Beta-2 agonists and exercise-induced asthma

A Cochrane systematic review has assessed the effects of short-acting and long-acting beta-2 agonists for the prevention of exercise-induced asthma in adults and children. The Medicines and Healthcare Products Regulatory Agency recommends that long-acting beta-2 agonists should not be prescribed for the relief of exercise-induced asthma symptoms in the absence of regular inhaled corticosteroids.

Overview: Asthma is a chronic inflammatory condition in which the airways are hyper-responsive and constrict easily in response to a wide range of stimuli. Physical exercise may trigger symptoms such as cough, chest tightness and shortness of breath in people with asthma that is not adequately controlled (exercise-induced asthma). Physical exercise can also trigger asthma symptoms and induce bronchial obstruction in people without clinical asthma (exercise-induced bronchoconstriction).

The prevalence of exercise-induced asthma ranges from 5% to 20% in the general population. However, some estimates suggest it may affect everyone with uncontrolled asthma. Exercise-induced asthma is reported to be more common in children, people with rhinitis and athletes (Bonini M et al. 2013).

See the NICE Evidence Services topic page on asthma for a general overview of this condition.

Current advice: The British guideline on the management of asthma (Scottish Intercollegiate Guidelines Network and British Thoracic Society) states that for most people, exercise-induced asthma indicates poorly controlled asthma. People who experience exercise-induced asthma should undergo review of their regular asthma treatment, including inhaled corticosteroids.

If exercise is a specific problem in people taking inhaled corticosteroids whose asthma is otherwise well controlled, the British guideline recommends considering adding one of the following treatments: leukotriene receptor antagonists; long-acting beta-2 agonists (LABAs); chromones; oral beta-2 agonists; or theophyllines. An inhaled short-acting beta-2 agonist (SABA) immediately before exercise is also recommended.

In a Drug Safety Update, the Medicines and Healthcare Products Regulatory Agency recommended that LABAs should not be prescribed for the relief of exercise-induced asthma symptoms in the absence of regular inhaled corticosteroids. Instead, a SABA should be used in this situation. The Commission on Human Medicines has issued advice for prescribers on the use and safety of LABAs for treating chronic asthma.

Recommendations on the diagnosis and management of exercise-induced asthma are available in the NICE Clinical Knowledge Summary on asthma.

New evidence: A Cochrane systematic review by Bonini et al. (2013) has assessed the effects of SABAs and LABAs compared with placebo in the prevention of exercise-induced asthma. The review included 53 double-blind placebo-controlled randomised trials. The studies assessed adults and children (age range 4–64 years) with a history of exercise-induced asthma, a positive response to a
standardised exercise challenge (a fall in forced expired volume in 1 second \[FEV_1\] of 10% or more from the pre-exercise value) or both. SABAs had to be given up to 1 hour before the standardised exercise challenge, and LABAs up to 12 hours before. The exercise challenges included treadmill running (35 studies), exercise bike (13 studies) and free running (5 studies).

In the 45 studies that looked at short-term (single-dose) administration of an inhaled beta-2 agonist (n=799), \(\text{FEV}_{1}\), fell significantly less in people who took a beta-2 agonist before the exercise challenge than in those who took a placebo (mean difference=−17.67%, 95% CI −19.51 to −15.84%, p=0.00001). Subgroup analysis for both LABAs (21 studies) and SABAs (40 studies) produced similar results. The total number of adverse events was similar with beta-2 agonists and placebo (45 versus 54, p=0.56).

The 8 studies that looked at long-term administration of an inhaled beta-2 agonist had a small number of participants (n=206) and differed in their study designs, which meant meta-analysis was not possible. However, overall evaluation of the long-term studies suggested a bronchoprotective effect for the first-dose of a beta-2 agonist, but that long-term use of both SABAs and LABAs induced the onset of tolerance and decreased the duration of drug effect, even after a short treatment period. The long-term studies had insufficient data on the safety of regular long-term use of beta-2 agonists for exercise-induced asthma.

**Commentary:** “Exercise-induced symptoms are a common problem in patients with asthma, and SABAs are frequently used before exercise as a preventive measure. This Cochrane review concluded that a single dose of a SABA before exercise is associated with a short-term benefit (reduction in mean fall of \(\text{FEV}_{1}\)). However, the evidence is of low-to-medium quality. In addition, the review found that long-term use of SABAs induced tolerance.

“The review also included studies that looked at the effect of LABAs before exercise. Although there was also a short-term protective effect with LABAs, evidence from safety data does not support the use of LABAs in this way. In asthma, LABAs should only be prescribed in conjunction with inhaled corticosteroids.

“For any patient experiencing frequent exercise-induced asthma symptoms, two things should be considered before simply advising that pre-exercise SABA should be the mainstay of treatment. First, consider whether the symptoms indicate poorly controlled asthma and if a review of the patient’s regular asthma treatment would be more appropriate. Second, bear in mind whether the symptoms are caused by dysfunctional breathing during exercise, in which case the management is very different.

“This review highlights that further studies are needed to look at the long-term effects of SABAs before exercise, not only in terms of effect on lung function but also on patient reported outcomes.” – *Dr Louise Fleming, Clinical Senior Lecturer and Consultant Respiratory Paediatrician, Imperial College London and Royal Brompton Hospital*

**Study sponsorship:** National Research Council, Institute of Translational Pharmacology, Italy; Italian National Drug Agency; and 21st Century Canada Research Chairs Programme, Government of Canada.

**About this article:** This article appeared in the April 2014 issue of the Eyes on Evidence e-bulletin. This free monthly e-bulletin from NICE Evidence outlines interesting new evidence and what it means for current practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

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