Review: Long-acting β-agonists increase severe asthma exacerbations and asthma-related deaths in children and adults

Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. **Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths.** Ann Intern Med. 2006;144:904-12.

Clinical impact ratings: Emergency Med ★★★★★☆☆ GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆ Allerg & Immunol ★★★★★★☆ Pulmonology ★★★★★☆☆

QUESTION

In children and adults with asthma, do long-acting β-agonists (LABAs) increase severe asthma exacerbations requiring hospitalization, life-threatening asthma attacks, and asthma-related deaths?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, CINAHL, and Cochrane databases (all from 1966 to December 2005); references of selected reviews; and the U.S. Food and Drug Administration Web site.

Study selection and assessment: Randomized controlled trials (RCTs) in any language that compared LABAs (salmeterol, formoterol, or eformoterol) with placebo and had ≥ 3-month follow-up. Patients were allowed to use short- acting β-agonists if needed. 19 RCTs (n = 33 826; mean age 37 to 38 y, 51% men) met the selection criteria. Quality assessment of individual studies was based on randomization procedure, allocation concealment, blinding, dropouts and withdrawals, and intention-to-treat analysis.

Outcomes: Hospital admission for asthma exacerbations, life-threatening asthma exacerbations, and asthma-related death.

MAIN RESULTS

More patients in the LABA group than in the placebo group were hospitalized for asthma exacerbations, had life-threatening asthma exacerbations, or died from asthma (Table). Subgroup analyses showed that increased hospital admission occurred in both children (< 12 y) (odds ratio [OR] 3.9, 95% CI 1.7 to 8.8) and adults (OR 2.0, CI 1.0 to 3.9), and with salmeterol (OR 1.7, CI 1.1 to 2.7) or formoterol (OR 3.2, CI 1.7 to 6.0). RCTs with > 75% use of concomitant inhaled corticosteroids (ICS) (mean 90% use) showed that LABAs also led to a greater rate of hospitalizations (OR 2.1, CI 1.3 to 3.4).

CONCLUSION

In children and adults with asthma, long-acting β-agonists increase hospital admissions for severe asthma exacerbations, life-threatening asthma attacks, and asthma-related death.

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Long-acting β-agonists vs placebo in children and adults with asthma at mean 6 months*

Outcomes	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Long-acting β-agonists	Placebo		
Hospital admission for asthma exacerbations	12 (5091)	1.5%	0.6%	158% (59 to 322)	107 (53 to 282)
Life-threatening asthma exacerbations	7 (29 981)	0.31%	0.17%	80% (10 to 189)	730 (308 to 5827)
Asthma-related death†	1 (26 353)	0.08%	0.02%	250% (30 to 828)	1759 (531 to 14 650)

*Abbreviations defined in Glossary; RRI, NNH, and CI calculated from odds ratios and control event rates in article using a fixed-effects model.
†Data from the SMART study; 2 other trials reported 1 death in the β-agonist group and 0 death in the placebo group.

COMMENTARY

The meta-analysis by Salpeter and colleagues showed that treating patients with asthma using LABAs results in a small but significant increase in death and other major adverse outcomes. Given the high prevalence of asthma and chronic obstructive pulmonary disease (COPD) and the convenience of taking long-acting medication, these findings are important.

Salpeter and colleagues speculate that LABAs may mask symptoms when underlying obstructive airways disease worsens. Of particular concern is the subgroup analysis that examined studies in which ≥ 75% of patients also received ICS. Even among these patients, the use of LABAs doubled risk for hospitalization, suggesting that ICSs do not fully protect against the adverse effects of LABAs. However, because the SMART study did not provide data on asthma-related hospitalization (1), the largest study was excluded from this subgroup analysis. Also, true use of concurrent ICS is important in these studies because these adverse outcomes may be a consequence of LABA monotherapy that would be expected to be ameliorated by the concomitant use of ICS. Furthermore, the review did not address combining LABA and ICS in one metered dose inhaler (MDI), which could be less expensive than separate MDIs, and hence more likely to be used. Limited data have been made available from the large multicentre TORCH study of mortality in COPD for participants receiving ICS plus LABA (2), but not for participants receiving LABA alone. As with mortality data from the SMART study (3), these data from the TORCH study are awaited with considerable interest. Heterogeneity of results of relevant studies in relation to actual ICS use also requires further assessment.

The meta-analysis is unable to provide insights as to whether the adverse outcomes may be related to racial or genetic factors (as has been suggested by post-hoc analysis in the SMART study), co-treatments (including combination inhalers and methylxanthines), or baseline disease severity. The bottom line is that LABA monotherapy should not be used in patients with asthma. At the least, this meta-analysis underscores the need for LABAs to only be used as a component of combined ICS and LABA therapy.

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Reference

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