( \beta_2 \)-agonist unavailable in the United States. The authors generalized their conclusion to include other \( \beta_2 \)-agonists and the new long-acting drugs. The design, interpretation, and conclusions of this study have been criticized.\(^7\)\(^8\) In a recent publication the same study is presented, but now in more detail showing that the differences between treatment periods were small and of doubtful clinical significance.\(^9\)\(^10\) The results of extensive clinical trial programs with salmeterol and formoterol\(^11\) also do not support the suggestions of the study by Sears et al.\(^6\)

The asthma exacerbation rate is possibly the most important measure of overall asthma control. The logical progression of the hypothesis of Sears et al,\(^6\) namely that regular use of \( \beta_2 \)-agonists leads to a worsening of asthma control, would be for the rate of exacerbations to rise following the use of more potent, selective, longer-acting \( \beta_2 \)-agonists in place of shorter-acting drugs used regularly or on demand. We have recently reported two large 12-month studies conducted outside the United States where salmeterol, 50 \( \mu \)g twice a day has been compared with albuterol, 200 to 400 \( \mu \)g four times daily.\(^12\)\(^13\) Far from suggesting that salmeterol might worsen asthma control, the results show significantly fewer exacer-

*From the Department of Respiratory Medicine, Glaxo Research and Development Usbridge, United Kingdom (Dr. Devoy and Fuller), and Glaxo Research Institute, Triangle Park, North Carolina (Dr. Palmer).

Reprint requests: Dr. Devoy, Glaxo Research and Development Ltd, Greenford Road, Greenford, Middlesex UB6 0HE
trary to treated with albuterol exacerbation of asthma ber albuterol, salmeterol were albuterol used formoterol, group daily, over rate highest most of regular albuterol, studies have however, albuterol and ular studies that incidence all rate number oral glucocorticosteroids. It may be considered a limitation of the above studies that they compared salmeterol only with regular albuterol and not with placebo. Similar results, however, have been published from two multicenter studies conducted in the United States evaluating salmeterol, 50 μg twice a day by comparison with regular albuterol, 200 μg four times daily, and albuterol used as required. Patients taking regular salmeterol were found to have the lowest rate of exacerbation (1.6/1,000 patient days) while those treated with albuterol on demand experienced the highest rate (2.9/1,000 patient days), which is contrary to what would be predicted if regular use of β₂-agonists was worsening asthma control.

Kesten et al compared treatment with formoterol, 12 μg twice and albuterol, 200 μg four times daily, over 12 weeks in 145 asthmatic patients. For most of the 12-week period, the mean weekly number of asthma episodes was significantly lower in the formoterol group than in the albuterol group. The study was extended for an additional 9 months in an open design with 112 patients taking regular formoterol during which there was no evidence of deteriorating asthma control.

**DOES REGULAR USE OF INHALED LONG-ACTING β₂-AGONIST THERAPY IMPROVE LUNG FUNCTION?**

In a study in Holland, van Schayck et al reported that regular use of short-acting β₂-agonists may be associated with a decline in lung function over a 2-year treatment period. Other investigators have suggested that there is evidence of a "rebound" effect, or a sudden deterioration in symptoms, on cessation of treatment. However, when the Dutch workers prolonged their study for 2 more years, they could find no significant difference in the rate of decline in lung function between patients using bronchodilators continuously or on demand. Long-term studies of salmeterol and formoterol have shown a significant and sustained improvement in lung function with no evidence of deterioration or rebound effects.

Kesten et al., in their 3-month study, found formoterol to be associated both with a significant and well-maintained improvement in FEV₁ as well as a significant reduction in diurnal variation in peak expiratory flow rate. When the study was prolonged for 9 more months, far from any evidence of a deterioration in lung function, patients showed a nonsignificant tendency to continued improvement. In particular, FEV₁ readings in patients who had transferred to formoterol from albuterol after the initial 3-month study improved significantly, maintaining that improvement for the duration of the 9-month extension.

By comparison with regular or on-demand treatment with albuterol, placebo-controlled studies using salmeterol show a sustained and significant
Throughout their 12-week study, Pearlman et al. found salmeterol to increase morning and evening peak flow significantly (24 and 25 L/min, respectively), and to be associated with significantly better FEV₁ readings than albuterol on demand at day 1 and at weeks 4, 8, and 12. Studies evaluating the effects of salmeterol over a 12-month period confirm this level of improvement to be maintained throughout, with no evidence of deterioration. In one of these studies, Britton et al. reported a 0.3-L increase in FEV₁ observed after 3 months’ treatment with salmeterol 50 μg twice a day, was maintained for a further 9-month study period. A consistent improvement in lung function over a 12-month treatment period has also been demonstrated by the two other long-term salmeterol studies. Elsewhere, data have been presented on formoterol usage in a 3-year open study involving 66 patients suffering from moderate to severe asthma. Compared with symptoms in the year prior to formoterol usage, the results show well-preserved pulmonary function and fewer asthma exacerbations requiring oral steroid therapy.

There is also no evidence of tachyphylaxis to the bronchodilating effects of salmeterol and formoterol in regular long-term treatment. In the study by Pearlman et al., the bronchodilator response to salmeterol was maintained throughout the 12-week period as reflected by the FEV₁ area under the curve for salmeterol at each of the four evaluations. Several studies have shown no tolerance to the bronchodilating effects of inhaled albuterol in patients receiving regular salmeterol or formoterol for up to a year. In one of these studies, 18 patients participated in a comparison of albuterol, 200 μg twice a day with formoterol, 12 μg twice a day. Of these 18 patients, 10 were randomly allocated to treatment with formoterol and 8 to treatment with albuterol. After 1, 2, and 3 months, patients were allowed to shift over to the alternative treatment if they were not satisfied with their asthma control. After 1 year, 13 of the 16 patients who completed the study were still using formoterol, for which they expressed a significant long-lasting preference. Dose-response curves for inhaled albuterol, recorded repeatedly during the study, showed no evidence of tachyphylaxis.

In another 12-month study involving 11 asthmatic patients taking salmeterol, 50 μg twice a day, cumulative dose-response curves to inhaled albuterol were performed prior to, and after 3, 6, 9, and 12 months’ treatment. Patient response to albuterol was well maintained over the 12-month period and showed no signs of tolerance. In the absence of any prettrial run-in period, however, during which β₂-agonist treatment was prohibited, the only definitive conclusion that may be drawn by this study is that salmeterol does not induce greater tolerance than any other β₂-agonist.

Salmeterol has not only been shown to exert a significant beneficial effect on lung function by comparison with placebo and other bronchodilators but has also been compared with increasing the dose of inhaled glucocorticosteroid. In two studies sponsored by a manufacturer (Glaxo), salmeterol has also been compared with increased doses of inhaled glucocorticosteroid in patients who remained symptomatic while receiving low or high doses of inhaled beclomethasone dipropionate (BDP). One of these studies compared the effects of adding salmeterol to the treatment regimen of 429 asthmatic patients who remained symptomatic while receiving 200 μg of BDP twice daily, with that of more than doubling the dose of BDP to 500 μg twice daily. The results, in terms of both lung function and symptoms, were consistently better in the salmeterol/corticosteroid group than in the higher-dose BDP group. There were no differences between the two groups in unwanted effects or exacerbations of asthma, indicating that, for this group of patients, regular salmeterol treatment was not associated with any evidence of deteriorating asthma control over a 6-month period and was better than increasing the dose of inhaled corticosteroids at improving lung function.

Similar results were obtained in the second study in patients with initially more severe asthma. Seven hundred thirty-nine patients symptomatic despite 800 to 1,000 μg of inhaled steroid per day entered one of three limbs: 1,000 μg of BDP per day plus either 50 μg or 100 μg of salmeterol twice daily, or increasing the dose of BDP to 2,000 μg/d. As in the previous study, the salmeterol/BDP groups were significantly better than the high-dose BDP group.
with respect to symptom control and lung function. There was no difference among the three groups with respect to asthma exacerbations and no evidence of any rebound in bronchial responsiveness in the salmeterol/BDP groups.

**Does Regular Use of Inhaled Long-Acting \( \beta_2 \)-Agonist Drug Therapy Improve Airway Responsiveness?**

The suggestion that short acting \( \beta_2 \)-agonists may have a clinically significant adverse effect on bronchial reactivity is not supported by a recent comprehensive review of available data. Nevertheless, a number of studies investigating the effects of short-acting \( \beta_2 \)-agonists have provided evidence of a possible rebound increase in bronchial reactivity once regular treatment has ended.

In single-dose studies, the long-acting drugs formoterol and salmeterol have been shown to provide long-lasting protection from histamine, methacholine, exercise, and cold air challenge. Salmeterol has been observed to inhibit both the early and late phase of allergen-induced airway obstruction over 34 h, together with inhibition of the concomitant allergen-induced rise in airway sensitivity to histamine. While researchers initially postulated the existence of an anti-inflammatory component within this prolonged protection, the exact mechanism of action remains unclear. It may simply be functional antagonism and as such an expression of the long-lasting bronchodilatory action of salmeterol. Functional antagonism was the mechanism favored by researchers when studying the reduction in allergen-induced increase in airway sensitivity recorded 24 h after patients inhaled a single dose of formoterol.

Most published studies examining the effects of long-term dosing with long-acting \( \beta_2 \)-agonists on bronchial reactivity have used salmeterol, the only \( \beta_2 \)-agonist shown to reduce the maximal response plateau to methacholine challenge. None of these studies shows evidence of rebound hyperresponsiveness after maintenance treatment and no tolerance has been seen to the acute bronchodilator effect after long-term dosing. One study comparing salmeterol, 50 \( \mu \)g twice daily, with placebo over an 8-week period found evidence of a partial reduction in the short-term protection afforded against methacholine challenge, 1 h after dosing. After 4 and 8 weeks' treatment, PC20 was reduced from 3.3 to 1.0 doubling doses, a reduction that nevertheless constituted a significant protective effect. This degree of protection is of similar magnitude to that reported by the same workers examining the effects of regular use of inhaled corticosteroids. The results of this study should be contrasted with those of Booth and colleagues who looked at protection against methacholine challenge 12 h after treatment in patients taking salmeterol, 50 \( \mu \)g twice daily for 8 weeks. Their results showed no reduction in protection throughout an 8-week period.

In another study, formoterol was shown to offer well-maintained protection against histamine-induced airway obstruction during 3 months' treatment, with no rebound increase after cessation of treatment. In conclusion, there appears to be little if any clinically relevant loss of protection during prolonged treatment with salmeterol or formoterol and no evidence of a "rebound" increase in bronchial reactivity.
IS THERE SUFFICIENT EVIDENCE TO SUBSTANTIATE A RELATIONSHIP BETWEEN LONG-ACTING \( \beta_2 \)-AGONIST USE AND MORBIDITY/MORTALITY OF ASTHMA?

The most plausible explanation for the reported association between \( \beta_2 \)-agonist use and asthma mortality is one of confounding by severity that views high usage of inhaled \( \beta_2 \)-agonists as a marker of severe, deteriorating asthma.\(^5\) This is the explanation favored by Suissa and colleagues\(^50\) in a recently published analysis of data submitted by the Saskatchewan Asthma Epidemiology Project. Mullen et al.\(^51\) in their recent meta-analysis of studies in this area, found no significant association between \( \beta_2 \)-agonist use and death when \( \beta_2 \)-agonists were delivered either orally or via a metered-dose inhaler. It was only when \( \beta_2 \)-agonists were administered via a nebulizer that any statistically significant relationship, albeit a weak one, was found. The relationship probably reflects only that nebulizers are used mainly for patients with severe asthma.

A clear link between \( \beta_2 \)-agonists use and asthma severity, however, was shown by Castle and colleagues.\(^52\) In one of the largest double-blind clinical studies ever conducted in the United Kingdom, involving over 25,000 asthmatic patients, researchers compared the effects of salmeterol, 50\( \mu \)g twice a day, with those of albuterol, 400\( \mu \)g four times a day over 4 months. On entry to the trial, patients were rated as having mild, moderate, or severe asthma by their physician, a rating that was closely correlated with use of all asthma treatments, \( \beta_2 \)-agonists, and inhaled and oral corticosteroids. The study found nothing to indicate that regular treatment over a 4-month period with either salmeterol or albuterol was associated with an incidence of asthma deaths in excess of that predicted for the study population (14 vs 15). The results demonstrated the importance of recognizing the symptoms of deteriorating asthma and giving appropriate treatment with inhaled and oral steroids.

Physicians and patients alike should be aware that asthmatics who require increasing doses of short-acting \( \beta \)-agonists to relieve symptoms are at risk of death. When Castle’s results were debated after publication,\(^55-56\) it was noted that the study had a relatively low power to detect a difference in asthma deaths.\(^54\) As the authors of this study pointed out,\(^56\) however, it would not have been feasible to mount and complete a larger study in a reasonable time frame. Another concern, expressed by Sears and Taylor,\(^57\) was the distribution of deaths among the younger patients involved in the study. Again, the authors explained\(^58\) that the study included a relatively large proportion of younger patients by comparison with older patients, an age distribution that was reflected in the distribution of deaths.

In addition to the data provided by Castle et al.\(^52\) the safety of salmeterol in clinical use in the United Kingdom has been studied in an independent prescription event monitoring study by the Drug Safety Research Unit in Southampton, United Kingdom.\(^50\) This study monitored exposure data based on prescriptions for salmeterol and was an attempt to provide safety data on the drug based on information gained from “real life” general medical use. In a cohort of 15,407 patients who were prescribed salmeterol for at least 1 year, there were 39 asthma-related deaths among patients who had been taking salmeterol during the last month of their life and 73 asthma-related deaths overall. These figures are considerably lower than the authors first estimated and indicate that the mortality rate was higher in the early part of the study. The authors suggest that these data reflect the fact that when salmeterol was first marketed in the United Kingdom, general practitioners prescribed it for patients with particularly severe and unstable asthma. The mean age of patients dying in this study was 60.5 years, which does not suggest that salmeterol was associated with a greater risk in younger patients.

The methods outlined above probably constitute the best techniques available to monitor the safety of new drugs and identify possible concerns not recorded in preregistration studies. However, useful information can sometimes also be gained from the case reports from individual clinicians. In relation to salmeterol, there have been at least two publications that are relevant.\(^60,61\) Clark and colleagues\(^60\) reported three cases of respiratory arrest in asthmatics recently prescribed salmeterol and expressed concern that there might be a relationship between the two events. However, as Shale\(^62\) pointed out in a subsequent letter, in each case, there were other plausible explanations for a deterioration in the patients’ asthma and that these case reports were circumstantial. In the other case report by Wilkinson and colleagues,\(^63\) the authors described six cases of acute bronchospasm induced by inhaling salmeterol by metered-dose inhaler but not by a dry powder formulation. This, however, seems to be a rare event based on data from a double-blind, parallel group study in 11,580 patients that compared salmeterol placebo aerosols containing either lecithin or oleic acid with a standard salmeterol aerosol containing lecithin dispersant.\(^63\) The incidence of paradoxical bronchospasm after salmeterol was 1.1%, which was significantly lower than either of the placebo groups.

An alternative way of looking for an association with asthma mortality is to examine asthma mortality figures in England and Wales since salmeterol has been available for use. Given the level of patient exposure to salmeterol, an overt effect on overall asthma
Table 1—Clinical Studies With Salmeterol as Referenced in Text*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration</th>
<th>n</th>
<th>Salmeterol Dose, μg</th>
<th>Comparator(s)</th>
<th>Morning PEF</th>
<th>Sympoms</th>
<th>β2-Agonist</th>
<th>Exacerbations</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britton et al12</td>
<td>12 mo</td>
<td>667</td>
<td>50 bd</td>
<td>Albuterol 200/400 qid</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>Fewer with S</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Lundbäck et al13</td>
<td>12 mo</td>
<td>303</td>
<td>50 bd</td>
<td>Albuterol 200/400 qid</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>Fewer with S</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Pearlman et al15</td>
<td>3 mo</td>
<td>234</td>
<td>50 bd</td>
<td>Albuterol 200 qid Placebo</td>
<td>S&gt;A&gt;P</td>
<td>S&gt;A=P</td>
<td>S&gt;A&gt;P</td>
<td>Fewer with S</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>D’Alonzo et al16</td>
<td>3 mo</td>
<td>322</td>
<td>50 bd</td>
<td>Albuterol 200 qid Placebo</td>
<td>S&gt;A&gt;P</td>
<td>S&gt;A=P</td>
<td>S&gt;A&gt;P</td>
<td>Fewer with S</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Ullman et al22</td>
<td>2 wk</td>
<td>12</td>
<td>50 bd</td>
<td>Albuterol 200 qid</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>S&gt;A</td>
<td>NR</td>
<td>Few reports</td>
</tr>
<tr>
<td>Lötvall et al23</td>
<td>12 mo</td>
<td>11</td>
<td>50 bd</td>
<td>...</td>
<td>No evidence of decreased β2-receptor sensitivity</td>
<td>S+B&gt;BB</td>
<td>S+B&gt;BB</td>
<td>S+B&gt;BB</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Greening et al24</td>
<td>6 mo</td>
<td>426</td>
<td>50 bd</td>
<td>BDP</td>
<td>S&gt;B&gt;BB</td>
<td>S&gt;B&gt;BB</td>
<td>S&gt;B&gt;BB</td>
<td>No difference between groups</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Woolcock et al25</td>
<td>6 mo</td>
<td>739</td>
<td>50+100 BDP</td>
<td>S&gt;B&gt;BB</td>
<td>S&gt;B&gt;BB</td>
<td>S&gt;B&gt;BB</td>
<td>No difference between groups</td>
<td>Well tolerated</td>
<td></td>
</tr>
<tr>
<td>Derom et al35</td>
<td>Single dose</td>
<td>12</td>
<td>50+100</td>
<td>Albuterol 200 μg Placebo</td>
<td>Long-lasting protection against methacholine challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newnham et al36</td>
<td>Single dose</td>
<td>12</td>
<td>50</td>
<td>Albuterol 200 μg Placebo</td>
<td>Long-lasting protection against exercise challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nowak et al37</td>
<td>Single dose</td>
<td>16</td>
<td>50</td>
<td>Albuterol 200 μg Placebo</td>
<td>Long-lasting protection against hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twentyman et al38</td>
<td>Single dose</td>
<td>10</td>
<td>50</td>
<td>Placebo</td>
<td>Inhibits early and late phase allergen-induced airway obstruction for 34 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl et al43</td>
<td>4 wk</td>
<td>12</td>
<td>50 bd</td>
<td>Placebo</td>
<td>Decrease in number of inflammatory cells</td>
<td>S&gt;A</td>
<td>No adverse events, no adverse effects on AR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beach et al44</td>
<td>6 wk</td>
<td>20</td>
<td>50 bd</td>
<td>Albuterol 200 μg bead</td>
<td>Decreased bronchial reactivity to histamine, no rebound hyperresponsiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts et al45</td>
<td>6 wk</td>
<td>23</td>
<td>50 bd</td>
<td>Placebo</td>
<td>Partial reduction in short-term protection afforded against methacholine challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheung et al46</td>
<td>8 wk</td>
<td>12</td>
<td>50 bd</td>
<td>Placebo</td>
<td>No reduction in long-lasting protection against methacholine challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booth et al47</td>
<td>8 wk</td>
<td>26</td>
<td>50 bd</td>
<td>Placebo</td>
<td>Agents not associated with an increase in mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castle et al52</td>
<td>4 mo</td>
<td>25,180</td>
<td>50 bd</td>
<td>Albuterol 200 qid</td>
<td>No reduction in long-lasting protection against methacholine challenge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*S=salmeterol; A=albuterol; P=placebo; BDP or B=beclomethasone dipropionate; BB=double dose of BDP; NR=not recorded; AR=airway responsiveness; S>A=denotes that salmeterol was significantly (p≤0.05) better than albuterol; S>A=P=denotes that salmeterol was significantly (p≥0.05) better than albuterol which was significantly better than placebo; S>A=P denotes that salmeterol was significantly (p≥0.05) better than albuterol which was equal to placebo; S+B>BB denotes that salmeterol plus BDP was significantly (p≥0.05) better than double the dose of BDP; bd=twice a day; qid=four times a day; PEF=peak expiratory flow.

The mortality would be apparent if the drug was associated with an increased risk of asthma death. As Figure 3 shows, while patient exposure to salmeterol increased to a level of 57,000 patient years in the first 2 years of availability in England and Wales, there was no increase in asthma mortality. This is consistent with the observation that there was an approximately threefold increase in the prescription of β2-agonists in the United Kingdom during the 1980s while the asthma mortality figures remained constant throughout the decade. A similar experience has been reported from Sweden.3
CONCLUSION

To our knowledge, there have been no studies published that unequivocally demonstrate a deleterious effect on asthma morbidity and mortality of regular β2-agonist use. Long-acting β2-agonists might be reasonably expected to exhibit more prominently any deleterious effects if these do occur. However, studies with both formoterol and salmeterol have not shown any evidence of reduced asthma control, deterioration in lung function, or increased airway responsiveness (Tables 1 and 2). Furthermore, there is no evidence of a relationship between these drugs and increased asthma mortality. On the contrary, large well-designed clinical trials have shown improvements in lung function and overall asthma control and strongly contradict the hypothetical arguments that propose that β2-agonists have a deleterious effect on asthma morbidity and mortality.

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