Is it time to move away from short-acting beta-agonists in asthma management?

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Frequent SABA use is associated with adverse asthma outcomes and evidence suggests replacing SABA with fast-acting LABA/ICS as reliever therapy reduces asthma exacerbation risk. We believe the time has come to move away from SABAs in asthma management. http://ow.ly/87UJ30nVGNc

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Asthma is a common chronic inflammatory disease of the airways, which continues to cause considerable morbidity and unnecessary mortality across the world [1, 2]. The recognition that even mild asthma is associated with airway inflammation led to the early and widespread use of inhaled corticosteroids (ICS) from the 1970s onwards [3, 4], transforming asthma care by significantly reducing severe exacerbations and asthma deaths. However, the persistently high levels of poor asthma control and ongoing asthma deaths in the 21st century are a growing concern [5, 6] and we believe the widespread use and overuse of short-acting beta-agonist (SABA) inhalers are a major part of the problem.

SABAs are highly effective bronchodilators which quickly relieve the symptoms associated with bronchoconstriction, the hallmark of asthma. Nevertheless, as highlighted in previous reviews [7], they have a chequered history in terms of safety. Epidemics of asthma deaths in the 1980s were linked to the use of high doses of potent non-selective SABAs [8] and it has been demonstrated that more frequent SABA use is associated with higher risk of future exacerbation [9], hospital admission [10] and increased levels of airway inflammation [11, 12]. Sears *et al.* [13] and Suissa *et al.* [14] demonstrated a link between increased SABA use and mortality from asthma leading to recommendations for regular anti-inflammatory medication and as-required SABA for all but the mildest cases of intermittent asthma.

Evidence suggests that SABAs continue to be responsible for high levels of poorly controlled asthma and even asthma deaths, not necessarily because of direct detrimental effects but because they are used preferentially by patients in place of regular ICS or long-acting beta-agonist (LABA)/ICS and in place of additional ICS when asthma control starts to deteriorate [15, 16]. Increased SABA use at the time of worsening asthma symptoms leads to symptom relief but does nothing to suppress the increased burden of airway inflammation, therefore masking the underlying problem. Factors associated with asthma death include: 1) lack of a recent asthma review (where underuse of ICS could be identified), 2) lack of seeking medical help (when oral corticosteroid treatment could have been initiated), 3) lack of written self-management plans (which may encourage regular ICS use and increased ICS treatment when asthma control is deteriorating), 4) overuse of SABAs and 5) underuse of ICS [5].

The 2016 revision of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines appear to have taken a step in the right direction by removing step 1 (SABA

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monotherapy) and proceeding straight to low dose ICS in suspected or confirmed asthma in their summary figure. However, the figure still recommends SABA monotherapy for those with "infrequent, short-lived wheeze" and guidance in the text recommends ICS for asthma patients using inhaled SABA three times a week or more, in patients with symptoms three times a week or more, or in patients waking one night a week or more [17]. Low dose ICS are highly effective even in very mild asthma [18], but unfortunately multiple surveys have shown that ICS adherence is poor, particularly in this group of patients, presumably due to their low symptom burden [15].

So is there an alternative? Papi *et al.* [19] demonstrated in 2007 that "as required" use of a combined beclomethasone/salbutamol inhaler is more effective than as required salbutamol and as effective as twice daily beclomethasone and SABA. More recently, the first of the two SYGMA studies confirmed that a quick-acting LABA/ICS combination inhaler provides superior symptom control and a reduction in exacerbation rate compared to SABA when used as required [20]. In the second SYGMA study [21] the benefits of as required LABA/ICS compared with regular low dose ICS were not as clear cut, with a similar risk of severe exacerbations observed for these two treatment strategies, but a statistically, although not clinically significant, difference in ACQ5 in favour of regular ICS treatment. However, being a regulatory, double-blind, placebo-controlled study adherence rates to maintenance treatment (~60%) were much higher than those generally observed in real life (~35%) [22] so the results of real-life studies comparing LABA/ICS *versus* low dose ICS [23, 24] are awaited with interest.

For patients with moderate persistent asthma treatment with regular ICS with or without a LABA is now the treatment of choice and is highly effective if used regularly. Unfortunately, once again, adherence with LABA/ICS combinations is poor despite many years of asthma education. A real-life study with the once daily combination inhaler Relvar and as required SABA suggested improved asthma control over standard asthma management with a similar rate of severe exacerbations, although the additional improvement in asthma control test score seen in the treatment group when compared to the standard care group did not exceed the minimal clinically important difference [25]. However, a major problem with any strategy that includes a SABA is how to deal with deteriorating asthma control. When experiencing worsening symptoms, patients once again rely on their SABA, which provides symptom relief but no anti-inflammatory effects and may aggravate the situation if taken regularly for symptoms with no background ICS due to poor adherence [13, 14]. Self-management plans are therefore recommended to encourage patients to increase their ICS dose to regain control and abort an exacerbation. Although we have recently shown that a four-fold increase in ICS is effective in this setting [26], it is less easily achieved in the majority of patients taking a LABA/ICS combination twice daily as the safety of increasing all types of LABA four-fold is unknown.

In patients taking regular ICS with or without LABA, replacing SABA with fast-acting LABA/ICS combinations makes it possible to avoid SABA overuse and ensures that each time a patient takes an inhaler for symptom relief they receive extra ICS rather than extra SABA. Many studies have shown the benefit of this approach, and a recent meta-analysis concluded that replacing SABA with fast-acting LABA/ICS reliever therapy results in a one-third reduction in risk of severe exacerbations and a 25% reduction in risk when compared with double the baseline maintenance ICS/LABA and SABA treatment [27]. It should be noted that most of the studies included in this meta-analysis recruited patients with at least one exacerbation in the previous year or poor asthma control, *i.e.* more "exacerbation prone" patients. In contrast, data from several "real-life" open-label studies comparing LABA/ICS reliever therapy and conventional best practice with no inclusion criteria related to prior exacerbations or control have shown little or no significant difference in exacerbation rate, although these have demonstrated that LABA/ICS reliever therapy results in the same or improved asthma control with a significantly lower daily ICS dose [28, 29]. The above does not seem to be reflected in the treatment algorithm in the most recent BTS/SIGN guidelines which recommends SABA reliever therapy in all patients and does not mention LABA/ICS as reliever therapy [17].

These problems are magnified many times in some low- and middle-income countries which have the highest worldwide asthma mortality rates [30]. In these countries, millions of patients with all severities of asthma are only able or willing to afford SABA treatment, even though ICS are available. An inhaler containing a SABA and ICS, provided it was no more expensive than SABA treatment, could therefore lead to a dramatic change in asthma mortality in the developing world.

There are, however, some practical concerns that need to be addressed and areas in which further evidence is required before a recommendation to end unopposed SABA use could easily be implemented. Firstly, the evidence supporting formoterol/ICS as a reliever therapy is much greater than for SABA/ICS, which is not available in most markets and is only approved for regular use in those that it is. Also, currently there are no data demonstrating the efficacy and safety of combining formoterol/ICS with maintenance treatment that does not contain formoterol. Therefore, at present all patients requiring combination

therapy would have to be treated with a formoterol containing combination licensed for both maintenance and relief, which would not be possible in countries such as the USA, where ICS/formoterol combinations are approved as maintenance therapy only. Secondly, the role of ICS/beta-agonist therapy in situations for which SABA monotherapy is currently used, such as acute severe asthma, needs to be evaluated.

In conclusion, we believe it is time to move asthma management away from SABAs for patients with confirmed asthma but further data is urgently required to make this a practical ambition. At best, SABAs mask ongoing airway inflammation by providing symptom relief and adversely affect adherence with anti-inflammatory treatment and, at worst, they potentiate inflammation when taken regularly for symptom control in patients who have stopped their ICS treatment [13, 14]. In our opinion, as required beta-agonists should always be combined with additional corticosteroid.

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