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Scientific letter

Clinical Consequences of the Overuse of Short-Acting β2-Adrenergic Agonists (SABA) in the Treatment of Asthma in Spain: The SABINA Study

Consecuencias clínicas del uso excesivo de los agonistas adrenérgicos β2 de acción corta (SABA) en el tratamiento del asma en España: el estudio SABINA

Dear Editor,

Short-acting β2-agonists (SABA), used as needed, have traditionally been prescribed for symptom relief for people with asthma. Nevertheless, evidence of the increased risks associated with high SABA use has grown substantially in recent years.[1] Moreover, increasing numbers of reports are emerging from clinical trials on the superiority of anti-inflammatory therapy with inhaled corticosteroids (ICS) combined with formoterol in symptom control and reduction in exacerbation risk.[2,3] Since 2019, the Global Initiative for Asthma (GINA) no longer recommends SABA-only treatment in asthma, relegating SABA use to symptomatic relief and suggesting that patients using ≥3 SABA canisters/year should be assessed for uncontrolled asthma due to the associated increased risk of exacerbations, hospitalisation, and mortality.[4] In contrast, GINA recommends low-dosed ICS-formoterol in the first steps, as maintenance in steps 3–5, and as relief in all severity steps. This decreases underlying inflammation and places ICS at the forefront of asthma management, even in mild forms.[4]

Recently, results from the SABINA programme have demonstrated that SABA overuse (≥3 SABA canisters/year) occurs in approximately one-third of mild-to-severe individuals with asthma across Europe, including Spain,[5] and nearly half of the patients from a recent study performed in Europe and North America.[6]

We hypothesised that asthma patients who overuse SABA underuse ICS, countering guidelines.[4] This study aims to evaluate SABA and ICS prescription patterns in Spanish asthma patients according to GINA severity classification and assess the relationship between SABA overuse, exacerbations, and mortality during one-year follow-up.

In this cross-sectional, longitudinal, and retrospective study in primary and specialised care in Spain, prescription data of a total of 39,555 patients aged ≥12 years diagnosed with asthma according to the International Classification of Diseases (ICD-10-MC: J45-J46) who attended two consultations minimum during 2017, with one-year follow-up data, were included from the BIG-PAC® Medical Records Database. Data confidentiality complied with the Law on Protection of Personal Data. The Spanish Agency for Medicines and Health Products classified the study as a post-approval observational study and approved by the Research Ethics Committee of the Hospital de Terrassa (Barcelona).

Almost one-third of these patients (28.7%) overused SABA, and this overuse was associated with age, general comorbidity, and severity levels according to the GINA classification[4] (Table 1A, B). SABA overuse was greater in individuals with moderate-to-severe asthma (GINA-3–5: 26.4%, 33.4%, and 48.7%) versus mild asthma (GINA-1–2: 25.4% and 17.3%) and this association was observed to be dose-dependent when ascending SABA use was analysed (≤1; 2; 3–6; 7–12; and ≥13 canisters/year) (Table 1B, C). These results were similar to previously published data of this program[5,6] and confirmed that SABA overuse ranges from 7.7% to 37.3%, as reported in other studies.[7,8]

ICS prescription dosage below the maximum recommended for each severity step was described in 13.4% of patients overall, with higher rates in GINA-2 (17.1%) and GINA-3 (15.8%) (Table 1B). The inflammatory nature of the disease should not be underestimated in these non-serious forms,[9] considering that most of the study asthma population have mild-to-persistent asthma. Importantly, ICS underuse was directly associated with the increasing number of SABA prescriptions and was inversely related to GINA severity steps (Table 1B, C). In milder asthma forms, this could be explained by the negative influence of infrequent or non-bothersome symptoms on patients' adherence to medications, especially ICS.[10,11] Consequently, these patients often rely on SABA alone to relieve symptoms, contributing to SABA overuse.[11]

During the one-year follow-up, 44.6% of patients experienced at least one mild-moderate exacerbation, distributed by GINA-1–5: 39.7%, 34.3%, 44%, 48.8%, and 59.4% (Table 1B). Most patients overusing SABA had ≥1 exacerbation at baseline (98%) or during follow-up periods (99%) (Table 1D). The increasing number of SABA canisters was also associated with an increased risk of exacerbations in a dose-dependent manner (Table 1D). Results from an adjusted multivariate linear regression model showed that SABA overuse was associated with the number of exacerbations during follow-up, corresponding to an increase of 1.52 times in the estimated number of exacerbations/years compared with patients who were prescribed ≤2 SABA canisters (Table 1D), and these results were in line with recent studies.[1,6]

Of 516 asthma-related deaths (13/1000 patient-per-year), 227 were reported in the group of appropriate SABA usage (8/1000 patient-per-years). In contrast, 289 deaths were reported in the SABA overuse group (25.5/1000 patient-per-years) (Table 1D), and the asthma-related death rates were directly associated with increased SABA use (Table 1C). In the logistic regression model, SABA overuse (adjusted for covariates) was associated with increased mortality (OR = 1.6; 95%CI: 1.35–1.96; $p < 0.001$) during follow-up (Table 1D).

Despite the availability of effective asthma treatments, some individuals have poorly controlled asthma because of overreliance

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Table 1
Baseline demographic and clinical characteristics, SABA overuse, ICS doses, exacerbations, and mortality during the follow-up period of patients according to GINA asthma severity and SABA overuse.

A. Clinical characteristics according to GINA asthma severity

	GINA-1	GINA-2	GINA-3	GINA-4	GINA-5	Overall
Patients, n (%)	6030 (15.2)	4506 (11.4)	15,884 (40.2)	10,104 (25.5)	3031 (7.7)	39,555 (100)
Female, %	58.7%	61.3%	65.3%	66.2%	67.3%	64.2%
Age (years), mean (SD)	42.5 (18.8)	45.1 (20.9)	49.8 (20.9)	52.1 (19.7)	64.3 (17.7)	49.8 (20.7)
Number of comorbidities, mean (SD)	2.1 (1.7)	2.3 (1.8)	2.6 (1.9)	2.8 (2.1)	4.1 (2.2)	2.6 (2.0)
Most frequent comorbidities, %						
Allergic rhinitis	48.9%	51.5%	55.3%	59.2%	66.1%	55.7%
Atopic dermatitis	37.1%	36.4%	35.4%	32.2%	29.1%	34.5%

B. SABA and ICS use, exacerbation, and mortality according to GINA asthma severity

	GINA-1	GINA-2	GINA-3	GINA-4	GINA-5	Overall
SABA use						
Number of canisters per year, mean (SD)	2.5 (2.1)	2.7 (2.6)	3.1 (3.4)	3.9 (4.4)	5.0 (4.1)	3.3 (3.6)
SABA ≥3 canisters per year	25.4%	17.3%	26.4%	33.4%	48.7%	28.7%
ICS use, %						
Underuse	0	17.1%	15.8%	9.9%	7.0%	13.4%
Recommended use	0	78.1%	80.9%	85.8%	88.8%	82.7%
Overuse	0	4.7%	3.3%	4.3%	4.1%	3.9%
Patients with follow-up exacerbations (one year)						
Mild–moderate	39.7%	34.3%	44%	48.8%	59.4%	44.6%
Severe (hospital admission)	9.8%	7.7%	13.4%	18.3%	22.7%	14.1%
Mortality (asthma-related), %	0.3%	0.8%	1.0%	1.7%	4.2%	1.3%

C. GINA asthma severity, ICS use, exacerbation, and mortality according to SABA canister use per year

	≤1	2	3–6	7–12	≥13
Patients n (%)	5238 (13.2)	22,977 (58.1)	7428 (18.8)	2283 (5.8)	1629 (4.1)
Asthma severity					
Mild (GINA steps1-2)	32.9%	28.3%	25.2%	12.8%	8.3%
Moderate to severe (GINA steps 3-4-5)	67.1%	71.7%	74.8%	87.2%	91.7%
ICS prescription dosage, %					
Below maximum recommended for step severity	0.8%	13.1%	17.4%	19.6%	23.9%
Exact maximum recommended for step severity	95.2%	84.3%	77.6%	72.4%	67.3%
Above maximum recommended for step severity	4.0%	2.6%	5.0%	8.1%	8.9%
Exacerbations					
Patients with ≥1 exacerbation per follow-up year,%	20.9%	23.8%	90.6%	95.8%	97.9%
Mortality rates (per 1000 patient-year)	6.3	8.4	19.7	36.8	36.2

D. Exacerbations and mortality according to SABA overuse

	SABA non-overuse[a]	SABA overuse	Adjusted OR (95%CI)	Unstandardised coefficient, *B* (95%CI)	*p*-Value
SABINA population, *n* (%)	28,215 (71.3)	11,340 (28.7)			
Mortality (asthma-related), *n* (%)	227 (0.8)	289 (2.5)	1.60 (1.35-1.96)[b]		<0.001
Mortality rates (per 1000 patient-year)	8.0	25.5			
At least one previous exacerbation, *n* (%)	10,002 (35.4)	11,116 (98.0)			
Number of follow-up exacerbations, mean (SD)	0.2 (0.4)	1.9 (0.7)		1.60 (1.35-1.96)[c]	<0.001
At least one follow-up exacerbation, *n* (%)	6565 (23.3)	11,230 (99.0)			

[a] The SABA overuse was defined as the use of ≥3 canisters per year.
[b] Logistic regression, adjusted for sex, age, time from diagnosis, Charlson Comorbidity Index, asthma severity, and previous exacerbations (12 months before the index date).
[c] Multivariate linear regression adjusted for sex, age, time from diagnosis, Charlson Comorbidity Index, asthma severity, and previous exacerbations (12 months before the index date).
BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in one second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; OR, odds ratio; SABA, short-acting β2-agonists; SABINA, SABA use IN asthma; SD, standard deviation.

on SABA and ICS underuse, which leads to exacerbations, many of which can be prevented. This is relevant since a seven-year follow-up study found that more than 25% of GINA-1 patients are at risk of severe exacerbations, 10.4% repeatedly,[12] and the concept of "zero tolerance" to exacerbations is becoming a goal of asthma management.[13]

Patients and physicians should be aware of poor asthma control. Both tend to overestimate control, resulting in undertreatment and misuse of therapy.[9] Insufficient asthma control has been demonstrated in many studies,[14] but the association between SABA overuse and the clinical impact on mortality and exacerbations should be underlined.[5–8] As a result, international and national guidelines state that SABA overuse indicates inadequate asthma control, no longer recommending SABA reliever without ICS.[4,9]

Our findings should be translated into actions to improve real-practice guidelines implementation. Changes in physician and patient behaviours towards SABA use, active engagement in adapting GINA recommendations to local guidelines, and updates to

national healthcare policies will be needed to ensure that individuals with asthma are not unnecessarily exposed to SABA alone in the treatment of their inflammatory disease. Additionally, pharmacy actions such as implementing alerts in electronic systems to detect high-frequency dispensing or promoting patient self-care through educational programmes from the early stages of asthma diagnosis are necessary.[12,15]

This study presents some limitations, including disease categorisation, possible bias in the patient classification when assessing mortality throughout follow-up, and selection of therapeutic groups, all of which are attributable to the data system applied. Other limitations are inherent to retrospective studies.

In conclusion, this study shows that a large proportion of asthma patients in Spain overuse SABA, which is strongly associated with increasing exacerbations and mortality rates. Monitoring SABA use and patient education thus become critical, as practitioners and patients need to understand the importance of anti-inflammatory management instead of SABA-only treatment. The future perspectives offered by this study are focused on promoting an alignment of treatments with the recommendations and furthering research into the evolution of SABA use and its impact on asthma-related outcomes.

Informed consent

Data confidentiality complied with the Law on Protection of Personal Data. The study was classified by the Spanish Agency for Medicines and Health Products as a post-approval observational study and approved by the Research Ethics Committee of the Hospital de Terrassa (Barcelona).

Existing patient registries comply with current regulations on personal data protection, namely Regulation (EU) 2016/679 of the European Parliament and Council of 27 April 2016 on Data Protection (RGPD) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights. All data are anonymised, and confidentiality of information is guaranteed.

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Authors' contributions

All authors equally contributed to all the following: (i) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; and (iii) final approval of the version to be submitted.

Conflict of interests

JM received speaker's fees in meetings sponsored by AstraZeneca, Chiesi, GSK, Menarini Group, and Sociedad Española de Medicina de Familia y Comunitaria; and was an advisor for AstraZeneca, GSK, and Pfizer. VP received speaker's fees in meetings sponsored by AstraZeneca, Chiesi, Gebro Pharma, and GSK; was an advisor for GSK and Sanofi; was sponsored to attend congresses by AstraZeneca, Chiesi, and Novartis; and received research project grants by Chiesi and Menarini Group. JN and MG are AstraZeneca employees. AS-M was an independent consultant involved the development of this manuscript. AV was an advisor for Sanofi, Uriach, AstraZeneca, ALK, and Allergy Therapeutics; received speaker's fees in meetings sponsored by AstraZeneca, Chiesi, Bial, and GSK; and received research project grants by Novartis and Uriach.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.opresp.2023.100232.

References

1. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55, http://dx.doi.org/10.1183/13993003.01872-2019.
2. Beasley R, Bird G, Harper J, Weatherall M. The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity. Eur Respir J. 2018;52, http://dx.doi.org/10.1183/13993003.00694-2018.
3. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018;378:1865–76, http://dx.doi.org/10.1056/NEJMoa1715274.
4. GINA2022. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2022. Available from: https://ginasthma.org/ [accessed May 2022].
5. Janson C, Menzies-Gow A, Nan C, Nuevo J, Papi A, Quint JK, et al. SABINA: an overview of short-acting beta2-agonist use in asthma in European countries. Adv Ther. 2020;37:1124–35, http://dx.doi.org/10.1007/s12325-020-01233-0.
6. Quint JK, Arnetorp S, Kocks JWH, Kupczyk M, Nuevo J, Plaza V, et al. Short-acting beta2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. J Allergy Clin Immunol Pract. 2022, http://dx.doi.org/10.1016/j.jaip.2022.02.047.
7. FitzGerald JM, Tavakoli H, Lynd LD, Al Efraij K, Sadatsafavi M. The impact of inappropriate use of short acting beta agonists in asthma. Respir Med. 2017;131:135–40, http://dx.doi.org/10.1016/j.rmed.2017.08.014.
8. Silver HS, Blanchette CM, Kamble S, Petersen H, Letter M, Meddis D, et al. Quarterly assessment of short-acting beta(2)-adrenergic agonist use as a predictor of subsequent health care use for asthmatic patients in the United States. J Asthma. 2010;47:660–6, http://dx.doi.org/10.3109/02770901003702824.
9. GEMA 5.2. Guía española para el manejo del asma. Comité Ejecutivo de la GEMA. 2022. Available from: https://www.gemasma.com/sites/default/files/2022-05/GEMA_52.pdf [accessed May 2022].
10. Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care. 2015;60:455–68, http://dx.doi.org/10.4187/respcare.03200.
11. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med. 2018;378:1877–87, http://dx.doi.org/10.1056/NEJMoa1715275.
12. Dominguez-Ortega J, Saez-Martinez FJ, Gomez-Saenz JT, Molina-Paris J, Alvarez-Gutierrez FJ, en nombre del Grupo Unidos por el A, et al. The management of asthma as a chronic inflammatory disease and global health problem: a position paper from the scientific societies. Semergen. 2020;46:347–54, http://dx.doi.org/10.1016/j.semerg.2020.01.001.
13. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet (Lond, Engl). 2018;391:350–400, http://dx.doi.org/10.1016/s0140-6736(17)30879-6.
14. Sicras-Mainar A, Huerta A, Sanchez D, Navarro-Artieda R. Use of resources and costs associated with non-adherence to inhaled corticosteroid treatment in asthma. Semergen. 2018;44:13–22, http://dx.doi.org/10.1016/j.semerg.2017.03.005.
15. Munoz-Cano R, Torrego A, Bartra J, Sanchez-Lopez J, Palomino R, Picado C, et al. Follow-up of patients with uncontrolled asthma: clinical features of asthma patients according to the level of control achieved (the COAS study). Eur Respir J. 2017;49, http://dx.doi.org/10.1183/13993003.01885-2015.

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