Long-acting Beta-Agonists with and without Inhaled Corticosteroids and Catastrophic Asthma Events

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ABSTRACT

BACKGROUND: It is unclear whether long-acting β-agonists with concomitant inhaled corticosteroids increase asthma-related intubations and deaths. We pooled data on long-acting β-agonists with variable and concomitant inhaled corticosteroids to evaluate the risk for catastrophic asthma events.

METHODS: We conducted searches of electronic databases, the US Food and Drug Administration website, clinical-trials registries, and selected references through December 2008. We analyzed randomized controlled trials in patients with asthma, which lasted at least 3 months, evaluated long-acting β-agonists compared with placebo or long-acting β-agonists with inhaled corticosteroids compared with corticosteroids alone, and included at least 1 catastrophic event, defined as asthma-related intubation or death.

RESULTS: In pooled trial data that included 36,588 participants, long-acting β-agonists increased catastrophic events 2-fold (Peto odds ratio [OR] 2.10; 95% confidence interval [CI], 1.37-3.22). Statistically significant increases were seen for long-acting β-agonists with variable corticosteroids compared with placebo (OR 1.83; 95% CI, 1.14-2.95) and for concomitant treatment with corticosteroids compared with corticosteroids alone (OR 3.65; 95% CI, 1.39-9.55). Similar increases in risk were seen for variable and concomitant corticosteroid use, salmeterol and formoterol, and children and adults. When the analysis was restricted to trials with controlled corticosteroid use, given as part of the study intervention, concomitant treatment still increased catastrophic events compared with corticosteroids alone (OR 8.19; 95% CI, 1.10-61.18).

CONCLUSION: Long-acting β-agonists increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.© 2010 Elsevier Inc. All rights reserved.

KEYWORDS: Asthma; Inhaled corticosteroids; Intubation; Long-acting beta-agonists; Meta-analysis; Mortality

There has been growing concern about asthma-related morbidity and mortality associated with the long-acting β-agonists salmeterol and formoterol, given with or without concomitant inhaled corticosteroids.1-3 Pooled trial data have consistently shown that long-acting β-agonists, when given with variable inhaled corticosteroid use, increase the risk for asthma-related hospitalizations, intubations, and deaths.4-8 In July 2005 an advisory committee to the US Food and Drug Administration (FDA) concluded that Boxed Warnings of an increased risk for asthma-related mortality should be placed on all products containing long-acting β-agonists, with recommendations for treatment only after other asthma drugs have failed.1 The FDA subsequently requested data from sponsors of long-acting β-agonists (GlaxoSmithKline, Brentford, London, England; AstraZeneca, Wilmington, Del; and Novartis, Basel, Switzerland) on asthma-related intubations and deaths that occurred during published and unpublished randomized trials, as of January 2008.9-11 Several meta-analyses have been performed, most with the cooperation or sponsorship of the pharmaceutical industry, which evalu-
ated long-acting β-agonists with concomitant inhaled corticosteroids. These analyses consistently reported more asthma intubations and deaths for combined treatment compared with inhaler corticosteroids alone, but none reached statistical significance. However, each of these studies restricted their analyses to a subset of the total available data, for example, including only trials with salmeterol, formoterol, adults, asthma deaths, published reports of events, single drug sponsors, or FDA-approved dosages of long-acting β-agonists.

In December 2008 a follow-up FDA advisory committee meeting concluded that the risks of salmeterol (Serevent, GlaxoSmithKline) and formoterol (Foradil, Novartis) outweighed the benefits and should be banned for use in asthma for all ages. The committee separately evaluated long-acting β-agonists combined with a corticosteroid in a single inhaler, such as salmeterol with fluticasone (Advair, GlaxoSmithKline) and formoterol with budesonide (Symbicort; AstraZeneca), and concluded that further safety studies were needed to assess risk.

The objective of this meta-analysis is to pool all the available data on long-acting β-agonists with variable and concomitant inhaled corticosteroids, evaluating the risk for asthma-related intubations or deaths. Subgroup analyses will compare results between variable and concomitant corticosteroids, salmeterol and formoterol, adults and children, and fatal and nonfatal events.

MATERIALS AND METHODS

Trial Inclusion
We performed a search of the MEDLINE, EMBASE, and Cochrane databases; the US FDA website; clinical-trials registries of drug manufacturers; and previous meta-analyses to identify trials on long-acting β-agonist use in patients with asthma published through December 2008. Studies were included if they were randomized controlled trials of long-acting β-agonists compared with placebo or long-acting β-agonists with inhaled corticosteroids compared with an equal or higher dose of inhaled corticosteroids alone of at least 3 months duration that reported at least 1 asthma-related intubation or death. We included reports of events that were provided by the investigator in the published trial or by the drug manufacturer in a subsequent account. In addition, we included pooled trial data from GlaxoSmithKline, because we were unable to obtain individual trial-level information for those events.

Outcome Measures
Two reviewers independently extracted data from the selected articles, reconciling differences by consensus. Outcomes assessed were catastrophic asthma events, defined as asthma-related intubations or deaths that were reported by the investigator or the industry sponsor. Attempts were made to contact investigators of previous meta-analyses and the industry sponsors to obtain additional information concerning trials and events.

Statistical Analysis
The proportions of patients with a catastrophic event to those without events from each trial were pooled using the fixed-effects method expressed as a Peto odds ratio (OR) with corresponding 95% confidence intervals. This method was chosen because we noted low event rates and minimal interstudy heterogeneity in the analysis. The results were then compared with those found with the random-effects method. Evidence of interstudy heterogeneity was evaluated, with statistical significance set at alpha = 0.1. The analysis was performed using Cochrane Review Manager 4.2 (Cochrane Library Software, Oxford, UK).

Only trials that reported at least 1 event could be used in the estimation of odds ratios. A subsequent analysis included all trials, published and unpublished, with and without reported events, to estimate an absolute increase in risk; these results are reported in the “Discussion” section.

Subgroup analyses, chosen a priori, were performed to evaluate the difference in results between trials with variable corticosteroids (use in <100% of participants) versus concomitant corticosteroids (use in 100% of participants), salmeterol versus formoterol, children (aged <12 years) versus adults, and fatal versus nonfatal events. Further subgroup analysis compared results between trials with no corticosteroid use at all and trials with the controlled use of corticosteroid as a study drug in combination with a long-acting β-agonist (either in a single inhaler or separate inhalers). The results of the subgroups were compared with each other using the test of interaction.

A sensitivity analysis was performed to evaluate the effect of excluding pooled trial data from GlaxoSmithKline, because individual trial-level information was not available for these events.

Role of the Funding Source
The funding for this analysis came from salary support from Santa Clara Valley Medical Center for Drs Salpeter and
RESULTS

Search Results

Figure 1 shows the results of the search for articles. The search identified approximately 6500 articles, of which 211 were potentially relevant trials. Of these, 10 individual trials met the inclusion criteria. 20-29 GlaxoSmithKline provided additional pooled trial data for long-acting β-agonists with and without concomitant inhaled corticosteroids. 9 For the meta-analysis, these data were considered to be 2 pooled trials of long-acting β-agonists, one without any concomitant corticosteroid use and one with background corticosteroid use in all patients.

Trials were excluded for the following reasons: Two trials were not randomized, 2 trials were of asthma and chronic obstructive pulmonary disease, 19 trials did not have the appropriate comparator groups, 70 trials were of less than 3 months duration, 23 trials provided duplicate data on participants from other trials, and 83 trials did not report adverse events.

Trial Characteristics

The meta-analysis included a total of 36,588 participants followed for 21,343 patient-years (Table 1, online). The mean trial duration was 7.0 months (range, 3-12 months), with a mean study size of 3183 participants (248-26,353). The mean (standard deviation) age of participants at baseline was 38.3 (1.7) years (45.3% were men) in the β-agonist group and 38.7 (1.1) years (44.8% were men) in the control group. The dropout rate was 19.2% in the β-agonist group and 21.4% in the control group. All trials were randomized, double-blind trials that performed analysis according to intention-to-treat.

Five trials evaluated β-agonists with variable inhaled corticosteroid use, with a total of 29,335 participants followed for 14,932 patient-years. Inhaled corticosteroids were used by 47.9% of the participants.

Seven trials evaluated β-agonists with concomitant inhaled corticosteroids, with a total of 7253 participants followed for 6044 patient-years. All participants received inhaled corticosteroids, either as uncontrolled background use or controlled as part of the study intervention. The combination of β-agonist and corticosteroid was compared with an equal dose of corticosteroid in 4 trials, an equal or higher dose of corticosteroid in 1 trial, and a higher dose of corticosteroid in 2 trials (Table 1, online).
Asthma-related Intubations and Deaths

For all trials combined, there were 59 catastrophic events in the \( \beta \)-agonist group and 26 events in the control group (Table 1, online), with a Peto odds ratio of 2.10 (95% confidence interval [CI], 1.37-3.22; Figure 2). For trials with variable corticosteroid use, the odds ratio for catastrophic events for long-acting \( \beta \)-agonists was 1.83 (95% CI, 1.14-2.95) compared with placebo. For trials with concomitant corticosteroids, the odds ratio for catastrophic events for long-acting \( \beta \)-agonists plus inhaled corticosteroids, compared with inhaled corticosteroids alone, was 3.65 (95% CI, 1.39-9.55).

Minimal interstudy heterogeneity was noted in the analyses (\( P > .8 \)). Similar results were seen when the analysis was performed using the random effects method, with significant increases in catastrophic events seen for variable corticosteroid use (OR 1.76; 95% CI, 1.08-2.89) and concomitant corticosteroid use (OR 2.7; 95% CI, 1.06-6.88).

In subgroup analysis, there was no statistically significant difference in results between concomitant and variable corticosteroids, with a \( P \) value for interaction of 0.24 (Table 2). Similar results were seen for trials with controlled corticosteroid use as part of the study intervention (OR 8.19; 95% CI, 1.1-61.18) and trials that used no corticosteroids at

### Table 2: Subgroup Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>( P ) Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS use: variable compared with concomitant use</td>
<td>Variable ICS</td>
<td>1.83 (1.14-2.95)</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>Concomitant ICS</td>
<td>3.65 (1.39-9.55)</td>
<td></td>
</tr>
<tr>
<td>ICS use: no use compared with controlled study drug</td>
<td>No ICS</td>
<td>2.2 (1.14-4.36)</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>Controlled ICS</td>
<td>8.19 (1.1-61.18)</td>
<td>.28</td>
</tr>
<tr>
<td>( \beta )-agonist used</td>
<td>Salmeterol</td>
<td>1.94 (1.24-3.04)</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>Formoterol</td>
<td>4.81 (1.12-20.68)</td>
<td></td>
</tr>
<tr>
<td>Age of participants</td>
<td>Adults</td>
<td>2.08 (1.35-3.20)</td>
<td>.69</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>2.58 (0.96-6.94)</td>
<td></td>
</tr>
<tr>
<td>Asthma event</td>
<td>Intubations</td>
<td>1.76 (1.08-9.55)</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>4.03 (1.7-9.55)</td>
<td></td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroid; CI = confidence interval.
all (OR 2.2; 95% CI, 1.1-4.36, \( P \) for interaction = .23). In further subgroup analysis, there was no significant difference in results for formoterol compared with salmeterol, children compared with adults, and asthma deaths compared with intubations (Table 2).

In sensitivity analysis, when the pooled data from GlaxoSmithKline were excluded, significant increases in catastrophic events were seen for variable corticosteroid use (OR 1.79; 95% CI, 1.09-2.92) and concomitant corticosteroid use (OR 7.34; 95% CI, 1.42-37.97).

**DISCUSSION**

Our pooled data show that the use of long-acting \( \beta \)-agonists, with and without concomitant inhaled corticosteroids, was associated with a significant increase in risk for asthma-related intubations and deaths. The magnitude of risk was, in fact, higher for trials with controlled concomitant corticosteroid use (OR 8.2) than for trials with no corticosteroid use at all (OR 2.2), although the difference between the 2 subgroups was not statistically significant. The results of this meta-analysis are based on a relatively small number of events, so they should be interpreted with caution. However, these findings provide evidence that long-acting \( \beta \)-agonists are associated with significant risk, even when used with concomitant inhaled corticosteroids.

This is the first meta-analysis to show that concomitant treatment with long-acting \( \beta \)-agonists and inhaled corticosteroids increased catastrophic asthma events. This is because our analysis was based almost entirely on reports of events provided by the drug manufacturers to the FDA, which were not released until December 2008. Of note, only 2 trials reported asthma-related intubations or death in their published article. We chose to use the composite outcome of asthma-related intubation or death because both of these catastrophic events are increased with long-acting \( \beta \)-agonist use. Similar increases in risk were seen for fatal and nonfatal events. We also chose to pool the data on salmeterol and formoterol, and on adults and children. We thought this was reasonable because little heterogeneity was seen in results between these subgroups. A consistent finding was a greater number of catastrophic events in the \( \beta \)-agonist group, compared with the control group, in each of the trials included in the analysis.

This meta-analysis was not designed to assess the absolute increase in catastrophic events associated with the addition of long-acting \( \beta \)-agonists to inhaled corticosteroids, because only those trials with at least 1 event are included in the calculation of odds ratios. To estimate the total number of patients at risk, we can use the cumulative trial data provided in the briefing material from the drug manufacturers, which includes published and unpublished trials with and without reported events. If all trials with and without events are included in the analysis, there were 14 events in 35,000 patients treated with combined therapy (0.04%) and 3 events in 29,000 patients treated with corticosteroids alone (0.01%) over an average trial duration of 5 months. This would indicate an absolute increase in risk of 3 catastrophic asthma events per 10,000 patients treated over a 5-month period. The magnitude of the potential problem is highlighted by the fact that several million patients are treated with long-acting \( \beta \)-agonists in the United States each year, the majority of whom also are receiving inhaled corticosteroids.

One proposed mechanism for the increase in catastrophic asthma events associated with long-acting \( \beta \)-agonists is the development of tolerance to their bronchoprotective effects over time. Regular use of short- and long-acting \( \beta \)-agonists is associated with down-regulation and desensitization of \( \beta \)-receptors, an increase in airway hyperreactivity, and an increase in asthma deaths and near-deaths. The use of inhaled corticosteroids, on the other hand, is associated with reduced airway reactivity and a reduction in life-threatening and fatal events. Although there is some evidence that corticosteroids might partially protect against the adverse effects of \( \beta \)-agonists, regular \( \beta \)-agonist use still results in substantial tolerance to its effects over time, despite concomitant treatment with corticosteroids.

The sole purpose of this meta-analysis was to evaluate the risk for catastrophic events associated with long-acting \( \beta \)-agonists. The study did not evaluate the benefits of long-acting \( \beta \)-agonists and therefore could not assess the risk-to-benefit ratio of these agents. A recent advisory committee to the FDA reviewed the available evidence and concluded that the risks of salmeterol (Serevent) and formoterol (Foradil) for asthma outweighed the benefits and should be banned for use in asthma for all ages. The committee agreed that further safety studies were still needed to clarify the risk of combination products, such as salmeterol with fluticasone (Advair) and formoterol with budesonide (Symbicort). If long-acting \( \beta \)-agonists were not used in the treatment of asthma, other treatment options include inhaled and oral corticosteroids, leukotriene inhibitors, short-acting anticholinergic agents, and as-needed short-acting \( \beta \)-agonists.

In the United States, the asthma mortality rate peaked in the 1990s and has now been steadily declining over the past several years. This reduction in mortality, despite the continued use of long-acting \( \beta \)-agonists, has been used as evidence against an adverse mortality effect of these drugs. However, one possible explanation for this trend could be that the asthma mortality rates are related to the ratio of \( \beta \)-agonist use to inhaled corticosteroid use over time. The sales of long-acting \( \beta \)-agonists were increasing over the past several years, but the sales of inhaled corticosteroids increased even faster during this time period, so that the ratio of \( \beta \)-agonist to inhaled corticosteroid use has gradually decreased at a rate that is proportional to the decreasing trend in asthma mortality rates. If there were, in fact, a causal relationship between the ratio of \( \beta \)-agonist to corticosteroid use and asthma mortality in the United States, then we would expect a further decrease in asthma deaths if the sales of long-acting \( \beta \)-agonists were curtailed.
STUDY LIMITATIONS

Our analysis has several limitations. Standard meta-analytic results can be uncertain when the numbers of events per study are small, as is the case with catastrophic asthma events. The assessment of intubations and deaths was further hindered by the fact that many trials did not report the events even when they occurred and by the difficulty in ascertaining the true cause of respiratory failure or death. We chose to include only those events reported by the investigator or drug manufacturer to be asthma-related intubations or deaths. If we had chosen to include other life-threatening events thought to be due to “status asthmaticus” or “severe acute asthma” without documentation of intubation, or to include respiratory arrests and sudden deaths of unclear cause, there would be 12 more events, with 9 occurring in the long-acting β-agonist group and 3 occurring in the control group.

We chose to compare the combination of β-agonist and corticosteroid with an equal or higher dose of corticosteroid to assess whether the addition of long-acting β-agonists to inhaled corticosteroids carried a greater risk than the use of corticosteroids alone. We also chose to exclude from the analysis trials that used an active-comparator drug, such as a short-acting β-agonist, in the control group. However, our analysis of the pooled data provided by GlaxoSmithKline indicates that the long-acting β-agonist salmeterol increases the risk for asthma intubation or death by 2-fold compared with active-comparator controls (OR 2.09; 95% CI, 1.04-4.21). 9

CONCLUSIONS

Despite these limitations, our pooled data suggest that long-acting β-agonists increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids. At present, guidelines suggest that long-acting β-agonists be added to inhaled corticosteroids in patients with moderate or severe asthma that is not well controlled with inhaled corticosteroids alone,38 but this approach might not in fact confer a meaningful health benefit compared with the use of other standard therapies.1 The results of this meta-analysis suggest that long-acting β-agonists carry significant risk for catastrophic asthma events, even when used concomitantly with inhaled corticosteroids.

ACKNOWLEDGMENT

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References

Table 1 (online) Studies Included in Meta-Analysis

<table>
<thead>
<tr>
<th>Study, Reference Duration</th>
<th>Intervention</th>
<th>No. (n)</th>
<th>Mean Age</th>
<th>Dropout (%)</th>
<th>Percent on ICS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foradil 040 trial20 12 wk</td>
<td>β-agonist Formoterol 12 μg or 24 μg BID</td>
<td>269</td>
<td>35.5</td>
<td>5.9</td>
<td>Not stated</td>
<td>Phase 3 study sponsored by Novartis (Basel, Switzerland), NDA20-831, Protocol 040. There was 1 nonfatal asthma intubation in patient aged &gt;12 y. Reported in Novartis FDA briefing material.10 Not reported in original trial.</td>
</tr>
<tr>
<td>Control Placebo</td>
<td>135</td>
<td>35.5</td>
<td>6.7</td>
<td></td>
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<td></td>
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<tr>
<td>Foradil 041 trial21 12 wk</td>
<td>β-agonist Formoterol 12 μg and 24 μg BID</td>
<td>275</td>
<td>32.6</td>
<td>6.2</td>
<td>45</td>
<td>Phase 3 study sponsored by Novartis, NDA20-831, Protocol 041 One respiratory arrest with nonfatal intubation in patient aged &gt;12 y. One asthma death in 66-year-old woman not on ICS, receiving formoterol 24 μg BID. Events reported in Novartis FDA briefing material.10 Asthma death reported in original trial but thought not to be related to study drug.</td>
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<td>Control Placebo</td>
<td>141</td>
<td>33.5</td>
<td>6.4</td>
<td>49</td>
<td></td>
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<tr>
<td>Foradil 230729 trial 12 wk</td>
<td>β-agonist Formoterol 12 μg and 24 μg BID</td>
<td>1054</td>
<td>38.8</td>
<td>13.8</td>
<td>65</td>
<td>Phase 4 safety study sponsored by Novartis, For258D-2307. One asthma intubation in a 53-year-old African-American man receiving formoterol 12 μg BID and 1 asthma intubation in a 51-year-old Caucasian man receiving formoterol 24 μg BID. Both events were reported in a clinical safety review on FDA website in 2005, but they were not reported in the Novartis FDA briefing material in 2008.</td>
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<td>Control Placebo</td>
<td>514</td>
<td>37.8</td>
<td>15.2</td>
<td>66.7</td>
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<tr>
<td>GSK pooled trials9 Not stated</td>
<td>β-agonist Salmeterol, dose not stated</td>
<td>296</td>
<td>Not stated</td>
<td>Not stated</td>
<td>0</td>
<td>Pooled trial data in GSK (Brentford, London, England) FDA briefing material. Three asthma intubations in the salmeterol group and 1 asthma intubation in the control group. All events occurred in randomized placebo-controlled trials without ICS use. After communication with Steven Yancey of GSK on 2/2/09, we were informed that GSK declined to provide individual trial-level information.</td>
</tr>
<tr>
<td>Control Placebo</td>
<td>298</td>
<td>Not stated</td>
<td>Not stated</td>
<td>0</td>
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<tr>
<td>SMART22 28 wk</td>
<td>β-agonist Salmeterol 50 μg BID</td>
<td>13,174</td>
<td>39.2</td>
<td>22.5</td>
<td>49</td>
<td>Phase 4 safety study, sponsored by GSK, Trial SLGA5011. There were 13 asthma deaths and 24 intubations in the salmeterol group, and 3 asthma deaths and 19 intubations in the placebo group. All events reported in original trial.</td>
</tr>
<tr>
<td>Control Placebo</td>
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<td>39.1</td>
<td>23.8</td>
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<tr>
<td>GSK pooled trials9 Not stated</td>
<td>β-agonist Salmeterol, dose not stated</td>
<td>633</td>
<td>Not stated</td>
<td>Not stated</td>
<td>100</td>
<td>Pooled trial data provided in GSK FDA briefing material. There were 8 asthma intubations in the salmeterol group and 3 asthma intubations in the placebo group. All events occurred in randomized placebo-controlled trials with concomitant ICS use in GSK database. After communication with Steven Yancey of GSK on 2/2/09, we were informed that GSK declined to provide individual trial-level information.</td>
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<td>Control Placebo</td>
<td>642</td>
<td>Not stated</td>
<td>Not stated</td>
<td>100</td>
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328.e1 Salpeter et al Safety of Long-acting β-Agonists

328.e2 Salpeter et al Safety of Long-acting β-Agonists

328.e3 Salpeter et al Safety of Long-acting β-Agonists

328.e4 Salpeter et al Safety of Long-acting β-Agonists

328.e5 Salpeter et al Safety of Long-acting β-Agonists

328.e6 Salpeter et al Safety of Long-acting β-Agonists

328.e7 Salpeter et al Safety of Long-acting β-Agonists

328.e8 Salpeter et al Safety of Long-acting β-Agonists

328.e9 Salpeter et al Safety of Long-acting β-Agonists

328.e10 Salpeter et al Safety of Long-acting β-Agonists

328.e11 Salpeter et al Safety of Long-acting β-Agonists
<table>
<thead>
<tr>
<th>Study, Reference</th>
<th>Duration</th>
<th>Intervention</th>
<th>No. (n)</th>
<th>Mean Age</th>
<th>Dropout (%)</th>
<th>Percent on ICS</th>
<th>Comments</th>
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<tr>
<td>Ind et al23</td>
<td>24 wk</td>
<td>β-agonist</td>
<td>Salmeterol 50 μg + fluticasone 250 μg BID</td>
<td>173</td>
<td>44.8</td>
<td>15.7</td>
<td>100</td>
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<tr>
<td>Kelsen et al24</td>
<td>24 wk</td>
<td>β-agonist</td>
<td>Salmeterol 42 μg + beclomethasone 168 μg BID</td>
<td>239</td>
<td>42.4</td>
<td>20</td>
<td>100</td>
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<tr>
<td>Kemp et al25</td>
<td>12 wk</td>
<td>β-agonist</td>
<td>Salmeterol 42 μg BID</td>
<td>252</td>
<td>42.0</td>
<td>9.9</td>
<td>100</td>
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<td>O’Byrne et al26</td>
<td>52 wk</td>
<td>β-agonist</td>
<td>Formoterol 4.5 μg + budesonide 200 μg or 400 μg BID</td>
<td>869</td>
<td>34.8</td>
<td>16</td>
<td>100</td>
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<tr>
<td>O’Byrne et al27</td>
<td>52 wk</td>
<td>β-agonist</td>
<td>Formoterol 4.5 + budesonide 80 μg BID</td>
<td>1834</td>
<td>35.5</td>
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<td>Von Berg et al28</td>
<td>12 wk</td>
<td>β-agonist</td>
<td>Formoterol 4.5 μg and 9 μg BID</td>
<td>165</td>
<td>11.4</td>
<td>6.1</td>
<td>100</td>
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BID = 2 times per day; FDA = Food and Drug Administration; GSK = GlaxoSmithKline; ICS = inhaled corticosteroid; SMART = Salmeterol Multi-center Asthma Research Trial.