In 2010, in response to a prolonged debate over the safety of long-acting beta-agonists (LABAs), the United States Food and Drugs Administration (FDA) issued guidelines for the use of LABAs in asthma, and mandated a very large trial examining the safety of LABAs used with concomitant inhaled corticosteroid (ICS). Strong voices have called for new safety data while others have expressed doubt regarding the need for, and likely outcomes of, new trials.

Fears regarding LABA safety were heightened further in 2006 when Salpeter et al published a meta-analysis, heavily weighted by data from the SMART trial, reporting the effect of LABAs on severe asthma exacerbations requiring hospitalisation, life-threatening asthma attacks and asthma-related deaths in adults and children. Randomised, placebo-controlled asthma trials of LABAs (salmeterol, formoterol, and eformoterol) with duration of more than 3 months were included in the meta-analysis, but those without placebo control groups were excluded. The authors suggested up to 80% of asthma deaths in USA could be attributed to salmeterol toxicity. This meta-analysis was extensively criticised but nevertheless strongly influenced public opinion.

Following publication of the SMART study, many reviews and meta-analyses were conducted by academia and industry. Bateman et al reported data from 20,966 participants in 66 studies of >1 week duration conducted by GlaxoSmithKline involving use of ICS with or without salmeterol examining asthma-related serious adverse events including hospitalisations and exacerbations requiring oral corticosteroids. Safety data relating to formoterol exposure in all AstraZeneca randomised, controlled, parallel-group asthma trials of 3–12 months duration involving formoterol were reported by Sears et al and further analysed by Nelson et al. A meta-analysis of all studies in which formoterol or salmeterol was used with concomitant ICS was completed by Jaeschke et al.

In each of these studies, the authors concluded that LABA use did not increase the risk of asthma-related oral steroid-requiring exacerbations or hospitalisations, but there were too few asthma deaths to establish the effect of LABA on mortality. Rodrigo et al examined asthma exacerbations requiring systemic corticosteroids or hospitalisation, life-threatening exacerbations and asthma-related deaths in LABA trials, and reported that asthma related deaths were increased with LABA, but ICS provided a protective effect. LABA with ICS was equivalent to ICS in terms of life-threatening exacerbations and asthma related deaths, and significantly reduced exacerbations (OR 0.73, 95% CI 0.67 to 0.79) and hospitalisations (OR 0.58, 95% CI 0.45 to 0.74). Cates et al compared adverse events in trials in which salmeterol was added to ICS, versus the same dose of ICS alone. Analysing 30 studies with 10,873 participants, there were no differences in asthma-related deaths (OR 1.05, 95% CI 0.52 to 2.00), or in asthma-related serious adverse effects (OR 0.95, 95% CI 0.52 to 1.73).
Figure 1 Timeline 1990–2012 of key long-acting beta-agonists (LABA) publications and Food and Drugs Administration (FDA) actions. FDA, Food and Drugs Administration; PAC, Paediatric Advisory Committee; PADAC, Pulmonary, Allergy Drugs Advisory Committee; RCT, randomised controlled trial; SMART, Salmeterol Multicentre Asthma Research Trial; SNS, Serevent National Surveillance.

THE FDA META-ANALYSIS OF LABA SAFETY

In 2008, in preparation for a major safety review requested by the Pulmonary, Allergy Drugs Advisory Committee and the Paediatric Advisory Committee, the FDA asked each of the pharmaceutical companies marketing LABA products in USA (AstraZeneca, GlaxoSmithKline and Novartis) to provide patient-based safety data from all blinded, parallel-arm, randomised, controlled trials conducted with LABAs in the treatment of asthma up to January 2008. The request included trials in which LABA was administered as randomised treatment, either with or without concomitant ICS or other adjunctive therapy, placebo-controlled and/or active-controlled trials, including trials in which there was a randomised blinded phase followed by an open label extension phase. For randomised, double-blind crossover design trials, only the first crossover period of the trial was included. Adverse events were blindly adjudicated for this meta-analysis.

Using data from 110 trials involving 60 954 subjects, Levenson calculated risk differences (RD) for LABA versus non-LABA.23 The RD for asthma-related death was 0.40 (95% CI 0.11 to 0.69) per 1000 subjects; 0.57 (95% CI 0.01 to 1.12) for asthma-related death or intubation; and 2.57 (95% CI 0.90 to 4.23) for asthma-related hospitalisation. For the composite outcome of all three end-points, the RD was 2.80 (95% CI 1.11 to 4.49) (table 1).

Levenson also reported composite outcomes stratified by ICS use.25 For patients receiving LABA without mandatory randomised ICS, the RD was 3.65 (95% CI 1.39 to 9.55). Even more alarming was the finding of no deaths associated with the combination salmeterol/fluticasone was further confirmed by Weatherall et al among 22 600 patients.24

Can efficacy studies serve as safety studies?

In 2010, Salpeter et al published a second disconcerting meta-analysis of existing data, reporting not only that LABA with or without ICS increased deaths and intubations more than twofold (OR 2.10, 95% CI 1.57 to 3.22), but also that use of concomitant ICS increased that risk to almost fourfold (OR 5.65, 95% CI 1.59 to 9.55).23 Even more alarming was the finding that LABA used with ICS as an integral part of the study intervention further increased the risk of deaths and intubations to eightfold above the risk of these events when using ICS alone (OR 3.19, 95% CI 1.10 to 16.18). These data differ markedly from those reported by the FDA in which LABA with mandatory ICS had no significant impact on safety outcomes.

Critical appraisal of the outcomes reported by Salpeter et al strongly suggests confounding by ICS dose. Although Salpeter et al correctly exclude the five trials which did not require concomitant ICS (use ranged from 0% to 67%), and report on data from seven trials or groups of studies26–31 in which ICS

Table 1 Risk differences for long-acting beta-agonists (LABA) versus non-LABA for asthma-related deaths, deaths and intubations, hospitalisations, and the composite outcome, reported in the Food and Drugs Administration (FDA) meta-analysis; data from Levenson table 5 and figure 1.23 Reprinted from Sears MR, CHEST 2008

<table>
<thead>
<tr>
<th>All trials</th>
<th>LABA n/N*</th>
<th>Non-LABA n/N*</th>
<th>Risk difference† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk differences for specific and composite outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma death</td>
<td>16/30 148</td>
<td>4/30 806</td>
<td>0.40 (0.11 to 0.69)</td>
</tr>
<tr>
<td>Death or intubation</td>
<td>44/30 148</td>
<td>27/30 806</td>
<td>0.57 (0.01 to 1.12)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>368/30 148</td>
<td>298/30 806</td>
<td>2.57 (0.90 to 4.23)</td>
</tr>
<tr>
<td>Composite outcome (death, intubation or hospitalisation)</td>
<td>381/30 148</td>
<td>304/30 806</td>
<td>2.80 (1.11 to 4.49)</td>
</tr>
<tr>
<td>Composite outcome stratified by use or non-use of randomised (mandatory) ICS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials of LABA without randomised ICS v no LABA</td>
<td>350/22 286</td>
<td>279/24 474</td>
<td>3.63 (1.51 to 5.75)</td>
</tr>
<tr>
<td>Trials of LABA with randomised ICS v randomised ICS</td>
<td>31/7862</td>
<td>26/7330</td>
<td>0.25 (–1.69 to 2.18)</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid.

*R = number of events / number at risk.

†Risk difference (RD) = additional risk of outcome per 1000 subjects treated with LABA compared with no LABA; 0.0 indicates no increased risk.
was used by all subjects, the fundamental error is that ICS doses were not necessarily equal between LABA and non-LABA study arms in those seven trials (table 2). Salpeter et al have unfortunately taken effectiveness studies designed to assess preferred treatments including higher and lower doses of ICS and used these as safety trials, not recognising that difference in outcomes likely reflects differences in doses of ICS. For a true assessment of safety of LABA, equal doses of ICS are required in each treatment arm with and without LABA to ensure any difference in safety signals reflect the addition of LABA. This critical fact has been clearly recognised and implemented in the FDA-mandated trial.

**What is the real safety issue?**

Is the issue really one of LABA safety due to intrinsic properties of LABAs, a worsening of disease by LABAs, or of potential for undertreatment with ICS? The concept has developed that LABAs are ‘steroid-sparing’, but this concept may be challenged. Lemans et al reported that the dose of ICS could be reduced by 50% when salmeterol was added, despite a doubling of the rate of treatment failures in the group with lower ICS, because this doubling (OR 2.2) failed to achieve traditional statistical significance. Thomas et al, in a real world study in general practice in the UK, showed that increasing the dose of ICS gave better outcomes in terms of fewer exacerbations and courses of oral corticosteroid than adding LABA. There is ample evidence that inadequate doses of ICS lead to more exacerbations, and even mortality, even before the introduction of LABA therapy. The potential of LABA to “mask” underlying inflammation because of increased symptom control and effect on lung function mandates that physicians ensure ICS doses are adequate to control airway inflammation.

**Is a further large LABA safety study justified?**

Essential criteria for a justifiable research study includes equipoise (the answer is not already known), feasibility (there are sufficient patients and resources to complete the study) and the likelihood that the study will provide an answer to the research question. Unfortunately, the new FDA study fails on each of these criteria.

| Trials comparing LABA + low dose ICS with higher dose ICS |
|-----------------|------------------|
| Kelson et al, 1999 |
| O'Byrne et al, 2005 |

| Trials comparing LABA + ICS with both high and low doses ICS |
|-----------------|------------------|
| Ind et al, 2003 |
| O'Byrne et al, 2001 |

| Trials with no information regarding ICS doses |
|-----------------|------------------|
| GSK pooled trials, 2008 |
| Kemp et al, 1998 |
| Von Berg et al, 2003 |

To address asthma mortality with certainty, a large randomised controlled trial, powered on death as the primary outcome, in patients all using ICS would be necessary. Based on the RD of 0.25 per 1000 calculated by the FDA for the composite outcome among patients using mandated ICS, and the number of deaths included in the composite outcome, over four million subjects would need to be randomised. Including intubations and deaths, a clinically relevant trial outcome (five excess deaths or intubations) would require over 750 000 subjects. Using the composite measure of deaths, intubations and hospitalisations as the outcome would certainly reduce the sample size, but would introduce major difficulties in interpretation. As already noted, several published analyses and meta-analyses, each using a subset of the data used by the FDA, have shown that LABA used with concomitant randomised ICS is either neutral in risk for exacerbations (dominantly hospitalisations), or in fact reduces the risk. Hence using the composite outcome would almost certainly produce results opposite to that suggested by the worst-case interpretation of the mortality data. Safety studies powered on exacerbations or hospital admissions are unnecessary and even unethical as clinical equipoise is lacking—the effect of adding LABA to adequate doses of ICS on these outcomes is already well documented.

The new FDA study is grossly underpowered for the outcome of interest, namely asthma death, and will take many years to complete. Countries outside the US have already accepted the safety of LABA used with mandatory ICS. Physicians with expertise in treating asthma within and outside the US use LABA confidently as add-on therapy to ICS, recognising that the initial concerns regarding adverse events were related to underuse of ICS. The multiple trials now available, and the benefits to patients previously struggling to achieve control with higher doses of ICS, have convinced consultant physicians and paediatricians that LABA therapy is efficacious and, with adequate ICS, is safe. Attempting to obtain new data from an impossibly large study may increase fear among patients, cause confusion among physicians and lead to inappropriate care for many asthmatics.

**PRACTICAL CONSIDERATIONS**

The LABAs under study include salmeterol, a partial agonist with a slower onset of action and formoterol, a more rapidly acting full agonist. One wonders how the data from differing LABAs and combinations with different ICS preparations will be able to be merged. What is being done to ensure adequate doses of ICS are used in the study?

The FDA in their 2008 meta-analysis of existing data showed conclusively that there was no safety signal when LABA and ICS were used as a combination in a single inhaler, yet has not mandated single-device combinations for all ages, but rather recommended this for children and adolescents. Are adults more compliant with multiple inhalers than teenagers and children? Fortunately, the use of a single inhaler is becoming the norm worldwide for the great majority of patients requiring both LABA and ICS therapies.

The new study will be large, long, resource-intensive and incredibly expensive. Given that we already know the only answer which will emerge from this study (that LABA added to ICS provides better control of asthma with fewer exacerbations than the same dose of ICS alone), one sadly muses on how else the dollars could have been spent—such as developing more effective medications, patient education, and promoting research to understand the fundamental causes of asthma which could eventually lead to its prevention or amelioration. Using these
dollars to ostensibly obtain a definitive answer to a question that is already answered appears to many of us to be unjustified and an exercise in futility.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

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Malcolm R Sears

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