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Commentary

Commentary on 'Regular treatment with formoterol and inhaled steroids for chronic persistent asthma: serious adverse events'

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This is a commentary on a Cochrane review, published in this issue of EBCH, first published as: Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD006924. DOI: 10.1002/14 651 858.CD006924.pub2.

Further information for this Cochrane review is available in this issue of EBCH in the accompanying Summary article.

The balance of safety and efficacy of long term long acting beta agonists (LABAs) in combination with inhaled corticosteroids (ICS) in the management of persistent asthma continues to be a subject of intense interest and the recent systematic review and meta-analysis by Cates *et al*. provides reassurance while raising questions about this treatment option (1). The review includes studies that randomized symptomatic children and adults to either twice daily formoterol and ICS, or to the same dose of ICS. Four deaths were noted in the 8,028 included adults (1 asthma-related), all in those randomized to formoterol and ICS; no deaths occurred in the 2788 included children aged 6–11 years. As might be expected with only one asthma-related death in a large exposed population, this difference was not statistically significant, a conclusion also supported by the lack of evidence of any increase in serious adverse events (SAEs) with even a decreased risk of asthma-related SAEs in adults randomized to formoterol and ICS. However, in children, a small non-significant increase in SAEs was observed in those randomized to formoterol and ICS.

Concerns regarding LABA were raised soon after their introduction in 1990s and confirmed in two large prospective studies (2–3) which reported an increased risk of deaths associated with salmeterol. No such evidence was available at that time for formoterol (4). Although both available LABAs are potent long acting bronchodilators, the more rapid onset of action of formoterol has subsequently resulted in its license extension as an asthma reliever in addition to asthma prophylaxis (5–6). Asthma management guidelines recommend that LABAs should not be used without concomitant ICS (7–9), and previous studies and meta-analyses have confirmed increased risks associated with LABA monotherapy (10–11). However, it is unclear to what extent concomitant ICS protect against fatal and non fatal SAEs, as addressed in the Cochrane review.

Several other meta-analyses have been performed to assess the safety of formoterol with or without concomitant ICS in adults and children (12–14) and the lower risk of asthma-related SAEs reported in the Cates review concur with the Jaeschke (12) and Sears meta-analyses (13). Jaeschke *et al*. reviewed 18 trials in adolescents and adults, and found no evidence of harm associated with the use of formoterol in combination with ICS compared to ICS alone at the same or higher dose (12). However, the frequency of asthma-related deaths and asthma-related SAEs, reflected in the need for endotracheal intubation, was too small to draw firm conclusions (12). In the Sears review, SAEs were lower in those randomized to formoterol with or without concomitant ICS in comparison to non-LABA treatments. However despite the large-included population ($n = 68,004$ adults and children), there was insufficient power to confirm any association between formoterol use and asthma mortality (13). In the Wijesinghe review and metanalysis, asthma mortality was the only outcome assessed and was, as in previous reviews, inconclusive because of insufficient power to assess this outcome by LABA exposure (14).

Despite the increasing number of studies, reviews and meta-analyses, little has changed regarding the controversy surrounding the risk: benefit ratio of LABAs. The findings from the recent Cates review (1) are not entirely reassuring, as analyses were

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restricted to trials assessing the efficacy and safety of formoterol and ICS in combination for prophylaxis. The rarity of asthma-related deaths in patients eligible for inclusion in randomized clinical trials in developed economies would require very large studies of long duration prompting the comment that such studies are 'both logistically and scientifically impossible' (15). If such studies are not practicable, what other approaches might help resolve the current controversy? Yet more systematic reviews and meta-analyses of existing and emerging data are unlikely to prove conclusive as the history of reviews and meta-analyses show. Case-control/observational studies, despite their recognized methodological flaws (16), and the lower level of evidence they contribute need to be considered, and clinicians, health care professionals and patients need to be encouraged to use their national reporting systems of pharmacovigilance.

There are issues that need to be addressed including patient adherence with fixed dose LABA/ICS combinations and assessment of long term safety in patients using formoterol and ICS combinations for both maintenance and relief of acute symptoms. This latter approach, which is licensed for adults over 18 years in the European Union carries the theoretical risk of overuse and, despite clear labelling warnings, could result in high cumulative doses of the accompanying ICS in addition to the LABA component.

Although current guidelines recommend LABAs in combination with ICS if low dose ICS fails to control persistent symptoms (7,8,9), remaining uncertainties and early unfavourable studies which included LABAs alone and/or in ICS combination (2, 3) have resulted in calls to withdraw the asthma indication from mono-component LABAs for patients of all ages (17). From current available evidence it seems that, at least in adults, and on the balance of probabilities, LABA/ICS combination therapy is safe in the short to medium term for uncomplicated chronic persistent asthma, albeit with remaining uncertainties about their safety in children and their use over many years in all age groups.

Declarations of Interest

None.

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