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JOURNAL ROUND-UP/BOOK REVIEWS

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

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Aims: To assess the risk of severe, life-threatening, or fatal asthma exacerbations associated with long-acting beta-agonists (LABAs).

Methods: Search of the MEDLINE, EMBASE, CINAHL, and Cochrane databases to identify randomised, placebo-controlled trials of LABA (salmeterol, formoterol and eformoterol) use in patients with asthma, published between 1966 and December 2005. Only studies over three months' duration were included. Concomitant inhaled corticosteroids (ICS) were used in 53.9% of participants in the LABA group and 53.2% of those in the placebo group. All studies allowed as-needed short-acting Beta-agonist use. Deaths were not measured against the use of ICS.

Results/Conclusions: Results were pooled from 19 trials with a total of 33,826 participants. The paper concluded that LABAs increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). Over six months, there was a small absolute increase in hospitalization of 0.7% (CI 1.1—3.9). The risk of asthma-related death was marginally increased with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%). The data for analysis of the odds ratio of deaths were obtained solely from the previously-published SMART study [1], which was found to be statistically significant. The absolute increase in risk was estimated by pooling all trials with and without deaths and was also found to be statistically significant.

Commentary

Concerns about LABA treatment as monotherapy for asthma — with increased exacerbation rates, hospitalizations and death — have been evident previously. Asthma Guideline recommendations worldwide emphasize the need for adequate anti-inflammatory therapy before starting any add-on treatment, including LABAs [2—4]. This meta-analysis from Salpeter et al. has only selected LABA vs placebo studies, and only 53% of patients studied were on ICS. The authors have then generalized their findings to all asthmatic patients. There are several conclusions in this paper which I feel are not justified;

1. The authors state: ''Concomitant inhaled corticosteroids do not adequately protect against the adverse effects [of LABAs].'' Whilst 53% of patients had been prescribed ICS treatment in the constituent studies, the details of patients' ICS use were not a key part of those studies. There are a large number of studies [5—8] that have tested LABA use with and without ICS (not just against placebo alone) which have **not** been included in this meta-analysis. In these, there was clear evidence of reduction of exacerbations, improvement in lung function, and improved quality of life, in patients on ICS with moderate to severe asthma who receive additional LABA treatment.
2. The authors state that; ''The use of LABAs could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions, and deaths each year.'' Monotherapy with LABAs might cause worsening, but if used in patients with at least

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moderately severe asthma, in combination with appropriate doses of ICS, this has not been proven [5–8]. In fact, the converse has been shown – i.e. that there is an improvement in exacerbations and mortality in patients using combination therapy with ICS and LABAs [8,9].

3. ''Black box warnings on the labeling for these agents [LABAs] clearly outline the increased risk for asthma-related deaths associated with their use...This information could be used to reassess whether these agents should be withdrawn from the market.'' The SMART study [1] has provoked questions internationally and has made us review our use of LABAs. At a recent update meeting of the Canadian Consensus guideline group, combination therapy (LABA plus ICS in one device) was recommended as a means to decrease the use of LABAs as monotherapy in asthma. Further confusion arises when studies using LABA alone (without ICS) are reported on subjects with asthma and COPD [10]. Monotherapy with LABAs is acceptable in COPD [11] but is unsafe in patients with asthma [1].

It is premature (and inappropriate) of the authors of this paper to suggest that withdrawal of LABAs should even be considered. LABAs have proven efficacy and safety if used in addition to ICS for patients with asthma.

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Review of ''Pharmacological strategies of self management of asthma exacerbations.'' Reddel H, Barnes D, on behalf of Exacerbation Advisory Panel. Eur Resp J 2006; 28: 182–199.

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Commentary

This is a useful review with a number of sensible aims. These were:

1. To determine the efficacy of using oral corticosteroids (OCS) in adults experiencing an asthma exacerbation, alone or in combination with combination therapy.
2. To determine the efficacy of using inhaled corticosteroids (ICS) in patients with asthma experiencing an exacerbation, alone or in combination with combination therapy.
3. To determine the efficacy of increasing the dose of combination therapy in adults experiencing an exacerbation, currently receiving combination therapy.
4. To determine the efficacy of using short acting B-agonists (SABA) in patients experiencing an exacerbation, both in general and in particular whilst receiving combination therapy.

Complicating the analyses was the fact that there was wide variation in the definition of an exacerbation. However, there are some important findings for primary care here. The studies chosen for the review, identified from a Medline search from 1990–2004, were taken from hospital settings (8 in total), Emergency Departments (ED) (11) and community settings (14). The authors made an