**ASTHMA**

**Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma**

M Masoli, M Weatherall, S Holt, R Beasley

**Background:** There is uncertainty as to the dose of inhaled corticosteroids (ICS) at which to start concomitant long acting β agonist (LABA) treatment in patients with asthma not adequately controlled by ICS alone.

**Methods:** A meta-analysis was carried out of randomised, double blind clinical trials that compared the efficacy of adding salmeterol to moderate doses of ICS (fluticasone propionate 200 μg/day or equivalent) with increasing the ICS dose by at least twofold in symptomatic adult patients with asthma. The main outcome measures were the number of subjects withdrawn from the study due to asthma and the number of subjects with at least one moderate or severe exacerbation. 

**Results:** Twelve studies with a total of 4576 subjects met the inclusion criteria for the analyses. The number of subjects withdrawn due to asthma and with at least one moderate or severe exacerbation was higher in the high dose ICS group (odds ratios 1.58, 95% CI 1.12 to 2.24 and 1.35, 95% CI 1.10 to 1.66, respectively). For the secondary outcome variables (forced expiratory volume in 1 second, morning and evening peak expiratory flow, and daytime β agonist use) there was significantly greater benefit in the salmeterol group.

**Conclusions:** This meta-analysis shows that the addition of salmeterol to moderate doses of ICS (fluticasone 200 μg/day or equivalent) in patients with asthma symptomatic at that dose results in significantly greater clinical benefit than increasing the dose of ICS by twofold or more.
symptoms between studies or because the information was not available in the format required. For withdrawals due to asthma, a continuity correction was used in the analysis because the data sets in the papers by Van Noord et al and Kalberg et al had “zero” cell counts.

Data analysis
For continuous variables a standard method of pooling means based on standardised mean differences using an inverse variance weighting approach was used. A weighted mean standard deviation was used to translate the standardised mean difference back into the original units. In the forest plots the area of the box is proportional to the variance of the estimate for the individual trials.

For the categorical variables the log odds ratio was pooled using the inverse variance weighting approach. The forest plots are presented as the log of the odds ratio and the area of the box is, where possible, proportional to the variance of the estimate for the individual trials. If the variance of individual trial estimates was too large to fit the scale of the plot, the area of the box is reduced to a quarter of the variance; this was required for the two primary outcome variables. Heterogeneity statistics and inconsistency measurements, the latter according to the method of Higgins and Thompson, were calculated for all the comparisons. SAS Version 8.2 was used.

RESULTS
Twelve studies with a total of 4576 subjects met the inclusion criteria for the analysis (table 1). The mean FEV1 was 64% of predicted normal values (range 40–85%), indicating that subjects had moderate to severe asthma. By virtue of the inclusion criteria used, the methodological quality of included studies was high with all studies achieving a Jadad score of 4 or more. In two studies subjects were only eligible to participate if they had been shown to be unstable on 200 µg/day fluticasone. They were then treated with fluticasone 500 µg/day in the run in phase, before randomisation to fluticasone 200 µg/day and salmeterol or fluticasone 500 µg/day. Comparisons were made between the addition of salmeterol to BD-400 v 1000 µg/day in one study, BD-400 v 800 µg/day in three studies, fluticasone 200 v 500 µg/day in six studies, fluticasone 200 v 400 µg/day in one study, and fluticasone 200 µg/day v budesonide 800 µg/day in one study. The study by Baraniuk et al was the combined publication of two separate studies (FLTA 4021 and FLTA 4022). The combination salmeterol/fluticasone (Advair/Seretide) inhaler was used in three studies.

Evidence of heterogeneity was found for several of the outcome variables including morning PEF (where the heterogeneous studies were in the same direction as the others), FEV1 (where one study was more positive and another more negative), daytime β agonist use (two studies showing less difference), and night time β agonist use (with two studies having more effect). For all these the confidence intervals became wider under the random effects models, and for FEV1 and night time β agonist use this led to the lower confidence limit being close to or at zero, consistent with no difference in effectiveness between the two strategies. For the other secondary outcome variables there was no substantive difference to the conclusions.

Main outcome measures
There was a significant reduction in the number of subjects withdrawn due to asthma in the low dose ICS/salmeterol group (59/2036) compared with high dose ICS treatment (86/1992) with an odds ratio of 1.58 (95% CI 1.12 to 2.24) (table 2, fig 2). There was a significant reduction in the number of subjects with one or more moderate or severe exacerbation in

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**Figure 1** Results of search of Medline, EMBASE and GlaxoSmithKline databases for clinical studies eligible for inclusion in meta-analysis.
the low dose ICS/salmeterol group (184/2312) compared with high dose ICS treatment (243/2264) with an odds ratio of 1.35 (95% CI 1.10 to 1.66) (table 2, fig 3).

Secondary outcome measures
Mean morning PEF and evening PEF were significantly greater and daytime β agonist use was reduced in those who received low dose ICS/salmeterol compared with high dose ICS, with differences of 23 l/min, 19 l/min, and −0.6 puffs per day, respectively (table 3). Significantly greater improvements were also observed for FEV₁, although the lower confidence limit was closer to no difference. For night awakenings and night time β agonist use, the lower confidence limits included no difference in effect although the point estimates favoured the ICS/salmeterol group.

DISCUSSION
In this meta-analysis we have shown that, in patients symptomatic on ICS at a dose of 200 µg fluticasone or equivalent, the addition of salmeterol is superior to increasing the dose of ICS by at least twofold for all major clinical outcome measures. For the main outcome variables of withdrawals due to asthma and at least one moderate or severe exacerbation, subjects receiving salmeterol had a 35–50% reduced risk compared with higher dose ICS treatment. The secondary outcome variables of lung function and β agonist use were also significantly improved compared with the higher ICS dose.

There are issues relating to the design of the study that are relevant to the interpretation of the results. The most important was the decision to restrict the analysis to studies that used a baseline dose of ICS of 200 mg/day fluticasone or equivalent.

Table 1 Summary of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Study duration (weeks)</th>
<th>Doses of FP/BDP/Sal (mg/day)</th>
<th>Device</th>
<th>Comparison dose (mg/day)</th>
<th>Range (mean) FEV₁ % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greening</td>
<td>426</td>
<td>26</td>
<td>BDP 400</td>
<td>MDI</td>
<td>BDP 1000</td>
<td>≥50 (PEF 74)</td>
</tr>
<tr>
<td>Kelsen</td>
<td>483</td>
<td>24</td>
<td>BDP 400</td>
<td>MDI</td>
<td>BDP 800</td>
<td>45–80 (65)</td>
</tr>
<tr>
<td>Murray</td>
<td>514</td>
<td>24</td>
<td>BDP 400</td>
<td>MDI</td>
<td>BDP 800</td>
<td>50–80 (66)</td>
</tr>
<tr>
<td>Kolberg</td>
<td>488</td>
<td>24</td>
<td>FP 200</td>
<td>MDI</td>
<td>−</td>
<td>40–80</td>
</tr>
<tr>
<td>Condemi</td>
<td>437</td>
<td>24</td>
<td>FP 200</td>
<td>MDI</td>
<td>FP 500</td>
<td>40–80 (61)</td>
</tr>
<tr>
<td>Van Noord</td>
<td>60</td>
<td>12</td>
<td>FP 200</td>
<td>Diskhaler</td>
<td>FP 400</td>
<td>≥50 (72)</td>
</tr>
<tr>
<td>Vermetten</td>
<td>233</td>
<td>12</td>
<td>BDP 400</td>
<td>Diskhaler</td>
<td>BDP 800</td>
<td>PEF &gt;60 (84)</td>
</tr>
<tr>
<td>Bloom</td>
<td>574</td>
<td>12</td>
<td>FP 200</td>
<td>Diskus (comb)</td>
<td>FP 500</td>
<td>65–95 (78)</td>
</tr>
<tr>
<td>Busse</td>
<td>558</td>
<td>12</td>
<td>FP 200</td>
<td>Diskus (comb)</td>
<td>FP 500</td>
<td>≥65 (81)</td>
</tr>
<tr>
<td>FLTA 4021</td>
<td>232</td>
<td>12</td>
<td>FP 200</td>
<td>MDI</td>
<td>FP 500</td>
<td>40–85 (63)</td>
</tr>
<tr>
<td>FLTA 4022</td>
<td>222</td>
<td>12</td>
<td>FP 200</td>
<td>MDI</td>
<td>FP 500</td>
<td>40–85 (63)</td>
</tr>
<tr>
<td>Johansson</td>
<td>349</td>
<td>12</td>
<td>FP 200</td>
<td>MDI</td>
<td>BUD 800</td>
<td>65–85 (77)</td>
</tr>
</tbody>
</table>

FP, fluticasone propionate; ICS, inhaled corticosteroid; BDP, beclometasone dipropionate; Sal, salmeterol; BUD, budesonide; Comb, combination fluticasone/salmeterol; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; MDI, metered dose inhaler.
Table 2  Numbers of subjects withdrawn due to asthma and number of subjects with at least one moderate or severe exacerbation, and associated odds ratios (95% CI) between treatment with salmeterol and increased dose of inhaled corticosteroid

<table>
<thead>
<tr>
<th>Study</th>
<th>Withdrawals due to asthma</th>
<th>Moderate or severe exacerbations*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sal</td>
<td>ICS</td>
</tr>
<tr>
<td>Greening</td>
<td>7/220</td>
<td>14/206</td>
</tr>
<tr>
<td>van Noord (low dose)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vermetten</td>
<td>6/113</td>
<td>10/120</td>
</tr>
<tr>
<td>Busse</td>
<td>14/281</td>
<td>20/277</td>
</tr>
<tr>
<td>Bloom</td>
<td>15/295</td>
<td>22/279</td>
</tr>
<tr>
<td>Kelsen</td>
<td>3/239</td>
<td>6/244</td>
</tr>
<tr>
<td>Murray</td>
<td>5/260</td>
<td>5/254</td>
</tr>
<tr>
<td>Kalberg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Condemi</td>
<td>2/221</td>
<td>6/216</td>
</tr>
<tr>
<td>FLTA4021</td>
<td>1/118</td>
<td>1/114</td>
</tr>
<tr>
<td>FLTA4022</td>
<td>1/113</td>
<td>1/109</td>
</tr>
<tr>
<td>Johansson</td>
<td>3/176</td>
<td>3/173</td>
</tr>
</tbody>
</table>

Pooled estimates of effect (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sal</th>
<th>ICS</th>
<th>OR (95% CI)</th>
<th>Sal</th>
<th>ICS</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed effect</td>
<td>1.58 (1.12 to 2.24)</td>
<td>1.35 (1.10 to 1.66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effect</td>
<td>1.58 (1.12 to 2.24)</td>
<td>1.37 (1.10 to 1.70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconsistency measurements</td>
<td>10.4 (0 to 49.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, Odds ratio for withdrawal (greater than 1 means ICS more likely to withdraw and favours salmeterol). Note that a continuity correction was used for this analysis because the van Noord data set had a “zero” cell count.

Table 3  Mean difference (95% CI) for all secondary outcome measures between the group receiving added salmeterol and the group receiving increased dose of ICS

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Difference in original units†</th>
<th>Fixed effects</th>
<th>Random effects</th>
<th>Inconsistency measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning PEF (l/min)</td>
<td>23 (19 to 28)</td>
<td>23 (15 to 30)</td>
<td>63.7 (25.5 to 82.3)</td>
<td></td>
</tr>
<tr>
<td>Evening PEF (l/min)</td>
<td>19 (15 to 23)</td>
<td>19 (13 to 24)</td>
<td>29.9 (0.00 to 82.3)</td>
<td></td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>0.12 (0.09 to 0.15)</td>
<td>0.12 (0.06 to 0.18)</td>
<td>71.0 (56.7 to 86.7)</td>
<td></td>
</tr>
<tr>
<td>Night awakenings (no/week)</td>
<td>-0.03 (0.00 to -0.07)</td>
<td>-0.03 (0.01 to -0.07)</td>
<td>15.8 (0.00 to 65.1)</td>
<td></td>
</tr>
<tr>
<td>Day time β agonist use (puffs/day)</td>
<td>-0.58 (-0.44 to -0.72)</td>
<td>-0.60 (-0.35 to -0.84)</td>
<td>70.3 (20.5 to 87.3)</td>
<td></td>
</tr>
<tr>
<td>Night time β agonist use (puffs/night)</td>
<td>-0.08 (-0.02 to -0.13)</td>
<td>-0.08 (-0.00 to -0.16)</td>
<td>58.0 (0.00 to 83.0)</td>
<td></td>
</tr>
</tbody>
</table>

†Mean difference represents the mean outcome measure for the group receiving added salmeterol minus the mean outcome measure for the group receiving increased dose of inhaled corticosteroid.

equivalent. While recognising the marked individual variability in response to ICS and the requirement for higher doses in certain circumstances, this ICS dose was chosen as its use results in 80–90% of the maximum obtainable benefit for all clinical outcome measures including exacerbations.

Consideration was given to broadening the inclusion criteria to include similar studies of the LABA formoterol. This was not undertaken due to the paucity of such studies which used an equivalent baseline daily dose of ICS and the lack of data presented in the same standardised format. However, the findings are complemented by the FACET study in which budesonide at 800 μg/day resulted in significantly fewer severe exacerbations than low dose budesonide (200 μg/day) plus formoterol. This study illustrates the importance of obtaining most of the therapeutic benefit from ICS therapy before considering add-on therapy in patients with symptomatic asthma.

By limiting the analysis to studies of salmeterol, we were able to include 12 studies involving over 4500 patients with asthma including five studies of 1995 subjects not included in the original MIASMA publication. We are confident that we obtained all eligible studies as a result of the comprehensive search strategy undertaken. However, even with the strict inclusion criteria employed, our meta-analysis did include studies in which salmeterol was added to different ICS (BDP and fluticasone), different inhaler devices (Diskus and MDI), and both combination and separate inhalers. We were provided with data in a standardised format from GlaxoSmithKline which, in addition to the data published in the original manuscripts and MIASMA, allowed data to be used in a standardised format across the studies included in the meta-analysis.

Another issue was the choice of the main outcome variables—withdrawals due to asthma and one or more moderate or severe exacerbations. This analysis differed from the original MIASMA study in that we did not include mild exacerbations which incorporated an increase in β agonist use as this would be expected to be reduced with concomitant LABA treatment. However, even with the use of withdrawals due to asthma, the results must be interpreted with some caution as the number of withdrawals due to asthma was relatively few in comparison with total withdrawals. With regard to moderate to severe exacerbations, this may have included some episodes that reflected “loss of asthma control” rather than clinically severe exacerbations, and the paucity of hospital admissions prevented this specific outcome measure being used. Furthermore, it is likely that there was a close correlation between withdrawals due to asthma and moderate or severe exacerbations. However, despite these limitations we consider that withdrawals and moderate or severe exacerbations...
are of greater clinical relevance than lung function measures, particularly with comparisons between ICS and LABA treatment. Consistent with the findings for these main outcome measures, the secondary outcome measures including lung function measures such as clinic FEV₁, morning and evening PEF, and β agonist use also favoured the salmeterol group.

Finally, it is worthy of comment that, although the studies in this meta-analysis were restricted to salmeterol as the LABA, the evidence that salmeterol and formoterol have similar efficacy in the long term treatment of asthma would suggest that the results are probably applicable to the class of LABAs.

In conclusion, recent meta-analyses of the dose-response of ICS demonstrate a relatively flat dose-response relationship with 80–90% of the maximum therapeutic benefit achieved with a daily dose of around 200 μg fluticasone or 400 μg budesonide.1–5 Notwithstanding the marked individual variability in response to ICS treatment, these studies would suggest that the 200 μg/day dose of fluticasone or equivalent is likely to represent the preferable level at which to consider the addition of salmeterol in an asthmatic patient not well controlled on ICS. The results of this meta-analysis support this view by showing that the addition of salmeterol to moderate doses of ICS (200 μg/day fluticasone or equivalent) is more effective than increasing the dose of ICS by twofold or more for clinical outcome measures including exacerbations and withdrawals due to asthma. These findings should provide clinicians with greater confidence when deciding the dose of ICS at which to consider adding salmeterol at step 3 in the asthma guidelines.

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Competing interests: The Medical Research Institute of New Zealand, the Wellington School of Medicine & Health Sciences, and P3 Research have all received research grants from Astra Draco, GlaxoSmithKline, and Novartis. R Beasley has received fees for consulting and speaking and reimbursement for attending symposia from Astra Draco, and GlaxoSmithKline and Novartis. M Masoli and S Holt have received reimbursement for attending symposia from Astra Draco and Novartis, and S Holt also from GlaxoSmithKline.

MM developed the protocol, organised the search, undertook data extraction and wrote the paper. MW was responsible for the data analysis, statistical methodology and manuscript preparation. SH contributed to the study concept and manuscript preparation. RB provided senior oversight for the study and was responsible for the manuscript preparation. MM will act as guarantor for this paper.

**REFERENCES**

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