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REVIEW ARTICLE

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Landscape of short-acting beta-agonists (SABA) overuse in Europe

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Abstract

This review article provides an overview of short-acting beta-agonist (SABA) use and prescribing trends in Europe, summarizing updated data on the results from the industry-funded SABINA program (SABA use IN asthma) and other studies on this matter. SABA use continues to increase worldwide. Overuse has been defined as ≥3 canisters/year. Almost a third of European patients with asthma, at all severity levels, overuse SABA. Guidelines recommend close monitoring of patients who overuse SABA and avoiding over-reliance on SABA monotherapy. SABA overuse is associated with increased risk of asthma exacerbations and mortality, increased use of health services and negative physical and mental health outcomes. Reliance on SABA monotherapy can be unsafe and therefore it is necessary to change asthma treatment approaches and policies. Changes in physician and patient behaviours towards SABA use are required to ensure that patients with asthma are not over-reliant on SABA monotherapy. Notwithstanding, the limitations of the studies on the use of SABA should be considered, taking into account that the prescription/purchase of medication canisters does not always represent the actual use of the medication and that associations between SABA overuse and poor asthma outcomes may not be directly causal. National health systems and asthma guidelines must align asthma management with global recommendations and adjust them to local needs.

KEYWORDS
asthma, Europe, overuse, prescription, public health, short-acting β2-agonist

1 | INTRODUCTION

Asthma is a major noncommunicable disease (NCD), affecting both children and adults. It is included in the WHO Global Action Plan for the Prevention and Control of NCDs and the United Nations 2030 Agenda for Sustainable Development. There are approximately 339 million people in the world with asthma[1] with a prevalence of 8% in Europe.[2]

Its fluctuating course has a worldwide impact, with 176 million asthma exacerbations occurring per year. Based on the pathophysiology, inflammation is the main underlying mechanism of the disease, both in symptoms and exacerbations, which points to the relevance of inhaled corticosteroids (ICS) to the treatment of asthma.[3,4] The use of short-acting β2-agonists (SABA) allows rapid improvement in symptoms during an exacerbation by producing bronchodilation, but does not treat the underlying inflammatory process. The increase in SABA prescriptions has not coincided with a decrease in the number of hospitalizations or deaths due to asthma.[5–7]

In the mid-20th century, SABA were introduced as inhaled therapy for asthma, initially with nonselective beta-adrenergic agonists such as isoprenaline and metaproterenol. These carried risks of cardiac adverse effects, as a result of their nonselective effect on the beta-1 receptor, which were most marked for fenoterol, perhaps due to its longer duration of action and therefore cumulative beta-1 effects. In monotherapy, the non-selective beta-adrenergic agonists, particularly fenoterol, were associated with increased risk of fatal

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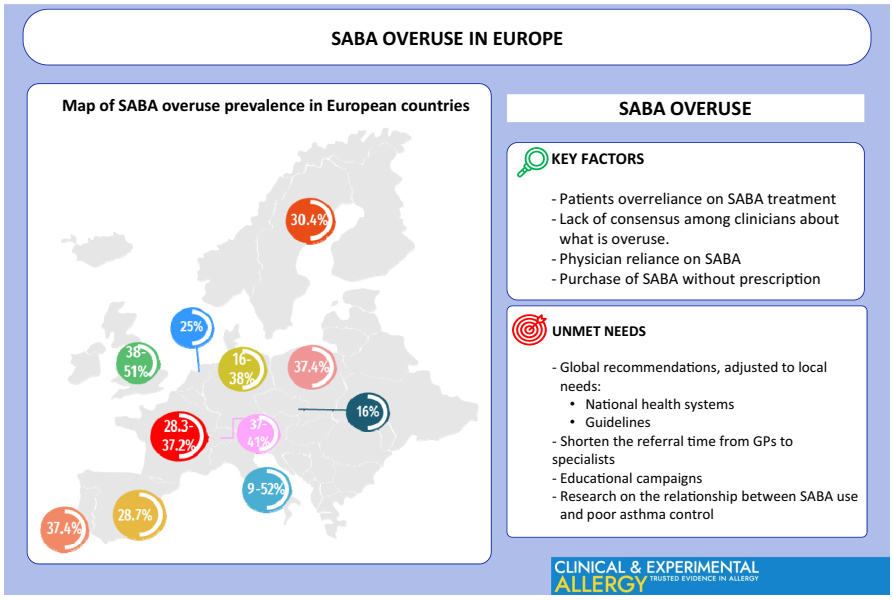

GRAPHICAL ABSTRACT

The use of SABA remains very common in Europe across all severities of asthma. SABA usage should be changed through educational campaigns targeted at clinicians and patients. It is crucial that national health systems align asthma management with global recommendations, while adapting to local needs for better and more effective implementation. More research is needed to find out how excessive use of SABA contributes to poor asthma control. GPs: general practitioners.

asthma.[8–10] The highly selective SABAs, including terbutaline and salbutamol, were subsequently introduced and have a better safety profile.[11] However, a relationship between increased use of SABA before an asthma attack continued to be described. Although this association is not surprising, it suggests that patients with increased SABA use may benefit from treatment re-evaluation. The question has also been raised as to whether excessive use of SABA might be a direct contributing factor to asthma pathology, in addition to being a marker of asthma symptoms.[10] In the early 1990s, highly selective long-acting beta2-adrenergic agents (LABA), such as formoterol and salmeterol, entered the market and were shown to improve asthma outcomes when used in combination with ICS.[11] Several studies have pointed out the relevance of including ICS in asthma therapy, either as needed or as maintenance regimen. A single maintenance and reliever therapy (SMART) with a fast-acting LABA (formoterol) and ICS has been recommended in patients in steps 3 and 4 of asthma management who are well trained in the identification of asthma symptoms, following a personalized asthma plan.[12] This strategy has better asthma outcomes than ICS alone or ICS + LABA in a fixed combination, particularly by reducing the risk of severe asthma exacerbations, and it also reduces the potential for overreliance on SABAs.[12] However, the SMART strategy also has some pitfalls and limitations.[13]

Despite the enhancement of the selective action of SABA, high-dose treatment is still associated with several adverse systemic effects.[11] Beta-2 adrenoreceptor activation increases glycolysis through adrenergic stimulation, inducing depletion of adenosine triphosphate levels and the subsequent inhibition of phosphofructokinase (a limiting enzyme in glycolysis).[14] This results in lactic acidosis that resolves after discontinuation of SABA.[15] Supraventricular tachycardia, especially in children, and electrolytic disturbances such as decreased serum potassium, magnesium, and phosphate are also adverse effects associated with SABA overuse, which can worsen the clinical picture of the exacerbations.[16] Recently, overuse of SABA has been associated with an increased risk of sepsis and septic shock in patients with asthma, in a study supported by a combination LABA/ICS inhaler manufacturer.[17]

The Global Initiative for Asthma (GINA) has not recommend as-needed SABA use in adults as monotherapy since 2019.[18] Increased SABA use without concomitant ICS is associated with an increased risk of exacerbations.[19–21] In addition, regular SABA use is associated with increased peak flow variability and non-specific bronchial hyper-reactivity.[6–8] Thus, frequency of SABA use is included in symptom control assessment.[5] The drawbacks and potential benefits of SABA use are shown in Figure 1.[11] The use of at least

Key messages

- High SABA use in Europe across all asthma severities is still a reality.
- National healthcare systems should align asthma management with global recommendations, adjusted to the local needs.
- More research is needed to understand associations between excessive SABA use and poor asthma control.

three SABA canisters per year is defined as excessive use by GINA 2019 and is associated with a lack of asthma control and increased asthma-related mortality[3,18,20,22–26].

GINA 2021 includes two paths to treat asthmatic adult and adolescent patients, which mainly differ in the relief medication (Figure 2)[27]: the preferred option has as-needed low-dose ICS-formoterol as reliever medication (Track 1), and the alternative approach just includes as-needed SABA as symptom relief treatment option (Track 2). When the first recommended track is not possible or the patient presents with appropriate disease control, including good adherence to ICS-containing controller medication, the second option can be applied.[28] In step 1, ICS is always included as a treatment when SABA is used, and in subsequent treatment steps, ICS is included in regular maintenance medication, using SABA as a reliever.[28]

Uncontrolled asthma impairs patients' quality of life and increases health care costs. In addition, excessive SABA users had 3 times and high SABA users had 2.2 times higher asthma-related healthcare costs than low SABA users.[29] However, SABA usage continues to increase across the globe with almost one-third of European asthmatic patients, across all severities, presenting SABA overuse.[23,30]

Based on the international guidelines, appropriate SABA use was defined as <3 puffs/week, equivalent to less than 150 puffs per year or ≤2 prescribed canisters per year, assuming that a canister contains 150 inhalations.[22]

Several studies have analysed SABA prescription and use in Europe and worldwide.[31–33] SABA use IN Asthma (SABINA) programme, the largest real-world study on SABA usage, sponsored by a commercial LABA/ICS combination inhaler manufacturer, integrates data from different countries generating a global overview but also country-specific data about SABA prescription trends and asthma-related clinical outcomes.[22] This programme has been developed in three phases including in SABINA I (a retrospective, observational database study with expanded objectives) data from the United Kingdom; in SABINA II (a retrospective observational database study) data from 6 European countries, Israel and Canada; and in SABINA III (a prospectively collected multi-country cross-sectional study) data from 25 countries of Africa, Asia, Oceania and South America. The last phase of the programme, SABINA+, is in progress, including data from countries across the globe, such as Poland, Switzerland or Romania, in Europe.[31] SABINA includes studies with disparities in the methodology and the intrinsic differences among countries such as the possibility of purchasing SABA canisters without a medical prescription or the number of doses in each canister. Furthermore, limitations such as translating SABA prescription/possession into a reflection of medication use should be kept in mind when reading the conclusions of these studies.

This review aims to provide an overview of SABA use and prescription trends in Europe (Table 1), summarizing updated data on the SABINA programme as well as the results of other studies.

2 | SITUATION IN EUROPE: LANDSCAPE OF SABA USE

Most of the data related to SABA use and prescription trends in European countries have been extracted from the industry-funded SABINA programme.[22,31] Recently, these data have been updated, including new countries in the analysis. Together with other studies out of the SABINA programme, we can gain new insights on the landscape of SABA use in Europe.

2.1 | France

A prospective study developed in France and United Kingdom by GPs analysed the relation between patterns therapy use and asthma exacerbations between 2013 and 2017.[34] The results were extracted from collecting prescribing data, telephone interviews, and text messages to assess medication use. Most of the population included in this cohort was from France (n = 747; 82.3%) with a 24-month follow-up period. Results showed that inhaled corticosteroids and fixed-dose combinations were often used intermittently (30%–35% of patients declared an irregular use), whereas SABA and LABA were used regularly and, as expected, were associated with increased exacerbations. Compared with non-users, the risk of exacerbation increased moderately under regular use of single LABA,

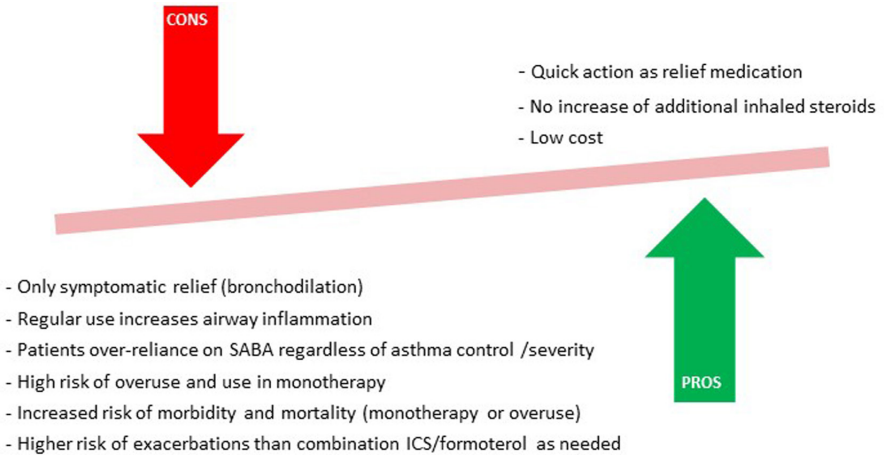

FIGURE 1 Main drawbacks (cons) and advantages (pros) associated with the use of SABA (adapted from[10]).

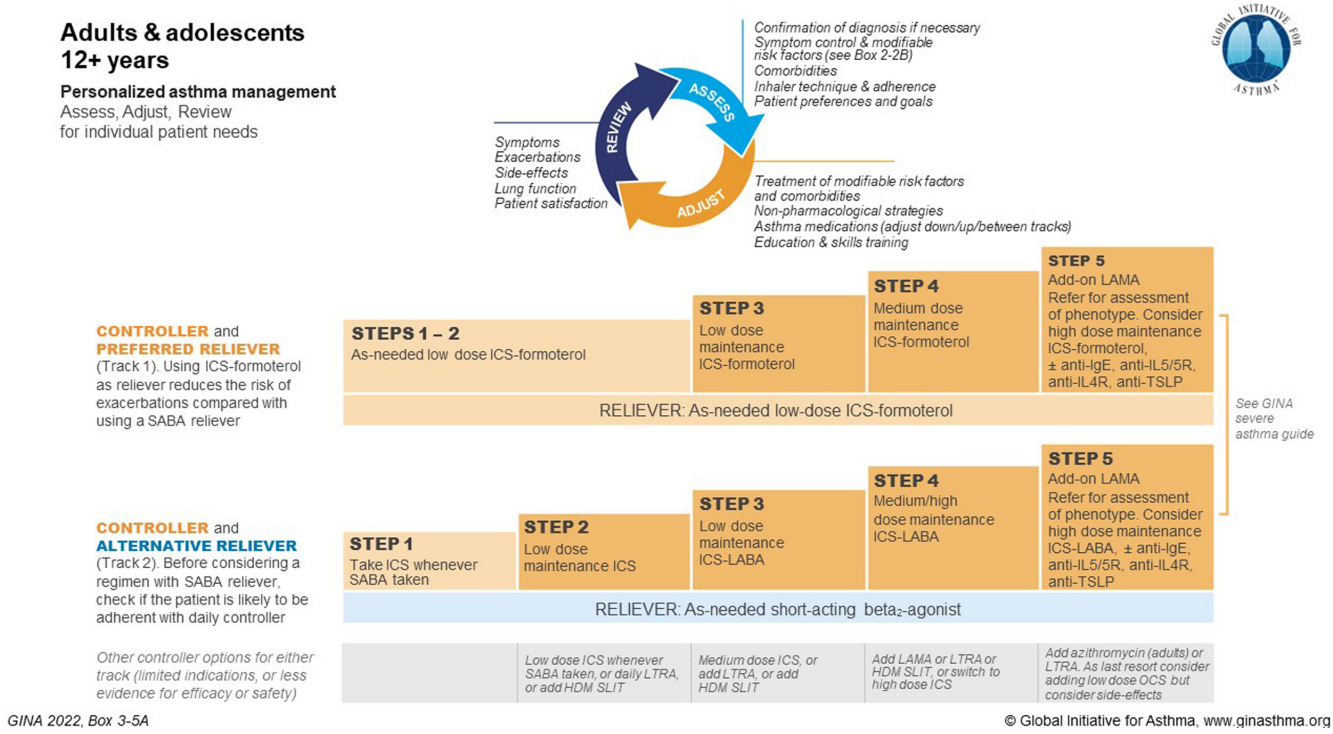

FIGURE 2 Asthma treatment for adults and adolescents from the Global Initiative for Asthma (GINA) 2022 illustrating the preferred and the alternative management strategy. When the first recommended track 1 is not possible or the patient is stable and adherent to ICS-containing controller medication, the alternative option (track 2) can be considered.[27]

which should never be used without concomitant ICS, whereas it doubled in regular SABA users (odds ratio 0.98 and 0.90 vs. 1.29 and 2.09), likely relating to poor overall asthma control. Related to the French population, the higher risk was observed in female patients, in those from 6 to 12 years old and in patients with severe asthma.[34]

Related to the SABA overuse (≥3 SABA canisters/year), the cross-sectional ASTHMAPOP survey develop in 2018, shown a prevalence of 28.3% with almost the half part of the population included in GINA steps treatment 1–2. This treatment habit was associated with a doubled risk of exacerbation, as well as the rate of hospitalizations and emergency visits due to asthma. SABA overuse has been identified as a sign of poor asthma control, and underuse of ICS is also associated with poor asthma control.[35]

Recently, data from the SABINA II programme that analysed 673 French patients revealed a 37.2% prevalence of SABA overuse.[31] 59.6% of the patients were in 1–2 GINA steps treatment and 40.4% in steps 3–5. Across all GINA treatment steps, use of more than 3 SABA canisters/year compared with lower use, was associated with increased risk of asthma exacerbation (OR 2.09) with a higher impact at steps 1–2 than in the 3–5 (OR 2.26 vs. 1.82).[31]

2.2 | Germany

In Germany, a retrospective study using anonymized electronic healthcare data from the Disease Analyser database (IQVIA) evaluated the SABA use in 15,640 patients aged ≥12 years with asthma. Asthma-treatment prescriptions were also compared between GPs and pneumologists; patients included had at least one SABA canister prescription the previous year and two visits with their physician during the study period.[36] Annually, 36% of all patients (GINA steps 1–5) in GPs treatment, and 38% in pneumologist practices received ≥3 SABA inhalers (in Germany and Spain, each canister contains 200 doses). Another observation was that the risk of SABA overuse increased with GINA steps: 34% and 85% higher in GINA steps 4 and 5, respectively, vs. GINA step 3. Also, it was 14% higher in patients treated by a GPs vs. a pneumologist. In this population, males presented with a 40% higher overuse compared with females and in patients on ICS/LABA maintenance therapy.[36] Previous published data, including 29,636 patients treated by GP's and followed-up for at least 12 months before and after study entry (SABINA program), had reported a 16% of SABA overuse in Germany.[37]

These two studies differed not only in the inclusion of data only derived from GPs prescriptions or including also patients treated by pneumologist but also in the required observation time.

2.3 | Hungary

A cross-sectional, non-interventional real-life study was conducted among 12,743 asthmatic patients treated by respiratory specialists in Hungary during 2015–2016.[38] The main aim of the study was to describe the frequency of specific risk factors for poor asthma control. The risk factors with the strongest

TABLE 1 Characteristics of SABINA programme and other studies about SABA use in European countries

Country	Reference	Study design	Data source	*n*	Age range	Physicians involved	SABA overuse	Impact of SABA overuse
FRANCE AND UK	[34]	Prospective	Prescribing data, telephone interviews, and text messages to assess medication use	908	≥6 years	GPs	*Daily/regular SABA use: 22.6%	Increase of exacerbation rates (OR 2.09) and poorer disease control
FRANCE	SABINA II[31]	Cross-sectional	Patients' survey	673	≥18 years		37.2% (more than 3 canisters/y)	Increase of exacerbation rates (OR 2.09)
	[35]	Cross-sectional	Patients' survey	15,587	≥18 years		28.3% (more than 3 canisters/y)	Poorer disease control: double exacerbation rate, more hospitalizations and emergency visits.
GERMANY	SABINA II[36]	Retrospective	Analyzer prescription database	15,640	≥12 years	GPs and pneumologists	36% and 38%, respectively (More than 3 canisters/y)	
	SABINA	Retrospective	Analyzer prescription database	29,636	≥12 years	GPs	16% (more than 3 canisters/y)	
HUNGARY	[38]	Cross-sectional	Doctor and patient questionnaire	12,743	≥18 years	Specialists respiratory	16.05% (more than 1 canister/month)	Increase of uncontrolled disease (OR 4.46)
ITALY	SABINA II[37]	Cross-sectional	Electronic medical records and secondary care physicians	22,201	≥12 years	GPs	9% (more than 3 canisters/y)	
	[39]	Cross-sectional	Pop-up survey on Pharmacies / Specialists' prescription routines	1,136/4,609	≥12 years	Allergists and pneumologists	52% acquisitions/32% prescribed (more than 2 canisters/year)	Prescribed by GPs, showed a 30% higher LH to present an exacerbation
POLAND	SABINA+[31]	Cross-sectional	Prescription pharmacy records	46,628	≥12 years		37.4% (purchase of more than 3 canisters/y)	Increase of exacerbations (IRR 2.15)
	[40]	Cross-sectional	Prescription records	91,673	≥18 years	GPs, allergists and pneumologists	29% (patients on ICS) and 37% (on ICS/LABA) purchase of more than 3 canisters/y	
PORTUGAL	SABINA+[41]	Cross-sectional	Electronic prescription and dispensing database	388	≥18 years		65% (purchase more than 3 canisters/y)	Poorer disease control (OR 2.6)
	[42]	Retrospective	Electronic prescription and dispensing database	61,835	≥15 years		SABA overuse (1 canister/month) of 24/100,000	SABA over-use was not associated with primary adherence

(Continues)

TABLE 1 (Continued)

Country	Reference	Study design	Data source	*n*	Age range	Physicians involved	SABA overuse	Impact of SABA overuse
SPAIN	SABINA II[31]	Retrospective	Electronic medical records	39,555	≥12 years		28.7% prescription (more than 3 canisters/y)	Increased of severe exacerbations (regression coefficient 1.523)
SWEDEN	SABINA II[23,37]	Retrospective	National registries drug collection	365,324	12–45 years		30.4% overuse (≥3 canister/y)	Incrementally increased mortality risk
SWITZERLAND	[47]	Retrospective	Prescription data from pharmacies	8145	>4 years		37%–41% prescription (more than 3 canisters/y)	
THE NETHERLANDS	SABINA II[31]	Retrospective	Electronic medical records	9,474	All residents	GPs	26% (more than 3 canisters/y)	Increase of severe exacerbation (IRR 1.40)
	[50]	Cross-sectional (Post hoc analysis)	Patients' survey	736	18–50 years		60% had used SABA more than 3 times the previous week (higher users)	More use of antibiotics, oral steroids and visits to the emergency room, including overnight hospitalizations
UK	SABINA I[30]	Retrospective	Electronic medical records	574,913	≥12 years	GPs	38% prescribed ≥3 SABA canisters/year	Doubled exacerbation rate
	SABINA I[31]	Retrospective	Electronic medical records	187,675	≥12 years	GPs	51% prescribed ≥3 SABA canisters/year	Increase of exacerbations (IRR 1.38)

relationship with uncontrolled disease (according to GINA) were incorrect inhaler technique (odds ratio, OR 4.86), previous severe exacerbation (OR 4.79), high SABA use (OR 4.46) and persistent low forced expiratory volume in 1 sec (FEV_1) (OR 3.14). Also, low adherence to ICS (OR 2.51) was presented in 55.1% of patients with poor control, and 64.55% with SABA overuse were uncontrolled at the time of the survey.[38] Overall, 16.05% of the patients included presented excessive SABA use, defined as more than 1 canister/month.

2.4 | Italy

Data extracted from electronic medical records from primary care physicians in Italy (SABINA II) during 2015–2018, showed a lower rate of SABA prescription compared with that observed in other European countries.[37] Of the 22,201 patients enrolled including all asthma severities, a 9% prevalence of SABA over prescriptions was found, with an 8% among patients classified as moderate–severe.[37]

Due to the difference regarding SABA use/prescription trends with the rest of Europe, and taking into account that SABA can be purchase directly in pharmacies without prescription, a recent analysis including SABA canisters acquired without prescription (from a pop-up survey on Pharmacies) and those prescribed by specialists (cross-sectional study) was performed.[39] In the first case ($n = 1136$), they found that the mean number of canisters prescribed per year was 4, and more than 52% of patients purchased more than 2 canisters per year. It is worth mentioning that 15% of patients bought SABA without prescription, and 36% were prescribed by specialists. Data from the cross-sectional study which analysed specialists' prescription routines (allergists and pneumologists) showed that 15% of patients enrolled (n = 4609) had a SABA prescription, and the majority were classified as Step 1 (28%). When patients with no SABA prescription were excluded from the analysis, the prevalence of more than 2 canisters per year was 32%, with a mean number of 3 canister/prescriptions/year and 9.8% with more than 6 canisters prescribed per year. Those patients with more than 2 canisters of SABA per year prescribed by GPs showed a 30% higher likelihood of presenting asthma exacerbations.[39]

2.5 | Poland

As part of the SABINA+ programme, the SABA use in Poland was analysed through drug purchase data extracted from the nationwide pharmacy records.[31] It included 46,628 patients with a prevalence of 37.4% of asthmatics using 3 or more SABA canisters/year, with a mean use of 3.5 (SD 5.2). Most of the patients included were on 3–5 GINA steps, with a strong association between SABA overuse and exacerbations across all treatment steps (Incident Rate Ratio [IRR] 2.15), which was higher in steps 1–2 (IRR 2.41) than in steps 3–5 (IRR 2.11).[31]

Recent data including prescription records from 5600 pharmacies has shown that out of 91,673 adults receiving asthma medications, 5.7% were only on SABA treatment. All the patients on ICS treatment and 40% of ICS/LABA users, had concomitant SABA prescriptions. The prevalence of SABA overuse was 29% (1730) of patients in the ICS group, and 37% (10,749) in the ICS/LABA group. Overall, 5.6% received 12 or more SABA canisters per year. When SABA prescriptions were analysed by the prescription source, GPs prescribed more than half part of SABA canisters in all groups of patients, followed by pulmonologists and allergists.[40]

2.6 | Portugal

As part of the SABINA+ programme, a cross-sectional study conducted in Portuguese pharmacies in 2018 analysed SABA purchases in patients who self-reported a diagnosis of asthma. In Portugal, the estimated prevalence of asthma is 10.2%. The study revealed that at least 65% of patients presented SABA overuse: 21.9% had bought 3 canisters in the previous 3 months and 17.5% more than that.[41] Across all GINA treatment steps, significant differences were found in the demographic characteristics and rate of exacerbations (visits to the emergency room, hospitalizations, oral corticosteroid treatment). Two variables were found to have a significant impact on asthma control: the use of SABA for more than 8 days during a period of 4 weeks, which was reported by the 50.2% of the patients, and one or more emergency room visits that included treatment with oral corticosteroids for at least 3 days, in the last year, which was reported by 39.7% of the patients.

Previously, a nationwide electronic prescribing and dispensing database analysis conducted in 2016 ($n = 61{,}835$) revealed that 17% of patients with SABA overuse had not been prescribed any controller medication, with a SABA overuse (1 canister/month) of 24/100,000.[42]

2.7 | Spain

The data extracted from the SABINA II study ($n = 39{,}555$), which includes electronic medical records of Spanish primary care specialists in 2017, showed a prevalence of SABA overuse of 28.7%. 19% of the patients used from 3 to 6 canisters per year and 4.1% used 13 or more canisters/year. 73% of the included patients had moderate–severe asthma. Overuse distributed by GINA treatment steps[1–5] was 25.4%, 17.3%, 26.4%, 33.4% and 48.7%, respectively.[31,43] It is relevant that 13.4% of patients presented low use of ICS, defined as 4 or fewer canisters per year.[43]

Regarding the treatment habits of the patients and their impact on asthma control, data extracted from a cross-sectional study carried out in 2016–2017 ($n = 406$), showed that 23.9% of the asthmatic patients included had used their reliever medication in the previous week, with a frequency of 7.2 days/month, and a mean of

2.8 inhalation/week.[44] This reliever medication included not only SABA (salbutamol or terbutaline) but also ipratropium bromide and ICS/LABA. Comparing patients with low (≤2 times/week) and high reliever use, the latter had poorer asthma control ($p < .001$), more night awakenings, hospital admissions in the previous year, unscheduled medical visits and higher use of ICS. High SABA use was also associated with older age and moderate asthma severity. There was moderate agreement between patients' perception of control and the ACQ score for the entire cohort.[36]

One of the points of greatest concern in Spain is that SABA can be purchased directly by the patient at the pharmacy without a prescription. This factor implies that SABA is the 8th best-selling drug in the country in 2021, and 40% is bought without a prescription.[37]

The latest version of GEMA, the Spanish Asthma Management Guidelines, has been more restricted when defining asthma control, with a limit of SABA use of 2 times a month, and defining as a risk factor for exacerbation the use of ≥3 canisters/year (≥2 puffs/day).[45]

2.8 | Sweden

As part of the SABINA programme, an observational study investigated the association between SABA use and asthma exacerbation risk and mortality in a nationwide Swedish asthma population.[23] In Sweden, each canister of salbutamol contains 150 doses and can be purchase without a medical prescription.[37] The estimated asthma prevalence is 6.1%.[46]

Of 365,324 patients (mean age 27.6 years, 55% women), SABA overuse was identified in 30.4% of patients, regardless of ICS use during the baseline 12-month period, and was distributed in 21% who collected 3–5 canisters, 7.4%, 6–10 canisters, and 2% who collected more than 11 canisters per year. Interestingly, 29% of asthma patients who collected ≥3 SABA canisters had no ICS collection.[23]

After the baseline period, patients who collected ≥3 SABA canisters were similar regarding age and sex compared with those collecting <3 canisters, but had more asthma exacerbations, asthma-related hospitalizations and outpatient hospital visits. Patients with SABA overuse had also a greater use of antidepressants, hypnotics and sedatives. Among asthma patients collecting 3 or more SABA canisters, 1.07% died compared with 0.54% of the patients in the group collecting 2 or fewer canisters/year at baseline. The higher the number of SABA canisters used, the greater the frequency of asthma-related exacerbations, defined as visits to the emergency room, hospitalizations or the need for oral corticosteroid treatment.[23,37]

2.9 | Switzerland

A retrospective study using prescription data from Swiss pharmacies between 2016 and 2019 analysed 8145 asthma patients (>4 years) with at least one prescribed asthma treatment per year. Overall, 14% of patients were prescribed SABA alone and 38% of patients were prescribed SABA with another asthma medication. Of these, 37% and 41%, respectively had been prescribed three or more canisters/year. Regarding the children population, 75% of them (4–11 years) had a SABA prescription.[47]

2.10 | The Netherlands

A retrospective study carried out in the Netherlands between 2018 and 2019 examined the current use of asthma medications in primary care in Utrecht, located in the centre of the country. Whether excessive use of SABAs is associated with exacerbations was analysed.[48] A total of 1161 patients were included, and SABA overuse was defined as ≥400 inhalations per year (2 SABA canisters). Of the 766 patients using SABA, 25% had overuse. For patients using asthma medications, the odds of having an exacerbation were 3 times higher if they used an inappropriate number of SABA.

Recently, the SABINA II programme has analysed data extracted from GPs electronic medical records. 26% of the 9474 asthmatic patients included presented SABA overuse, with a significant association with severe exacerbation (IRR 1.40) across all GINA treatment steps.[31]

Previously, data extracted from a patients' survey about their inhaler treatment during the previous week (REALISE study),[49] showed that 60% of 736 asthmatic patients, reported use of SABA at least 3 times during the previous week.[50] This group, considered as "higher users", had more use of antibiotics, oral steroids and visits to the emergency room, including overnight hospitalizations. They also had more comorbidities such as diabetes, hypertension and rheumatoid arthritis.

These studies confirm that SABA overuse is still common in this country and that it is associated with asthma exacerbations.

2.11 | United Kingdom

In the United Kingdom, 574,913 asthmatic patients were included in SABINA I and classified according to the British Thoracic Society (BTS) guidelines. Data were extracted from the electronic medical records of general practitioners (GPs) from 2008 to 2018. 38% of patients had been prescribed ≥3 SABA canisters per year.[30] High SABA prescription was observed in 27% of patients with mild asthma (BTS steps 1–2) and 58% of patients with moderate-to-severe asthma (BTS 3–5). Across all treatment steps, patients in the high SABA group experienced approximately twice as many exacerbations compared with patients in the low SABA group. Overall, there was an increased risk of exacerbations in patients prescribed ≥3 SABA canisters per year compared with patients prescribed 0 to 1 SABA canisters per year in both mild asthma (Hazard Ratio [HR] 1.20) and patients with moderate–severe asthma (HR 1.24).[30] Compared with other European countries, the United Kingdom had

the lowest percentage of subjects receiving treatment for moderate-to-severe asthma and the highest average number of annual SABA prescriptions (mean 4.2).[37]

Recently, updated data from the SABINA programme increased the SABA overuse to 51% among the 187,675 patients included.[31] 63.4% were treated as 3–5 GINA steps. In addition, a higher incidence of severe exacerbations was shown in the SABA overuse group, regardless of prescribed ICS. The mean number of SABA prescriptions was still the highest (mean 4.1) compared with other countries. This could indicate that individuals with uncontrolled asthma in the United Kingdom are more likely to be prescribed SABA rather than being reviewed and prescribed a higher dose of their anti-inflammatory maintenance therapy as recommended by guidelines.

This trend of increasing use of SABA in the United Kingdom has been shown previously. The inappropriate use of SABA (defined as a prescription of more than 12 canisters per year) had increased from 8.6% in 2007 to 10.5% in 2013, and in terms of the child population from 6 years old, 1.6% in 2013 were also overexposed to SABA.[44]

3 | DISCUSSION

SABAs have been used in the treatment of asthma for more than 50 years. Patient satisfaction and confidence in SABA treatment are enhanced by its rapid relief of symptoms, its prominence in emergency care and hospital management of exacerbations, along with its low cost.[51] From the beginning of the 20th century to the present, the short-term safety and selective profile of SABAs have improved, reducing side effects.[11] A paradoxical reaction to high SABA use has been described when used as maintenance treatment,[25] and the use of 6 inhalations or more of SABA per day doubled the possibility of presenting an exacerbation in the following 6 months, with increased morbidity and mortality.[46]

Several studies have shown the relevance of including ICS in combination with LABA in asthma therapy, either as needed or as maintenance regimen.[11–13] These studies have not shown that selective LABAs are safer than selective SABAs, but they did show that patients take their ICS medication more correctly, with less overreliance on SABAs that can increase airways inflammation.

Taking all these aspects into account, the asthma guidelines have recently updated the recommendations on the use of SABA. As of 2019, GINA no longer recommends treating asthma symptoms in adults and adolescents with SABA as needed without concomitant ICS.[52,53] The frequency of SABA use is included in the evaluation of symptom control and in some national guidelines such as the GEMA in Spain, the "acceptable" use of SABA has been strictly restricted to indicate the need for an increase in maintenance treatments.[38] A recent study has shown the benefits of a fixed combination of salbutamol/budesonide as rescue medication, when compared with salbutamol alone, in reducing the risk of severe asthma exacerbations among patients with moderate-to-severe asthma who were on treatment with a variety of ICS-containing maintenance therapies.[54]

All these recommendations are made for adult and adolescent asthma patients, but based on the good clinical results of the use of a combination as reliever medication, it has also been proposed to include the child population in this recommendation.[54,55] However, more real-world studies in children are needed to get a real insight into the impact of these therapeutic recommendations in this specific group.[56]

The SABINA program and other recent studies in European countries clearly show that excessive use of SABA (≥3 canisters dispensed in a year) remains a reality in Europe and is a potential risk factor for exacerbations, regardless of ICS. In the updated data from SABINA programme, related to European countries, 36% of treated asthma patients were prescribed/possessed ≥3 SABA canisters/year.[31] Overall, SABA overuse was associated with a 32% increase in the incidence of severe exacerbations. High SABA use was prevalent across all asthma severities and has increased in recent years in European countries[31] (Figure 3). These findings indicate that there is still a significant group of European patients who do not receive optimal treatment according to current GINA recommendations. They also confirm that there is underestimation of asthma severity, with patients remaining uncontrolled despite prescribed maintenance therapy. Likewise, the "Italian case" has shown us the relevance of considering the specific regional characteristics of the health systems and the purchase/prescription restrictions, in order to better bring the design of the studies closer to reality.[23,31,37] One of the main limitations of studies looking at SABA use is that prescription/possession of the canister may not accurately reflect SABA use. However, covariant analyses have shown a strong relationship between prescribing more than 2.7 canisters/year and a 20% higher incidence of severe exacerbations.[30,31,57] So, there is evidence on the association between excessive use of SABA and poor asthma control.

The SABINA program has provided relevant data on the use of SABA in real life Settings that may have important implications in the management of asthma; however, it cannot be forgotten that this is an industry sponsored study program and therefore should be interpreted with caution and balance.

Whether SABA overuse is a consequence of uncontrolled asthma or a cause is a matter of debate.[58] In fact, the concept that SABA overuse directly causes increased severe asthma exacerbations is still controversial. There is a clear relationship between high SABA use and poor asthma outcomes, SABA overuse cannot be considered itself the cause of a higher asthma mortality rate but a confounding factor: the higher SABA use in uncontrolled patients or the most symptomatic ones, is likely to be a direct consequence of the underlying asthma severity.[10]

When SABA use was investigated in different groups of asthma patients based on speed of exacerbation onset, there were no differences in SABA treatment on days prior to hospital admission between them.[59] These results were not aligned with previous reported data extracted from clinical trials, which showed an increase of SABA use from around 5 days preceding emergency hospitalization.[60,61] Also, the concomitant underuse of ICS or its discontinuation may play a

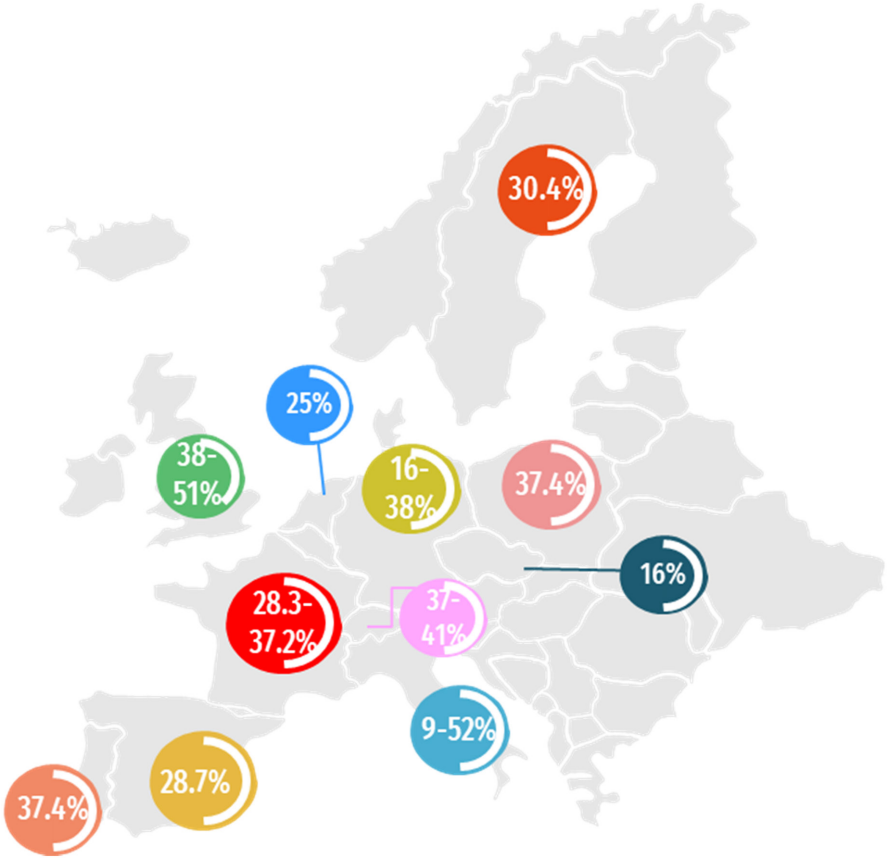

FIGURE 3 Map of SABA overuse prevalence in European countries.[31,39–41,47]

relevant role in increasing the risk of asthma exacerbation and decrease lung function in those patients with SABA overuse.

The challenging fact of implementing guidelines in clinical practice exists. Progressively, national quality standards for asthma have been defined, however, it is still a necessity in some European countries such as Poland.[40] In addition, the lack of approval by regulatory agencies constitutes a limitation to implement the combination of beta2 agonist plus ICS as needed treatment in clinical practice, being used off-label in some countries.[56] Despite the evidence linking SABA overuse and risk of exacerbations, there is still a lack of consensus among different clinicians on what should be considered overuse and even indulgent behaviour with SABA use. McKibben et al.[62] interviewed asthma experts from different backgrounds and GPs who provide asthma care. A significant disparity was found in how acceptable use of SABA is defined, ranging from 0.5 to 12 inhalers of SABA, as well as complacency in the perception that excessive use was not a risk marker for death from asthma. In addition, in the study carried out in Germany on the use of SABA, it was shown that general practitioners prescribe SABA more frequently compared with pulmonologists, which points to the need to provide educational information to all physicians involved in the care of patients with asthma.[36] These data show that defining excessive use of SABA in asthma is difficult and even more difficult to disseminate among patients, primary care physicians, emergency department physicians, and specialists such as pulmonologists and allergists. Physicians' overreliance on SABA medication is reflected in prescribing behaviours such as those found in the Swiss population. Despite an intensification of anti-inflammatory treatment, the prescription of SABA does not decrease compared with those patients who were on SABA monotherapy.[47] Educational campaigns to disseminate the latest guideline updates, also targeting GPs, could improve this landscape.[63–66]

Other issues that need to be addressed include the possibility of purchasing SABA without a prescription in some countries such as Germany, Sweden and Spain.[37] In all, 90% of patients express a preference for rescue medication over maintenance therapy and 39% believe that daily medication is not necessary if they do not present any symptoms.[51] Some factors, such as a high emotional attachment to SABA (due to rapid relief of symptoms) and a lack of understanding of the benefits of ICS, have been identified as key points in patients' perception of both the disease and its treatment.[67] This combination of factors led to insufficient anti-inflammatory therapy.

On the other hand, it should be noted that some patients are well controlled with regular anti-inflammatory treatment and SABA medication as needed. Recently, it has been proposed to identify these patients by analysing the canisters used per year and the use of SABA per week, considering that if the patients on SABA as needed had a use of less than 2 canisters/year or less than 2 inhalations/week, were well controlled, assuming good adherence to maintenance treatment.[68]

Reducing the time before referral from GPs to specialist is another concern to be addressed, with data from the United Kingdom showing that the median waiting time between patient eligibility and specialist referral could be around 880 days (IQR = 1428 days).[69] Several

studies have shown that proper characterization of patients is crucial for good management of the disease and to prevent life-threatening asthma exacerbations.[70] The incorporation of non-pharmacological patient insight approaches to symptom and exacerbation management is growing in regional asthma strategies[63,64] and has been shown to be useful in identifying uncontrolled asthma.[59,70]

Recently, an observational cohort study has quantified the carbon footprint associated to SABA overuse, based on the global warming potential of hydrofluorocarbon propellants contained in metered-dose inhalers (MDIs).[71] After analysing data from Europe and Canada, the authors conclude that SABA overuse dispensed by MDIs is associated with the excess of greenhouse gas emissions per capita, which increase the carbon footprint of respiratory treatment.[72]

4 | CONCLUSION

The high use of SABA in Europe across all asthma severities continues to be a reality with an increase in recent years. Despite the efforts of the guidelines to reduce it, and the existing data that confirm its association with an increased risk of exacerbations, use of health services and negative impact on the physical and mental health of patients, European patients continue to be exposed to monotherapy with SABAs and to an excessive use of these drugs. Overreliance on SABA treatment is another factor making it difficult to change prescribing trends in Europe. In addition, the identification of patients who are well controlled on regular anti-inflammatory treatment and SABA as a reliever, should be explored for a better tailored approach to asthma management. National health systems, together with the guidelines, should urgently align asthma management with global recommendations, adjusting them to local needs as necessary.

AUTHOR CONTRIBUTION

All authors contributed to drafting and revising the manuscript. The literature search was carried out by all authors; hereby SQ fulfilled an advisory and supervisory role. All authors gave the final approval of the version to be published and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

S. Quirce has received speaking and consulting honoraria from ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GSK, Mundipharma, Novartis, Sanofi, and Teva. L. de las Vecillas has no conflicts of interest to declare related to this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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