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Manifesto on the overuse of SABA in the management of asthma: new approaches and new strategies

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***Abstract*:** The risks of overusing short-acting β_2-agonists (SABA), including an increase in asthma-related deaths, are many and well known. The Global Initiative on Asthma (GINA) 2019 and 2020 updates recommend as-needed inhaled corticosteroid (ICS)/formoterol as the preferred rescue medication in mild asthma as monotherapy and also in moderate to severe asthma when the maintenance and reliever therapy (MART) strategy is used. Using SABA for symptom relief, however, was the standard of treatment for many years, and consequently this practice persists, particularly in patients not taking ICS regularly. Here, we examine the rationale for this shift from a long-standing recommendation for as-needed SABA treatment to the use of as-needed ICS/formoterol and consider clinical evidence on strategies for asthma treatment and patient management.

Keywords: asthma, control, GINA, ICS/formoterol, SABA

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Background

As-needed treatment with short-acting β_2-agonists (SABA) has traditionally been used for symptom relief across all severities of asthma, and as monotherapy in patients with mild asthma.[1,2] During the 1980s and 1990s, there was an accumulation of evidence regarding the risks associated with SABA overuse, including an increased risk of asthma-related death.[3] By the late 1990s, while most guidelines still advised SABA monotherapy as initial treatment, it was recommended only on an as-needed (symptomatic relief), rather than regular, basis in patients with mild asthma.[3] Daily inhaled corticosteroid (ICS) controller therapy was recommended for patients with more frequent symptoms.[3] Although this led to a reduction in asthma-related deaths, asthma control remained inadequate in a large proportion of patients, and the scientific community identified several paradoxes in this treatment approach.[2,4] These included, first, that although asthma is a disease of chronic airway inflammation, SABA bronchodilator monotherapy was recommended in patients with mild disease; that is, the symptoms rather than the underlying disease mechanism were treated, which reinforced to patients that this was an acceptable approach.[2] Prescribing SABA alone as initial therapy also delayed the prescribing of ICS therapy, and evidence suggests this may reduce the long-term effects of ICS.[4] In addition, there is evidence that using ICS plus fast-onset long-acting β-agonist (LABA) as reliever therapy reduces the overuse of β-agonist therapy, the number of days of overuse without medical review, and the number of days without self-administration of maintenance ICS.[5] Notably, SABA overuse was one of the factors associated with an increased risk of asthma mortality in the United Kingdom.[6]

The Global Initiative on Asthma (GINA) 2019 and 2020 updates acknowledged the risks associated with SABA overuse and the tendency of patients to underuse ICS and overuse SABA.[3,7,8] Therefore, GINA recommended a significant shift in the management of asthma, recommending as-needed ICS/formoterol as the preferred rescue medications in mild asthma as monotherapy

(steps 1 and 2) and also in moderate to severe asthma (steps 3–5) when the maintenance and reliever therapy (MART) strategy is used.[3,7,8]

Here, we examine the rationale for this shift from a long-standing recommendation for as-needed SABA treatment to the use of ICS/formoterol as-needed, and consider clinical evidence on strategies for patient and asthma management. We conducted an EMBASE literature search for publications between 2000 and 2019 that included β_2-agonists, the key word 'overuse' and asthma disease terms. Studies with fewer than 50 patients, case reports, conference abstracts, narrative reviews and non-English language articles were excluded. Results of hand searching and literature already known to the authors were also included.

We know

Despite the availability of effective controller treatments,[8] SABA overuse remains a problem;[9] definitions, and the extent, of overuse, however, vary between studies.[10–18] Compared with appropriate use, inappropriate use of SABA (excessive SABA plus underuse of ICS) has been shown to be associated with increased risk of exacerbations and mortality,[19] lower self-perception of overall and mental health and an increased risk of limitations in cognitive function and walking.[10] GINA guideline identifies the use of as-needed SABA more than twice a week as one of the indicators of poorly controlled asthma.[8]

The role of patient behaviour and self-management in SABA overuse and concomitant underuse of ICS has been recognised.[2,4,20] Patients learn from clinicians to use a reliever to alleviate their symptoms, making it difficult to transition to daily maintenance therapy with ICS, especially in the absence of symptoms.[21] In a study assessing predictors of future adverse asthma outcomes, higher reliever use was found to be a strong predictor of future extreme SABA overuse.[22]

It has been observed that the most common reason for an SABA refill request was that it was needed to treat current symptoms.[15]Patient perceptions play a role in their management of asthma.[10,18] In one study, SABA overuse was associated with patient-perceived severity of symptoms, although it has been shown that there is a poor correlation between lung function and patient-perceived symptoms.[18] Another study showed that among patients who discontinued ICS after a short time, the main reasons patients gave for discontinuation were 'not effective' and 'contains steroids'.[13]

The risk of severe asthma outcomes and increased mortality with SABA overuse are well known.[7,23–25] The 2019 GINA update states that regardless of asthma severity, receiving three or more canisters of SABA/year (which correspond to an average of $\geqslant$1.5 puffs/day) is associated with an increased risk of visiting the emergency department or being hospitalised. In the UK National Review of Asthma Deaths (published May 2014), for 165 patients who died from asthma, the median number of prescribed SABA inhalers in the year before death was 10 (range = 0–112).[6] In the year before they died, only three of the 165 patients received no SABA prescriptions; 92 (56%) received six or more, 65 (39%) received 12 or more and six patients (4%) had received 50 or more SABA inhalers; these data may be explained by the lack of an adequate regular maintenance treatment. In addition to an increase in asthma-related death, adverse outcomes associated with SABA overuse include increased airway hyperresponsiveness, reduced bronchoprotection and reduced bronchodilator response.[3]

Although ICS treats the underlying inflammation of the airways, they are frequently underused, and this underuse is associated with increased asthma burden.[20] The Swedish SABINA study showed that approximately 85% of asthma patients overusing SABA at baseline had continuous overuse during the observation period, whereas the proportion of patients not collecting any ICS had more than doubled by the end of observation.[19] In a 2008–2010 US medical expenditure study, of patients who had a recent exacerbation (n = 5005), 53.7% had never used long-term control medication, compared with 29.2% who were using daily preventive medication.[26] In addition, patients who overuse SABA may be more likely to underuse regular ICS.[20]

We intend

Here, we examine recent evidence supporting the change in approach to asthma treatment as advocated in the 2019 GINA update.[7]

Adults and adolescents should no longer receive SABA alone but should be prescribed a symptom-driven ICS in association with the

rapid-acting bronchodilator in mild asthma[27] or ICS-containing daily[7] treatment. Evidence for mild asthma treatment with as-needed low-dose ICS/formoterol was provided by real-world data from the randomised Novel START trial in patients with mild asthma who had been treated with SABA alone.[28] In this trial, as-needed budesonide/formoterol was significantly better at preventing asthma exacerbations than as-needed albuterol in adults with mild asthma.

The preferred controller therapy in GINA step 2 is now as-needed low-dose ICS/formoterol or daily low-dose ICS.[3,7] Key evidence for step 2 treatment with as-needed low-dose ICS/formoterol was provided by the results of two 52-week randomised controlled trials, designed in parallel, in patients with mild asthma requiring GINA step 2 treatment.[21,29] The real-world PRACTICAL study, a 52-week open-label randomised controlled trial, confirms the efficacy of low-dose ICS/formoterol in patients with mild-to-moderate asthma.[30] In this study ($N = 885$), the rate of severe exacerbations was significantly lower with as-needed budesonide/formoterol than with low-dose budesonide maintenance plus as-needed SABA (terbutaline), and symptom control was similar in the two treatment groups.

For adolescents and adults in steps 3–4, GINA 2020 recommends ICS/formoterol reliever therapy as the preferred option in patients prescribed maintenance ICS/formoterol, with an alternative option of regular ICS/LABA plus rescue SABA.[8] The efficacy and safety of the ICS/formoterol approach have been demonstrated in several clinical trials in GINA steps 3–5 patients, in which patients receiving ICS/formoterol as both MART had a reduced risk of exacerbations and similar asthma control compared with the standard of care at the time (usually ICS/LABA plus as-needed SABA).[31–38] These results have been confirmed by real-world studies of the 'Maintenance and Reliever' approach of using ICS/formoterol as regular and rescue therapy.[5,39,40] Furthermore, a meta-analysis showed the superiority, in terms of reducing the risk of asthma exacerbations, of using ICS/formoterol as MART *versus* using ICS (with or without LABA) as maintenance therapy plus SABA as reliever therapy, at both equal and higher dosages of ICS, in patients with persistent asthma.[41]

For step 5 patients, the new GINA 2019 difficult-to-treat and severe asthma guide recommends optimising treatment, including switching to ICS/formoterol MART where possible, and to consider adding a long-acting muscarinic antagonist or, when indicated, biological treatments.[42]

Through using ICS/formoterol reliever therapy at every asthma step, the aim is to provide a simple, patient-centric approach that can be adapted to asthma action plans to achieve better control of their pathology.[43]

We know that individual patients' needs and specific conditions have to be considered when choosing the right treatment approach. Physicians should take all steps to minimise any potential side effects of the abovementioned strategies by collecting a thorough clinical history and undertaking a detailed patient evaluation.

We advocate for

1. Widespread education on the revised GINA guidelines for all health professionals involved in asthma management, including primary care physicians, nurses and pharmacists.
2. Treatment of asthma across all severities to address the underlying inflammation, as recommended by the latest GINA guidelines.
3. Taking steps to prevent overuse of SABA, and therefore prevent the related risks, including
    (a) Appropriate patient education, especially to stop self-medication with SABA without proper medical advice;
    (b) Transitioning patients from as-needed SABA monotherapy to as-needed ICS/formoterol to reduce the risk of exacerbations, mortality and hospitalization; and
    (c) Initiating newly diagnosed patients on GINA-recommended Step 1 therapy, not on SABA monotherapy.
4. A call to action for all stakeholders:
    (a) Institutions and payers need to be aware of the risk of SABA overuse and to monitor the effective switch of approach through all available channels;
    (b) Health care providers need to encourage all colleagues to learn the GINA

recommendations and apply them in clinical practice;

(c) Patients' associations need to inform patients of all risks linked to SABA overuse and to encourage a change of behaviour; and

(d) Scientific societies need to be a reliable partner of the abovementioned stakeholders, being the pivot of this change based on a patient-centric philosophy.

5. And finally, further research in real-world clinical studies where patients are treated according to the evidence-based recommendations.

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