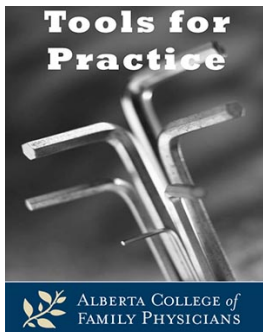


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Reviewed: August 22, 2016

Evidence Updated: Large trial of LABA + inhaled steroid versus inhaled steroid alone
Bottom Line: Strengthened conclusion of safety of LABA + inhaled steroid

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Long-Acting Beta-Agonist Inhalers in Asthma: Breathing Evidence Into the Debate?

Clinical Question: Are the serious adverse events associated with long-acting beta-agonists (LABAs) in asthma important enough to limit their use?

Bottom-line: In asthmatics, LABA should not be used without inhaled steroids. LABAs increase serious adverse events when used alone, but not when combined with an inhaled steroid (at least in patients >12 years-old). LABA monotherapy does not increase adverse events in COPD patients.

Evidence:

- FDA meta-analysis¹ (and related publications^{2,3}) of 110 Randomized Controlled Trials (RCTs) of 60,954 patients including 11% adolescents and 6% children with a median follow-up of 24 weeks.
 - LABA statistically significant increased risk of serious asthma-related event (asthma-related death, intubation or hospitalization):
 - 2.8 extra events per 1,000 asthmatics treated with LABA, Number Needed to Harm (NNH)=358.
 - Examining risk +/- inhaled steroid.
 - LABA alone versus no therapy: Statistically significant increase of 3.63 extra events per 1,000 asthmatics, NNH=276.
 - LABA + inhaled steroid versus inhaled steroid: Non-statistically significant 0.25 extra events per 1,000 asthmatics.
 - The risk increases with decreasing age (2/1,000 in adults age 18-64 and 15/1,000 in children 4-11).
- Three RCTs⁴⁻⁶ of 29,580 asthmatics (mean ages 43.5 years^{4,5}, 7.6 years⁶) comparing LABA + steroid combination inhaler versus inhaled steroid alone over 6 months, in author-pooled analyses:
 - No significant difference in serious asthma-related event: LABA/steroid 0.7%, steroid 0.64%.
 - Statistically significant reduction in severe asthma exacerbations: LABA/steroid 8.7%, steroid 10.4%, Number Needed to Treat (NNT)=59.

Context:

- These findings are supported by four Cochrane reviews⁷⁻¹⁰ and four other meta-analyses¹¹⁻¹⁴ of LABA safety in asthma:
 - Statistically significant increase in non-fatal serious adverse events versus placebo with formoterol (NNH=149 over 16 weeks)⁷ and salmeterol (NNH=188 over 28 weeks).⁸
 - LABA + inhaled steroid: No statistically significant increase in serious adverse events with formoterol/steroid⁹ or salmeterol/steroid¹⁰ versus steroid alone.
 - In one meta-analysis of LABA + inhaled steroid,¹⁴ statistical significance reached, but actual difference was very small (NNH_≥3,334).
- Serious adverse events with LABA are not increased in COPD. LABA alone does not increase mortality in COPD patients, and statistically significantly reduces the risk of COPD exacerbations requiring hospitalization (NNT=56).¹⁴

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Tools for Practice is a biweekly article summarizing medical evidence with a focus on topical issues and practice modifying information. It is coordinated by G. Michael Allan, MD, CCFP and the content is written by practising family physicians who are joined occasionally by a health professional from another medical specialty or health discipline. Each article is peer-reviewed, ensuring it maintains a high standard of quality, accuracy, and academic integrity. If you are not a member of the ACFP and would like to receive the TFP emails, please sign up for the distribution list at <http://bit.ly/signupfortfp>. Archived articles are available on the ACFP website.

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