INHALED CORTICOSTEROIDS AND LONG-ACTING BETA AGONISTS IN FIXED-DOSE COMBINATIONS VERSUS MONOTHERAPY

Combinations of inhaled corticosteroids (ICSs) and long-acting β-agonists (LABAs) are recommended as treatment options for patients unable to attain sufficient symptom control with ICSs alone, literature comparing the effectiveness of the available fixed-dose combinations to monotherapy with either agent is limited. This issue of CLIPs briefly summarizes an article that performed a systematic review of the available literature to assess the effectiveness of ICS (e.g., fluticasone propionate and budesonide) and the inhaled LABAs (e.g., formoterol fumarate and salmeterol xinafoate) either alone or in fixed-dose combinations (FDCs) for the treatment of asthma. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Methods
- This review sought to compare treatment outcomes with ICS and LABA agents in terms of lung function, symptom-free days, rescue medication use, asthma exacerbations, and tolerability profiles.
- Studies were obtained from Ovid Medline database with search results updated through September 2009.
- The search was limited to articles on asthma and randomized clinical trials that assessed forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), symptom-free days (SFDs), rescue medication use, and exacerbations.
- Articles that provided only information on discontinuation, onset of action, outcomes of daily activities, quality of life, adherence and persistence, healthcare utilization, or direct costs were excluded.
- Mean differences in treatment outcomes were calculated between treatment comparisons.
- Tolerability was evaluated in terms of death, serious adverse events, and adverse events.

Results
- Eighty articles were included in the review. For the majority of study comparisons (n=89), the effects on lung function were assessed as between treatment difference with respect to the change in outcome from baseline to endpoint.
- In twelve comparisons, treatment differences were determined by assessing the change in lung function from randomized baseline to endpoint for each comparison or by assessing the difference between treatments in lung function outcome over the study period or at endpoint.
- In all but one comparison involving other treatment outcomes, the difference between treatments in terms of lung function were assessed over the study period or at endpoint.

Fluticasone vs. budesonide
- Seven of 13 articles (54%) comparing fluticasone and budesonide documented statistically significant PEF improvements with fluticasone.
- Two and 3 studies, respectively, demonstrated FEV1 improvements and more SFDs in favor of fluticasone vs. budesonide.

Formoterol vs. salmeterol
- Of 16 articles reviewed, 4 studies demonstrated statistically significant FEV1 improvement with formoterol vs. salmeterol, while 5 studies found no significant improvement in FEV1 between the two treatments. Five studies reviewed did not report FEV1 values.
- Significant differences were identified between study designs including short duration, small sample size, and differences in dosing.

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**Budesonide/formoterol FDC vs. monotherapy with budesonide or formoterol**
- Eighteen studies were reviewed with 19 of 20 comparisons (95%) demonstrating significant improvement in PEF in the budesonide/formoterol group and 9 of 18 comparisons (50%) showing reduced use of rescue medication with FDC vs. budesonide monotherapy.
- All outcomes significantly improved with budesonide/formoterol vs. formoterol alone in 2 of 4 studies reviewed. However, one study reported no difference in PEF, rescue medication use, or SFDs but did find statistically significant improvements in FEV$_1$ with budesonide/formoterol.

**Fluticasone/salmeterol FDC vs. monotherapy with fluticasone or salmeterol**
- Thirty-one of 34 studies (91%) reviewed comparing FDC to fluticasone monotherapy demonstrated significant improvements for $\geq 2$ outcomes.
- All 9 studies comparing FDC to salmeterol monotherapy demonstrated significant improvement in $\geq 1$ outcome while 4 of 6 studies revealed significant improvements in asthma exacerbations with FDC.

**Safety Profiles**
- No significant differences in treatment-related deaths were reported with FDCs vs. monotherapy.
- Two comparisons demonstrated significantly greater growth in children receiving budesonide/formoterol vs. budesonide monotherapy.

**Discussion**
- Results from this review support results of two previous meta-analyses that reported better outcomes with fluticasone than with budesonide. Additionally, this review suggests that fluticasone provided greater improvement in outcomes in both pediatric and adult populations.
- Results support that FDCs provide greater improvements in lung function and symptom control while reducing exacerbations than do monotherapies of individual agents.
- A small number of studies also suggested that formoterol provided greater improvements in lung function and SFDs while reducing need for rescue medications compared to salmeterol, but some of these studies lacked statistical significance. Since formoterol has a more rapid onset of bronchodilation and is more potent than salmeterol, these differences seem reasonable.
- Studies comparing FDCs of ICSs and LABAs reported no significant differences in primary outcome measures between the two groups.
- Increased safety risks with the FDCs were not detected in this review.

**Conclusion**
- Results from this review coincide with the Global Initiative for Asthma and Expert Panel Report-3 recommendations of the use of ICS/LABA combinations in patients unresponsive to low- or moderate-dose ICSs.
- Monotherapy with fluticasone and formoterol demonstrated improved outcomes compared with budesonide and salmeterol monotherapies, respectively.
- FDCs in both adults and children provide greater benefit than with ICSs or LABAs alone.

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