Medicine by the Numbers

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Combination LABA Inhalers Compared with High-Dose Inhaled Steroids for Adults with Asthma

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Details for This Review

Study Population: Adult patients of any age and sex with known asthma of differing severities, already receiving an inhaled steroid

Efficacy End Points: Mild asthma exacerbation/attacks (defined as taking oral steroids), severe attacks (leading to hospitalization), life-threatening attacks (requiring mechanical ventilation), asthma-related deaths, and overall deaths

Harm End Points: Death, asthma-related death, life-threatening asthma attack

Narrative: Long-acting beta agonists (LABAs) relax smooth muscle in asthmatic lungs, potentially preventing attacks and improving symptoms. Although inhaled steroids are the accepted first-line controller, adding LABAs is common. LABAs increase severe attacks and asthma deaths when used alone.[1] This summary examines the effectiveness and safety of LABAs when combined with steroids. There are many LABA and LABA/steroid comparisons. We focused on trials addressing a common and relevant clinical dilemma among patients with asthma: When taking an inhaled steroid and seeking better control, should the steroid dose be increased or should a LABA/steroid combination be used?

The relevant Cochrane review examined 48 trials of more than 33,000 patients with asthma, assigning one group to a higher steroid dose and the other to a LABA/steroid. One in 73 patients in the LABA/steroid group avoided a mild attack (defined as requiring three to five days of oral steroids). However, adding a LABA did not reduce hospitalizations, deaths, or severe attacks. Moreover, for those with a 20% short-term risk of attack, one in 45 patients benefited; for those with a 1% risk of attack, one in 673 benefited. The more severe the asthma, the more likely the benefit. Adding a LABA also improved symptoms more than increasing the steroid dose, but at levels modest enough that asthma-related quality of life was unchanged.

Previous reviews have reached differing conclusions concerning safety. Two large reviews found that LABAs increase fatalities even when combined with steroids,[2,3] suggesting approximately one in 1,400 patients will experience an asthma-related death. An updated 2014 review could neither confirm nor refute this danger, perhaps because of a lack of power. The authors' estimate for increased overall deaths was an odds ratio of 1.4 (0.6 to 3.4), suggesting the possibility of a 40% relative increase.[4] An identical 40% increase was seen in the Salmeterol Multicenter Asthma Research Trial (SMART; odds ratio = 1.4, 0.7 to 2.9),[1] although in both cases, the results were statistically insignificant.

The 2016 AUSTRI trial was one of five commissioned by the U.S. Food and Drug Administration to address the dangers of LABAs. AUSTRI compared LABA/steroid combinations with a steroid alone in nearly 12,000 adults with asthma. There were no asthma deaths in either group and just two life-threatening attacks, making it impossible to assess any differences in these outcomes. Based on similar hospitalization rates, the authors concluded that serious events were equal in both groups.[5]

Caveats: There are many reviews addressing LABA effectiveness and safety. For safety, we focus on a comparison we think reflects a common clinical choice, which is increasing the inhaled steroid vs. adding a LABA. However, other comparisons can be more relevant, for instance, when steroid doses are maximal or when other pharmacologic options with no safety problems (e.g., anticholinergics, leukotriene inhibitors) have been ineffective.[6,7]

The length of trials complicates interpretation because they typically last just 12 or 26 weeks. The longer the use, the more patients may benefit. The Cochrane authors note that in the few longer-duration studies LABA benefits seemed to diminish or disappear after six months.

Symptom benefits with LABA/steroid therapy were small, typically 0.5 fewer pumps per day of a rescue inhaler and about 10% more symptom-free days, with no quality-of-life advantage. However, those with more symptoms may benefit more. They may also be at higher risk of a fatal attack, making LABAs tricky. The AUSTRI trial investigators' conclusion that LABA/steroid combinations are safe based on

equivalent hospitalization rates is questionable. Hospitalizations are often unaffected by LABAs (see efficacy results above) and may not correlate with asthma deaths. Careful readers may also note that LABAs slightly reduced mild attacks; however, steroid doses were identical in the groups. Had doses been higher in the steroid group, the benefit for mild attacks might have disappeared. This is consistent with the finding that low-risk patients with asthma—the AUSTRI population—experience no meaningful benefit from LABAs. Future studies should focus on medium-risk and high-risk patients with asthma in whom fatal attacks are an uncommon but consistent threat, and for whom the potential benefit may be meaningful.

Finally, picking the most appropriate end point to review for numerical estimates is difficult, which is why we offer a range of values. All-cause mortality is a more patient-centered outcome than asthma-related deaths, but it is often not reported. We chose the Salpeter review as a primary source because it was the most transparent and conservative, and other reviews found the same or nearly identical point estimates.

We have chosen to designate this therapy red (no benefits) according to our rating system because of a small potential benefit of questionable clinical utility (avoiding a brief burst of oral steroids) and the possibility of a fatal harm. We considered black (harms greater than benefits); however, there is uncertainty about these fatal harms, and we hope physicians and patients can discuss these issues, share decisions, and come to their own conclusions.

This series is coordinated by Dean A. Seehusen, MD, MPH, *AFP* Contributing Editor, and Daniel Runde, MD, from the NNT Group.

A collection of Medicine by the Numbers published in *AFP* is available at http://www.aafp.org/afp/mbtn.

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