



It is time to end our love affair with short-acting β_2 -agonists in asthma

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In this issue of *ERJOR*, Noorduyn *et al.* add data to the growing literature showing that SABA overuse in asthma is both common and associated with severe exacerbations. It is time to take note and act to tackle this global issue. <https://bit.ly/3BfwhfS>

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Asthma is the most prevalent chronic respiratory disease worldwide and despite advances in our understanding of asthma and its treatment, it continues to be associated with significant, and largely preventable, morbidity and mortality [1, 2].

The world's love affair with short-acting β_2 -agonists (SABA) began in the 1960s when Sir David Jack discovered salbutamol, the first selective β_2 -adrenoceptor agonist for the treatment of bronchospasm, heralding a paradigm change in asthma management [3, 4]. Salbutamol was quickly marketed and is the most widely prescribed asthma treatment to this day. Around the same time, the inhaled corticosteroid (ICS) beclomethasone dipropionate was also developed [5] but it took longer to prove efficacy and consequently was almost discarded as “useless” [6]. Now, the inflammatory nature of asthma is well understood and we recognise that the advent of ICS was associated with significant reductions in asthma mortality [7]. But while biologic agents have transformed the management of severe asthma; overall, improvements in asthma outcomes have stalled in recent years and our relationship with SABA may be to blame.

In this issue of *ERJ Open Research*, Noorduyn *et al.* [8] report the findings of the latest in the series of the SABA in Asthma (SABINA) studies [9–15], SABINA Canada (table 1). In this study, the authors use administrative claims data from two Canadian cohorts with a combined population of 115 478 patients to assess the prevalence of SABA overuse and its association with severe asthma exacerbations. For the purpose of their analysis, a severe exacerbation is defined as dispensation of a course of oral corticosteroids of ≤ 10 days duration or hospitalisation or emergency department attendance with asthma as the primary complaint. Consistent with other studies in the SABINA programme [12, 13, 16], Noorduyn *et al.* [8] identified a high prevalence of SABA overuse in both Canadian cohorts (28% in the Alberta cohort and 39% in the Nova Scotia cohort), and an association between SABA overuse and severe exacerbations, with the highest exacerbation rate observed in those with the highest SABA use.

These findings should not come as a surprise. While SABA provide effective rapid relief of bronchoconstriction and its associated symptoms, a trait that leads patients to develop a strong emotional attachment to them [17], SABA have no inherent anti-inflammatory properties [18] and therefore fail to address the core underlying problem in asthma. A wealth of data has accrued over recent years demonstrating that SABA overuse in asthma is associated with adverse outcomes such as exacerbations [9, 10, 12, 14], hospital admissions [19] and death [1, 14]. However, there is a lack of understanding and complacency about the implications of SABA overuse among patients and clinicians, contributing to acceptance of poor asthma control [17, 20]. The UK Royal College of Physicians National Review of Asthma Deaths (2014) identified excessive prescribing of reliever medication and under prescribing of



TABLE 1 Summary of the association between short-acting β_2 -agonist (SABA) overuse (three or more SABA canisters per year compared with fewer than three canisters per year) and exacerbations in a selection of SABA in Asthma (SABINA) programme studies

| First author [ref.] | Country | Population size (n) | Prevalence of SABA overuse (% patients) | Association between SABA overuse and asthma exacerbations |
|---------------------|--------------|---------------------|---|--|
| NOORDUYN [8] | Canada | 115 478 | | SABA overuse was associated with an increased mean \pm sd exacerbation rate |
| | Alberta | 107 444 | 28.0 | 0.31 \pm 0.86 versus 0.17 \pm 0.62 |
| | Nova Scotia | 8034 | 39.4 | 0.46 \pm 1.11 versus 0.3 \pm 1.36 |
| NWARU [14] | Sweden | 365 324 | 30 | Positive association observed between number of SABA cannisters issued and exacerbation risk (hazard ratio (95% CI)) \leq 2 cannisters: 1.00 3–5 cannisters: 1.26 (1.24–1.28) 6–10 cannisters: 1.44 (1.41–1.46) \geq 11 cannisters: 1.77 (1.72–1.83) |
| BLOOM [12] | UK | 574 913 | 38 | SABA overuse was associated with increased risk of exacerbation across asthma severities (adjusted hazard ratio (95% CI)) BTS steps 1 and 2: 1.2 (1.16–1.24) BTS steps 3–5: 1.24 (1.20–1.28) |
| BATEMAN [10] | Multicountry | 8351 | 38 | SABA overuse was associated with increased exacerbation incidence (adjusted incidence rate ratio (95% CI)) 3–5 cannisters: 1.40 (1.24–1.58) 6–9 cannisters: 1.52 (1.33–1.74) 10–12 cannisters: 1.78 (1.57–2.02) \geq 13 cannisters: 1.92 (1.61–2.29) |

BTS: British Thoracic Society.

preventer medication as a factor in asthma deaths [1]. Despite this, community prescribing data from England (2017) reveal SABA to be the most commonly prescribed class of inhaled treatment, with 21.9 million SABA inhalers prescribed per year. This compares with 6.7 million ICS and 14.1 million ICS/LABA combination inhalers [21].

The concept of combining ICS with fast-acting bronchodilators in order to improve asthma control is not new [22]. But it is only recently that recognition of the risk associated with treating asthma with SABA alone and the association between SABA overuse and exacerbations has led the Global Initiative for Asthma (GINA) [23] to change their guidance. In mild asthma (steps 1–2), GINA cite combined ICS/formoterol as the preferred reliever, escalating to ICS/formoterol maintenance and reliever therapy (MART) for those requiring regular preventer therapy (step 3).

In mild asthma, combined budesonide/formoterol used as required is associated with reduced risk of exacerbation, hospitalisation and systemic corticosteroid exposure when compared with use of a fast-acting bronchodilator (SABA or formoterol) alone [24]. Likewise, use of either budesonide or beclomethasone in combination with formoterol as MART, has also consistently been shown to improve asthma control and reduce exacerbation risk and systemic corticosteroid exposure compared with fixed-dose ICS/LABA combination preventer therapy with SABA reliever [25, 26].

When faced with such data about the negative association between SABA overuse and patient outcomes, and the existence of an alternative approach to asthma management that could render SABA obsolete for many; we must ask ourselves why SABA remains the most prescribed asthma treatment? Indeed, this question becomes even more pertinent when we consider the global challenge faced by climate change. Because in addition to the negative implications that SABA overuse has for asthma patients, there is increasing recognition that SABA is a major contributor to the carbon footprint of inhaled therapies. This is particularly true in countries like the UK, where 94% of the 21.9 million SABA inhalers prescribed each year are greenhouse gas-containing pressurised metered-dose inhalers [21], the consequence being that SABA account for 70% of the UK's inhaler-related carbon footprint, totalling 863 kt carbon dioxide equivalent annually [27]. Such recognition is clearly cause for concern as climate change represents a significant risk to global health and mitigating this risk is a World Health Organization priority [28].

But, with recognition comes opportunity, providing another reason why tackling SABA overuse should be a priority for policymakers as well as clinicians and their patients.

Stopping SABA overuse is not easy, and the reasons why clinicians continue to prescribe and patients continue to overuse SABA are multiple and complex. Achieving asthma control, and thereby rendering patients free of symptoms and not reliant on reliever inhalers, would solve this problem. But in practice, important elements of asthma care such as adherence review, provision of written asthma action plans and structured symptom assessment are often not performed [29]. Patients' lack of understanding about asthma, failure to recognise the importance of ICS and normalisation of their symptoms also make this more difficult to achieve [17, 29]. While most physicians recognise that a major barrier to medication adherence is patients only taking their treatment "when needed", awareness of MART as a therapeutic option is variable and some primary care clinicians have never prescribed it [29].

There are therefore many barriers that need to be overcome if we are to tackle SABA overuse. However, through understanding the barriers, interventions can be developed to overcome them. We can start by equipping patients and clinicians with the required knowledge and resources to identify and address SABA overuse, ensuring patients can access high-quality asthma care through structured reviews and enabling access to ICS/formoterol reliever or MART for appropriate patients [30, 31].

Data can be a powerful tool, both in terms of identifying the problem, as Noorduyn *et al.* [8] have in their study, but also to provide feedback to patients, clinicians, funders and policy makers when practice change takes place. The time has come to act on the data and resurrect the improvements in global asthma outcomes that began with the discovery of ICS.

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