

Overview of Reviews

The Cochrane Library and safety of regular long-acting beta₂-agonists in children with asthma: an overview of reviews

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Background: Two large randomized trials of regular salmeterol monotherapy in adults with asthma found an increased risk of asthma-related mortality for salmeterol versus placebo or regular salbutamol. There are no similar large trials in children, and the safety of monotherapy with salmeterol or other long-acting beta₂-agonists in children with asthma is unclear. Current guidelines recommend that regular long-acting beta₂-agonist therapy should be given only in combination with regular inhaled corticosteroids. However, the safety of combination therapy in children with asthma is also unclear.

Objectives: We used the paediatric trial results from Cochrane systematic reviews to assess the safety of regular long-acting beta₂-agonist therapy, either as monotherapy or as combination therapy with inhaled corticosteroids, in children with asthma.

Methods: We searched the Cochrane Database of Systematic Reviews in May 2012 for Cochrane reviews relating to the safety of regular formoterol and salmeterol, and ran updated searches for trials for each of the Cochrane reviews. We used odds ratios (ORs) to summarize the direct randomized evidence on safety from trials comparing regular formoterol or regular salmeterol as monotherapy versus placebo and then as combination therapy with inhaled corticosteroids versus the same dose of inhaled corticosteroids. We indirectly compared the safety of monotherapy and combination therapy by testing for differences between the pooled ORs for monotherapy and for combination therapy. We used ORs to summarize the direct randomized evidence on safety from trials comparing regular formoterol with regular salmeterol. We also compared the safety of regular formoterol and regular salmeterol indirectly by calculating an OR for the pooled results of trials assessing formoterol and the pooled results of trials assessing salmeterol, and then combined the direct and indirect evidence by calculating an overall OR for this comparison.

Results: We identified four Cochrane reviews examining the safety of regular formoterol or salmeterol as either monotherapy or combination therapy. The reviews included 19 trials in children and we found two additional studies on salmeterol combination therapy, for a total of 21 trials in 7318 children. We identified two Cochrane reviews comparing the safety of formoterol with salmeterol, which included a single trial in 156 children. We found a statistically significant increase in the odds of suffering a nonfatal serious adverse event in children on formoterol monotherapy [OR = 2.48; 95% confidence interval (CI) = 1.27–4.83, $I^2 = 0%$, five trials, $N = 1335$] and smaller nonsignificant increases in odds for salmeterol monotherapy (OR = 1.30; 95% CI = 0.82–2.05, $I^2 = 17%$, five trials, $N = 1333$), formoterol combination therapy (OR = 1.60; 95% CI = 0.80–3.28, $I^2 = 32%$, seven trials, $N = 2788$) and salmeterol combination therapy (OR = 1.20; 95% CI = 0.37–2.91, $I^2 = 0%$, five trials, $N = 1862$). There was no significant difference between the pooled ORs of a serious adverse event on monotherapy (OR = 1.60; 95% CI = 1.10–2.33, 10 trials, $N = 2668$) and combination therapy (OR = 1.50; 95% CI = 0.82–2.75, 12 trials, $N = 4650$). However, there was an absolute increase of 21 children (95% CI = 4–45) suffering a severe adverse event of any cause for every thousand children treated over six months on monotherapy, compared with an absolute increase of three (95% CI = 1 fewer to 12 more)

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per 1000 children over three months on combination therapy. The evidence comparing the safety of regular salmeterol to regular formoterol was limited, and even when direct and indirect evidence were combined, the CI around the effect on serious adverse events was too wide to tell whether there was a difference in the comparative safety of formoterol and salmeterol (OR = 1.26; 95% CI = 0.37–4.32). Only one child died across all the trials, so the impact on mortality could not be assessed.

Authors' conclusions: Although regular combination therapy is likely to be safer than monotherapy in children with asthma, the safety of regular combination therapy with formoterol or salmeterol in children remains uncertain, particularly in terms of mortality. The relative safety of formoterol and salmeterol is also unclear. There are currently large ongoing surveillance studies that may clarify the risks of combination therapy in children and adolescents with asthma.

Keywords: asthma, Cochrane Library, long-acting beta₂-agonist, LABA, overview, safety

Background

Why use regular formoterol or salmeterol for children with asthma?

Asthma is a chronic inflammatory condition of the airways, associated with an overreaction to inhaled allergens causing wheezing, breathlessness, tightness of the chest and coughing (1). The inflammation of chronic asthma is treated with regular inhaled corticosteroids (ICSs), while wheezing and breathlessness are due to the constriction of the smooth muscle around the airways and can be relieved by inhaled beta₂-agonists.

The beta₂-agonists relax the airways' smooth muscle and relieve bronchoconstriction, and short-acting beta₂-agonists, such as salbutamol (albuterol), are recommended as intermittent first-step treatment for children with asthma (2). In children who require treatment (or who have asthma symptoms) more than twice a week, the second step in treatment is to add ICS to reduce inflammation in the airways. The addition of a regular long-acting beta₂-agonist (LABA) to an ICS is the current recommended next step for adults and children over five years of age, whose asthma symptoms are not controlled with regular ICS alone (2).

Is it safe to use regular formoterol or salmeterol as monotherapy in children with asthma?

It is relatively straightforward to assess the symptomatic benefits of regular LABAs in children who have asthma, as the relief of symptoms can be experienced straight away. What is more difficult is to assess the long-term safety of regular LABAs. The risk of rare but serious adverse events (SAEs), such as admission to hospital or even death from asthma, cannot be assessed by judging the response of an individual child to LABAs, but needs evidence from large populations of children who have been treated.

Observational studies and post-marketing surveillance suffer from the limitation that the children who have been prescribed LABAs may have major differences in their risk of a SAE from those who have not been prescribed LABAs. For this reason the most reliable evidence of safety comes from the combined

evidence of randomized trials, especially large surveillance studies designed to assess safety.

Two very large randomized trials of regular salmeterol monotherapy have been carried out in adults. The first compared regular salmeterol with regular salbutamol in 25 180 adolescents and adults with asthma in the UK (3), and this was followed by a trial in the US in 26 355 adults and adolescents comparing regular salmeterol with placebo (4). Both trials showed an increased risk of death from asthma on regular salmeterol.

The mechanism by which beta₂-agonists might cause harm is not currently known. There are several theories (5) that include the possibility of direct toxicity of beta₂-agonists causing adverse cardiac effects, tolerance induced by regular use of beta₂-agonists so that they become less effective bronchodilators in acute asthma exacerbations (6,7), delay in seeking medical help (if the beta₂-agonists mask the severity of an attack) or reduced use of corticosteroids (which are needed to treat bronchial oedema and excess mucus production due to increased inflammation during exacerbations).

In 2007, the Pediatric Advisory Committee of the Food and Drug Administration reviewed the safety of regular salmeterol in children. As a result, a meta-analysis of individual patient data was carried out by the Food and Drug Administration to assess the outcomes in different age-groups (8). The analysis found a significant trend for younger patients to have greater risk differences in relation to a composite index of serious asthma events (hospitalization, intubation or asthma-related mortality). In 2008, the advisory committee voted to restrict the use of LABAs to combination ICS/LABA products for children and adults. At a further meeting in 2010 labelling changes were made, including a recommendation that, for children, LABAs should be used as combination ICS/LABA products (8).

Regular treatment with LABA is not recommended without regular ICS (2,9), but the Food and Drug Administration's advice to use regular LABA for 'the shortest duration possible to achieve control of asthma symptoms and then be discontinued' has been

challenged as not evidence-based by the Canadian Thoracic Society Asthma Committee Group (9).

Objectives and methods

How safe is regular formoterol or salmeterol combination therapy with ICS in children with asthma?

In view of the concerns regarding the safety of regular LABA monotherapy in children with asthma (8), it seems fair to ask about the safety evidence for LABA combination therapy with ICS in children with asthma. This was addressed in a recent overview of Cochrane systematic reviews of the safety of regular formoterol or salmeterol (10).

We used the overview to summarize the direct randomized evidence from trials in the Cochrane reviews comparing regular formoterol or regular salmeterol as monotherapy versus placebo and then as combination therapy versus the same dose of ICS. We went on to indirectly compare the safety of LABA monotherapy with LABA combination therapy from the pooled results of the trials in children, and to compare the safety of regular formoterol with regular salmeterol (using direct and indirect evidence from the reviews).

We included Cochrane reviews from a search of the Cochrane Database of Systematic Reviews conducted in May 2012 relating to the safety of regular formoterol and salmeterol; please refer to Appendix 1 for the search strategy. We ran updated searches for each of the included reviews to locate any new trials that may have been published after the review was completed; for those we used the search strategy published in each review. New trials were independently assessed. All the reviews were independently assessed for quality using the assessment of multiple systematic reviews (AMSTAR) tool (11). Two authors independently extracted the data relating to children from each review and from new trials found in the updated searches (including risks of bias, study characteristics, SAE outcomes and control arm event rates). Serious adverse event, as defined by the Expert Working Group (Efficacy) of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (12), falls in any of the following categories: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapability, or results in a congenital anomaly/birth defect. In practice, most SAEs relate to an admission to hospital.

Results

Cochrane reviews identified

We identified six high quality, up-to-date Cochrane reviews (13–18). Four of these related to the safety of

regular formoterol or salmeterol (as monotherapy or combination therapy), and these included 19 studies in children 4–17 years of age. See Table S1 (Supporting information) for detailed characteristics of the included reviews. We added data from two recent studies on salmeterol combination therapy in 689 children 4–11 years of age, which were published after the relevant Cochrane review had been completed (19,20), making the total 21 trials in 7318 children. Characteristics of the two new trials can be found in Table S2). The two remaining reviews compared the safety of formoterol with salmeterol from trials randomizing participants to one or other treatment, but the reviews included only a single trial in 156 children (6–17 years old).

All included reviews were of good quality and scored 9–11 points on the 11-point AMSTAR scale (see Table S3).

Mortality results in the trials

Of the 7474 children included in all the trials, one child died of a sub-arachnoid haemorrhage while taking regular formoterol monotherapy, so the impact of regular LABA combination therapy on mortality could not be assessed.

Results of direct randomized evidence on nonfatal serious adverse events of any cause

The results of the direct randomized evidence from trials comparing formoterol or salmeterol monotherapy with placebo and combination therapy with regular ICS are shown in the summary of findings table (Table 1). The table shows that the monotherapy and combination therapy trials all showed an increase in the odds of children suffering an SAE, which was statistically significant for formoterol monotherapy. The overview also found similar increases for asthma-related SAEs, and the increase was statistically significant for formoterol monotherapy [odds ratio (OR) = 4.06; 95% confidence interval (CI) = 1.78–9.22] and salmeterol monotherapy (OR = 1.72; 95% CI = 1.00–2.98) (10).

How does the safety of monotherapy compare with combination therapy?

The children in these trials were not randomized to monotherapy versus combination therapy, so it was not possible to make a direct (randomized) comparison to assess how much safer LABA treatment is when used in combination with ICS. However, it is possible to make indirect comparisons of the relative safety of monotherapy and combination therapy by contrasting the pooled ORs of SAEs from the monotherapy versus placebo trials, with the pooled ORs from the combination therapy trials.

This is shown in Figure 1, where the top half of the Forest plot shows that the pooled OR from the trials of LABA monotherapy versus placebo was 1.60

Table I. Summary of findings of the overview: children with a serious adverse event (SAE) of any cause

Comparison	Illustrative comparative risks* (95% CI)			Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Regular LABA (salmeterol or formoterol)	Relative effect (95% CI)		
Regular formoterol versus placebo (14) Follow-up: mean 27 weeks	12 per 1000	30 per 1000 (15–56)	OR = 2.48 (1.27–4.83)	1335 (five studies)	⊕⊕⊕⊕ High
Regular salmeterol versus placebo (13) Follow-up: mean 31 weeks	56 per 1000	72 per 1000 (46–108)	OR = 1.3 (0.82–2.05)	1333 (five studies)	⊕⊕⊕⊖ Moderate [†]
Regular formoterol and ICS versus ICS (18) Follow-up: mean 13 weeks	Eight per 1000	14 per 1000 (7–27)	OR = 1.62 (0.80–3.28)	2788 (seven studies)	⊕⊕⊕⊖ Moderate [†]
Regular salmeterol and ICS versus ICS (17) Follow-up: mean 15 weeks	Five per 1000	Six per 1000 (2–19)	OR = 1.20 (0.37–3.91)	1862 (five studies)	⊕⊕⊕⊖ Moderate [†]
Regular formoterol versus regular salmeterol (16) Follow-up: mean 13 weeks	Salmeterol 13 per 1000	Formoterol 12 per 1000 (1–168)	OR = 0.95 (0.06–15.33)	156 (one study)	⊕⊕⊖⊖ Low ^{‡,§}

* The assumed risk is the mean event rate in the control arm of the trials. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[†] Confidence intervals include the possibility of an increase and a decrease in SAEs on regular LABA;

[‡] Single unblinded study.

CI: confidence interval; GRADE: Working Group grades of evidence; LABA: long-acting beta₂-agonist; OR: odds ratio; SAE: serious adverse event. High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

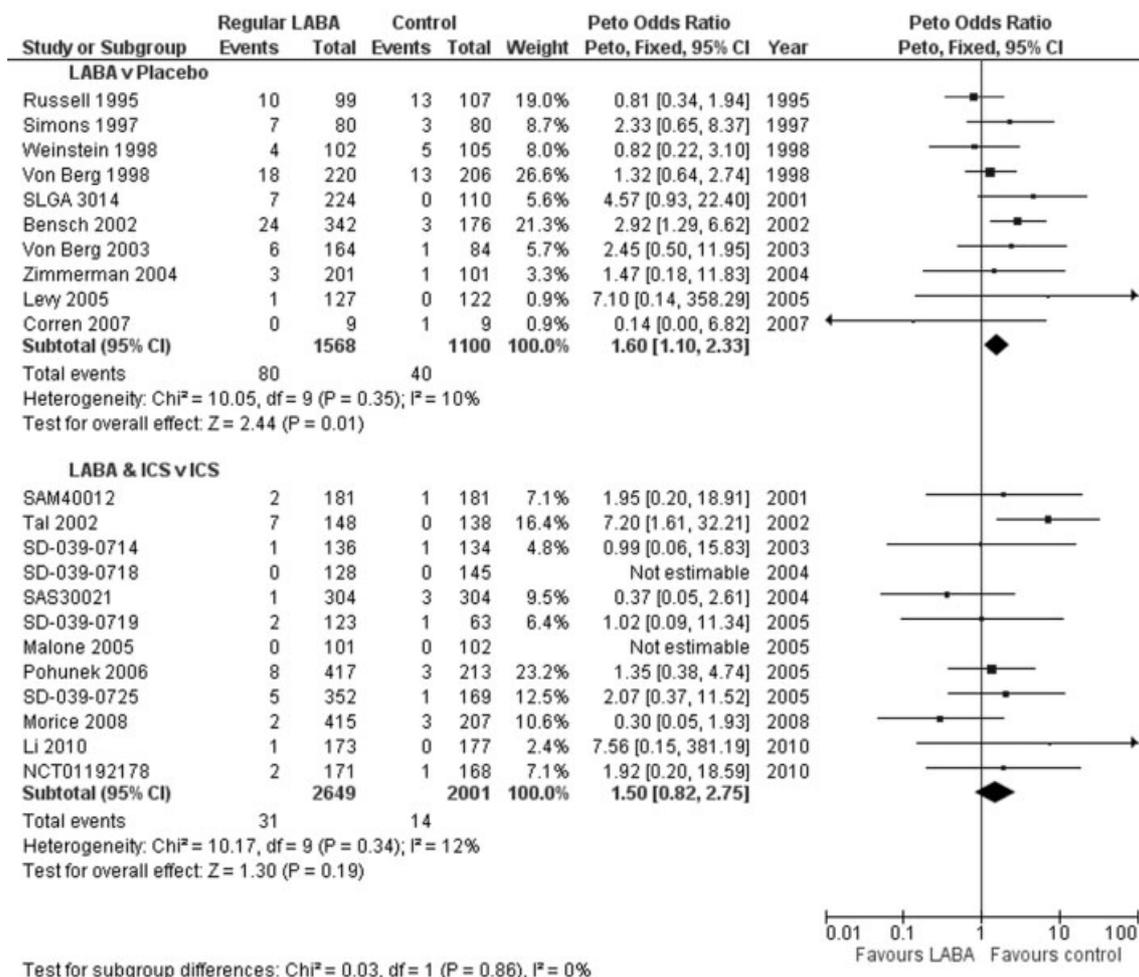


Figure I. Comparison of children suffering a serious adverse event of any cause in monotherapy versus placebo trials and combination therapy versus ICS trials

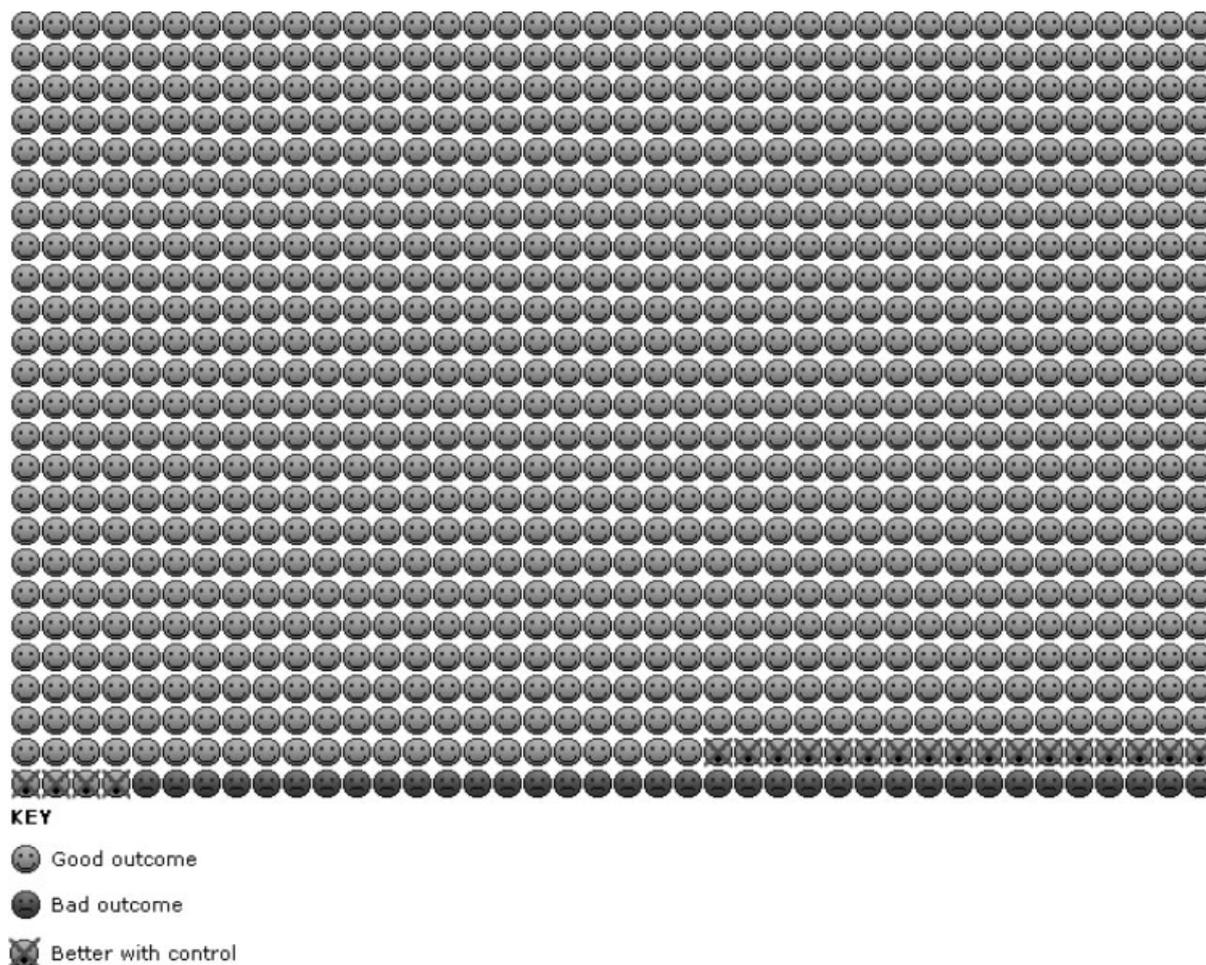


Figure 2. Cates plot of monotherapy versus placebo trials: In the placebo group 36 children out of 1000 had nonfatal serious adverse events of any cause over 29 weeks, compared with 57 (95% CI = 40–81) out of 1000 for the LABA monotherapy group

(95% CI = 1.10–2.33, $I^2 = 10\%$, 10 trials, $N = 2668$). The lower half of the Forest plot shows that for LABA combination therapy versus ICSs the pooled OR was 1.50 (95% CI = 0.82–2.75, $I^2 = 12\%$, 10 trials, $N = 4650$). These ORs are very similar, and there was no significant difference between the ORs from the monotherapy and combination therapy trials in children [test for subgroup differences: $\chi^2 = 0.03$, $df = 1$ ($p = 0.86$)].

The striking difference between these two sets of trials is that there were considerably fewer children who suffered from an SAE of any cause in the ICS control arms of the combination therapy trials (14/2001 = 7 per 1000) in comparison with the children in the placebo arms of the monotherapy trials (40/1100 = 36 per 1000). This means that in absolute terms we found important differences between the combination and monotherapy trial results.

This is illustrated in the two Cates plots (Figs. 2 & 3), which have been generated from the respective pooled OR (and its 95% CI), and applied to the mean risk in the control groups using an online calculator, Visual Rx (21). The Cates plots demonstrate the consequences of treating 1000 children in each case.

In the monotherapy trials, for every 1000 children on placebo over 29 weeks there were 36 who suffered an SAE of any cause (the red faces in Fig. 2). On LABA monotherapy 21 additional children (95% CI = 4–45 more) suffered an SAE, and these are shown as the crossed-out green faces. The green faces show that 943 of 1000 children did not suffer an SAE, whichever treatment they were given.

By contrast, there were only seven children per 1000 with an SAE on regular ICS treatment over 14 weeks, with three additional children (95% CI = one fewer to 12 more) with an SAE on LABA combination therapy (shown as three crossed-out green faces in the Cates plot in Figure 3).

How does the safety of regular formoterol compare with the safety of regular salmeterol?

We found only a single trial in 156 children comparing the safety of regular salmeterol to regular formoterol monotherapy. As there is very little direct evidence comparing the safety of the two products, we assessed the relative safety of formoterol versus salmeterol combination inhalers indirectly. To do this we compared the pooled ORs from the formoterol combination versus budesonide trials with the pooled ORs

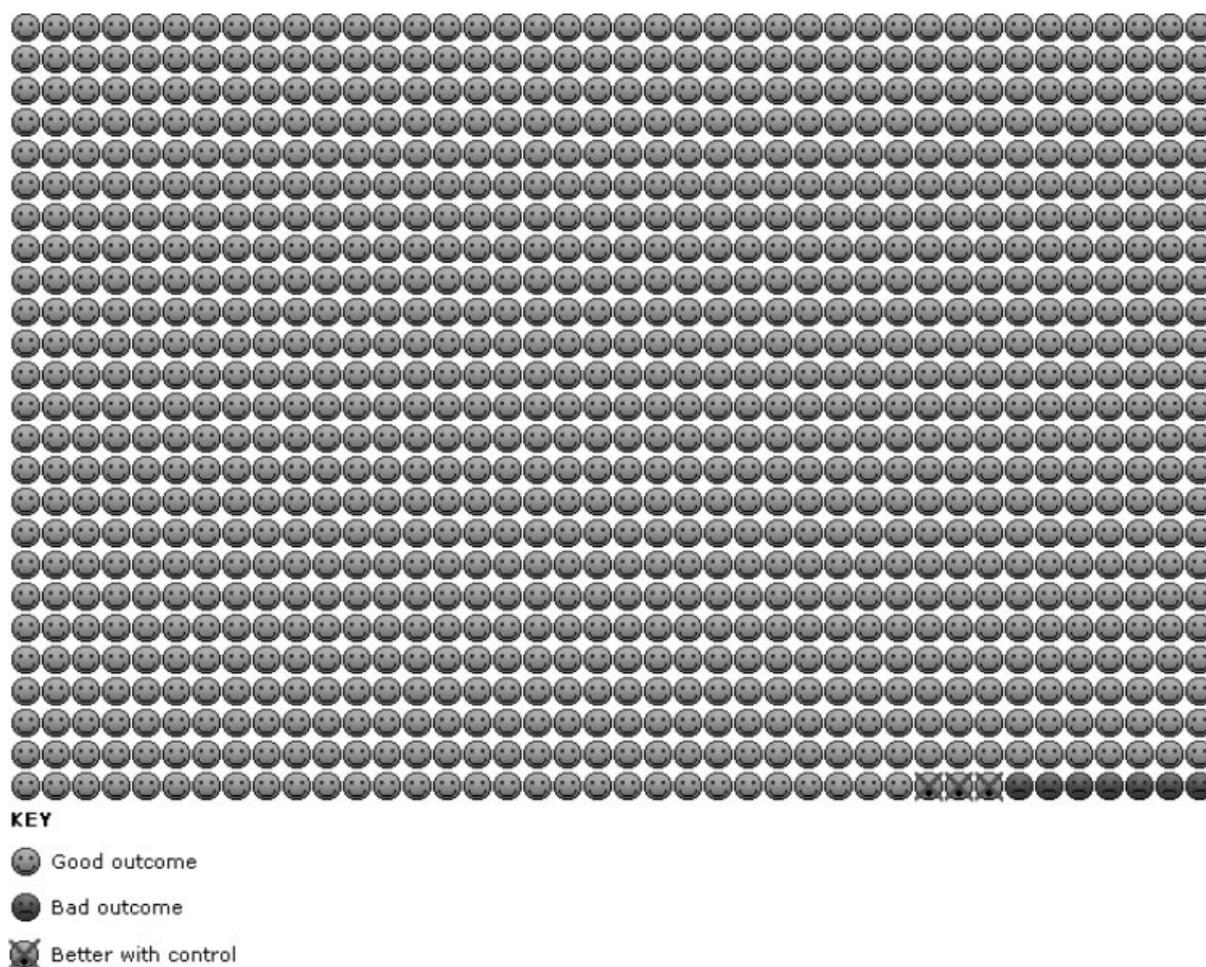


Figure 3. Cates plot of combination therapy versus ICS trials: In the ICS control group seven children out of 1000 had nonfatal serious adverse events of any cause over 14 weeks, compared with 10 (95% CI = 6–19) out of 1000 for the LABA combination therapy group

of the salmeterol combination versus fluticasone trials, and calculated the relative ORs and its CI.

Even when the evidence from indirect comparisons between the combination formoterol and salmeterol trials is added to the direct evidence from this trial (10), the CI around the effect on SAEs is still too wide to tell whether there is a difference in the comparative safety of the two products (OR = 1.26; 95% CI = 0.37–4.32).

Interpretation of the results of the cochrane overview

So where does this leave us? We do not currently have enough evidence to reach any conclusion about whether combination therapy with LABA and ICS has any impact on the risk of children *dying* from asthma or any other cause. This is of some concern, as we know that LABA monotherapy has been shown to increase the risk of death from asthma in adults, and the lack of evidence means that we cannot be sure whether there is a similar risk in children or not. Moreover, there have been reported problems on regular salmeterol, even when accompanied by regular

ICS, in two adolescents who suffered very severe exercise-induced asthma exacerbations (6).

As far as nonfatal SAEs are concerned, we could not demonstrate that combination therapy compared with ICS was safer than monotherapy compared with placebo when the results were analysed as ORs. The absolute differences were smaller in the combination therapy trials because there were less SAEs in the children on regular ICS than in those on placebo; this is demonstrated by the red faces in the two Cates plots (seven per 1000 on ICS in Fig. 3 in comparison to 36 per 1000 on placebo in Fig. 2). The key question is why were there less SAEs on ICS?

This was not a randomized comparison, so we cannot be certain that the presence of the ICS treatment was responsible for the lower rates of SAEs, as there may have been other differences between the placebo and ICS comparison arms. The level of supervision of the children, severity of their asthma, shorter duration of the combination therapy trials or other unknown factors could have contributed to the differences seen between the Cates plots of the monotherapy and combination therapy trial results.

Finally, we do not have enough evidence to say whether combination therapy with formoterol and ICS

is safer or less safe than combination therapy with salmeterol and ICS in children with asthma.

Authors' conclusions

Implications for practice

Monotherapy with regular formoterol or salmeterol is no longer advocated in clinical guidelines. If separate inhalers are used to deliver LABA and ICS, there is the risk of children defaulting on their ICS treatment while continuing to take LABA, so combination inhalers should be used to deliver LABA and ICS in a single inhaler for children with asthma.

Regular combination therapy is likely to be safer than monotherapy in children (aged four years or more) with asthma, but we cannot say that combination therapy is risk free. There are probably an additional three children per 1000 over three months who suffer a nonfatal SAE on combination therapy, in comparison to ICS. This is currently our best estimate of the risk of using LABA combination therapy in children and has to be balanced against the symptomatic benefit obtained for each child.

We do not know if regular combination therapy with formoterol or salmeterol alters the risk of dying from asthma. The relative safety of formoterol and salmeterol in children also remains uncertain, and we found no trials for any comparison that recruited children under four years.

Implications for research

Large surveillance trials of combination therapy in adults and children have been mandated by the Food and Drug Administration (22–25). The safety results of regular salmeterol/fluticasone combination therapy in children with asthma from these trials are awaited. The adult trials will also contain at least 10% of participants as adolescents less than 18 years, so the safety data on both salmeterol and formoterol combination therapy will be available for these adolescents.

Contributions of authors

All authors of this overview contributed in its preparation. ES carried out the searches for Cochrane reviews; ES and SW assessed the quality of included reviews. ES also carried out the updated searches for each included review; MO and CJC assessed search results and extracted data from the new trials. CJC carried out the statistical analysis. DT and LB commented on various sections of the draft. CJC is the primary author of the overview. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of interest

CJC is the author of the included systematic reviews on the adverse events of long-acting beta₂-agonists in adults and children and was not involved in the assessment of the quality of the reviews.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of the included reviews.

Table S2. Characteristics of the new trials.

Table S3. AMSTAR rating.

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Appendix 1

#1 MeSH descriptor Asthma explode all trees
#2 (asthma*):ti,ab,kw
#3 (#1 OR #2)
#4 (formoterol):ti,ab,kw
#5(salmeterol):ti,ab,kw
#6 MeSH descriptor Adrenergic beta-2 Receptor Agonists
explode all trees
#7 LABA:ti,ab
#8 ((long-acting or "long acting") NEAR/3 beta*):ti
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 (#2 AND #9)
[Restricted to Cochrane Database of Systematic Reviews]