What drives rescue bronchodilators overuse in asthma patients? Demographic features, low forced expiratory volume in 1 s and high sputum eosinophil counts

This article has an editorial commentary: https://doi.org/10.1183/23120541.00864-2025

Received: 14 Feb 2025
Accepted: 3 June 2025

To the Editor:

Excessive use of short acting β2 agonists has been associated with increased asthma mortality [1], and recent large epidemiological studies conducted worldwide have clearly shown that exacerbation rate in asthma patients was correlated with the consumption of β2 agonist canisters [2, 3]. These studies rely on prescription records from electronic medical files and/or dispensation of the drug at the pharmacy level. However, there are far fewer studies based on patient interviews, as well as on the factors driving the overuse of bronchodilators in a real-world setting.

To the best of our knowledge, there has been no study exploring the relationship between patient-reported overuse of β2 agonists and the measurement of lung function and airway inflammation. Here, we have conducted a large retrospective study leveraging our asthma clinic database to investigate the factors associated with high consumption of rescue bronchodilators as reported by the patient.

A cross-sectional retrospective study was conducted on asthma patients recruited from the asthma clinic of CHU Liege between 2011 and 2023. We selected 2167 asthma patients who had already been prescribed any asthma treatment other than biologics. Among them, 589 were treated only with short-acting beta-agonists (SABA) or a combination of SABA/SAMA (short-acting muscarinic-antagonist) as needed, while the majority of patients were receiving maintenance treatment including ICS/LABA (inhaled corticosteroids/long-acting beta-agonist), with or without a long-acting muscarinic-antagonist (LAMA) and/or montelukast and/or oral corticosteroids. Patients underwent blood sampling, sputum induction and fraction of exhaled nitric oxide (F_{ENO}) was measured by NIOX, as previously reported [4]. They filled in an Asthma Control Questionnaire and were classified in three categories according to their answers to item six: "on average, during the past week, how many puffs of short acting bronchodilators have you used each day?" [5]. Category 1 was non-users, category 2 was moderate users (one to four puffs per day), category 3 was the overusers (five to >16 puffs per day). Using more than four puffs per day exceeds the dose of 400 µg inhaled salbutamol which yields optimal bronchodilation [6].

The database used for this study was approved by the Ethics Committee of CHU Liege B70720096732 (2009/161) and all patients signed an informed consent.

Data from continuous variables were expressed as mean±SD or median (interquartile range) according to the distribution of the variable. As for continuous variables, demographic, spirometry and inflammatory features were compared between the three categories by using ANOVA or Kruskal–Wallis according to the distribution of the variables. In case of significance, pairwise comparisons were made by an unpaired t-test or a Mann–Whitney test. Data from categorical variables were expressed as proportion and the difference between the groups were analysed by performing a chi-square test. Multiple logistic regression was performed to determine the variables which where independently associated with usage of rescue bronchodilators. p-values<0.05 were considered as statistically significant.

Thirteen % of the patients (n=278) were classified as overusers, 42% were moderate users (n=900) and 45% (n=989) were non-users of rescue bronchodilators. The use of rescue bronchodilators increased with

Shareable abstract (@ERSpublications)
In a large cohort of 2167 patients seen in a secondary/tertiary hospital, we found that overuse of rescue bronchodilators was associated with young age, smoking habit, overweight, impaired spirometry and uncontrolled airway eosinophilic inflammation https://bit.ly/44buBSr

Cite this article as: Louis F, Guissard F, Paulus V, *et al*. What drives rescue bronchodilators overuse in asthma patients? Demographic features, low forced expiratory volume in 1 s and high sputum eosinophil counts. *ERJ Open Res* 2025; 11: 00224-2025 [DOI: 10.1183/23120541.00224-2025].

the burden of maintenance treatment. The proportion of overusers was 8% (45 of 589), 7% (5 of 71), 7% (4 of 59), 10% (80 of 778) and 21% (118 of 570) in patients treated by SABA/SAMA only, montelukast only, ICS only, ICS/LABA and ICS/LABA+others, respectively. The proportion of overusers in patients receiving oral corticosteroids was 28% (19 of 69) and 22% (7 of 31) in a group of patients receiving other treatments (LAMA only, LABA only, LABA/LAMA and theophylline). Demographic, lung function and inflammatory parameters according to the use of rescue bronchodilators are given in figure 1a.

The proportion of current smokers gradually increased from 15% in the category of non-users to 29% in that of overusers ($p<0.001$). Body mass index was slightly higher in overusers than in non-users ($p<0.05$). Exacerbations rates in the 12 months prior to the visit were higher in overusers as compared to non-users and moderate users ($p<0.0001$ for both) and higher in moderate users as compared to non-users ($p<0.0001$).

Forced expiratory volume in 1 s (FEV_1) % predicted, FEV_1/FVC (forced vital capacity) % as well as provocative concentration of methacholine causing a 20% fall in FEV_1gradually decreased from non-users to overusers ($p<0.0001$ for all). Moreover, the magnitude of the bronchodilation to salbutamol expressed as % pred increased from non-users to overusers ($p<0.01$).

Overusers had the greatest sputum eosinophil counts ($p<0.0001$ *versus* non-users, $p<0.01$ *versus* moderate users) while sputum neutrophil counts did not differ between the three groups. The proportions of patients with sputum eosinophil count $\geqslant$3% were 35% (251 of 712) in non-users, 39% (264 of 679) in moderate users and 51% (107 of 211) in overusers. There was no difference regarding F_{ENO} levels between the three groups. With respect to systemic inflammatory parameters, overusers had significantly higher levels of total serum IgE, blood eosinophils and neutrophils as compared to non-users and moderate users (figure 1a). The proportion of patients with blood eosinophil counts $\geqslant$300 per µL was 25% (236 of 937) in non-users, 26% (220 of 860) in moderate users and 36% (97 of 268) in overusers.

After multiple logistic regression (figure 1b), young age, high body mass index, current smoking, high exacerbations rate, low FEV_1 % pred, low FEV_1/FVC %, high blood neutrophil counts and high sputum eosinophil counts increased the risk of being overusers (n=156) compared to being non-overusers (n=1146, merging moderate users and non-users).

This study shows that overusers of rescue bronchodilators represent 13% of the patients seen in an asthma clinic of a secondary/tertiary care centre, in which most of the patients were receiving maintenance treatment with ICS/LABA.

The relationship between rescue bronchodilators overuse and the rate of exacerbations is striking. Adding overuse of rescue bronchodilators into a risk prediction model of exacerbations in the future may enhance the value of a model limited to biomarkers [7, 8]. While the link between overuse of rescue bronchodilators and current smoking, overweight and exacerbation rate aligns with previous studies [2, 3, 9, 10], it is the first study to show a relationship between overuse of rescue bronchodilators and the magnitude of sputum eosinophil counts in a real life setting. Our finding supports the concept that uncontrolled airway eosinophilia may trigger symptoms pushing patients to use reliever medications. Overuse of rescue medication should prompt the clinician to investigate the airway eosinophil content. Our study lends support to the MART (maintenance and reliever therapy) strategy, as well as to adding anti-IL-5 treatment in severe eosinophilic patients who continue to overuse bronchodilators. In two recent studies, sputum eosinophils have been found to correlate with the intensity of cough [11, 12]. Interestingly, in contrast to sputum eosinophils, F_{ENO} levels did not show the same relationship with rescue bronchodilators overuse. The impact of current smoking, known to dramatically reduce F_{ENO} [13, 14], may blunt the relationship. Along with sputum eosinophil counts, blood eosinophil and neutrophil counts and total IgE were also increased in overusers. However, these systemic biomarkers were no longer considered as independent risk factors after the multiple logistic regression, thereby indicating that sputum eosinophils remain the main determinant of reliever overuse among inflammatory parameters. Even when selecting patients without smoking history, F_{ENO} was not associated with overuse of bronchodilators after multiple logistic regression (n=606, data not shown).

Another finding that emerged from the current study is the importance of airflow limitation in triggering the use of rescue bronchodilators. In a large cohort of asthma patients receiving ICS/LABA we have recently found that impaired FEV_1 was related to dyspnoea and chest tightness [11]. It is understandable that patients seek to improve airway calibre by using their bronchodilator when feeling out of breath, even more so that the magnitude of bronchodilation to salbutamol appears to be greater in our cohort of

a)

	Total population (n=2167)	Non-users (n=989)	Moderate users (n=900)	Overusers (n=278)	ANOVA/ Kruskal–Wallis test
Age, y	51 (36–62)	53 (37-63)	48 (35–60)***	48.5 (40–60)	0.0037
Female gender, N (%)	1274 (59)	576 (58)	536 (60)	166 (60)	
BMI, kg·m^{-2}	26.7±5.190	26.4±5.007	26.8±5.360	27.4±5.261*	0.0403
Atopy, N (%)	1045 (52)	465 (50)	429 (52)	151 (57)	
Smoking status, N (%)					
Nonsmokers	1176 (54)	562 (57)	492 (55)	122 (44)	
Current smokers	422 (20)	149 (15)	190 (21)***	82 (29)****##	
Ex-smokers	570 (26)	278 (28)	218 (24)	74 (27)	
Season, N (%)					
Summer	20 (441)	22 (215)	18 (160)	24 (66)	
Autumn	29 (633)	27.5 (272)	32 (287)	27 (74)	
Winter	25 (532)	23 (230)	26 (232)	25 (70)	
Spring	26 (561)	27.5 (272)	24 (221)	24 (68)	
Exacerbations in previous 12 months (n·patient^{-1}·y^{-1})	0 (0–1)	0 (0–1)	0 (0–1)***	1 (0–2.75)********####	<0.0001
FEV_1, % predicted	83±21	87±19	83±21****	68±22********####	<0.0001
FEV_1/FVC, %	74±11	76±10	74±12**	68±13********####	<0.0001
BDR, % pred	4.1±10	3.3±10	4.8±10**	5.4±9*	0.0019
$PC_{20}M$, mg·mL^{-1} (n=1125)	3.4 (0.6–22)	4.7 (1–22)	2.5 (0.5–22)***	1.7 (0.2–7.7)**	<0.0001
F_{ENO}, ppb (n=2073)	22 (13–40)	22 (13–37)	21 (12–41)	24 (11–52)	0.6702
Sputum eosinophils, % (n=1602)	1.4 (0.2–7.2)	1.2 (0.2–5.6)	1.6 (0.2–7.6)	3 (0.4–20)****##	<0.0001
Sputum neutrophils, % (n=1602)	61 (37–80)	63 (41–79)	59 (34–80)	58 (35–80)	0.1681
Blood eosinophils, cells·µL^{-1} (n=2067)	172 (100–316)	160 (92–300)	178 (101–300)	221 (107–386)***#	0.0009
Blood neutrophils, cells·µL^{-1} (n=2067)	3996 (3160–5312)	3954 (3108–5016)	3942 (3146–5315)	4662 (3600–6109)**##	0.0024
Total serum IgE, kUA·L^{-1} (n=2018)	101 (33–292)	96 (31–281)	96 (32–272)	136 (6–472)**##	0.0024

b)

Variables	Overusers *versus* non-overusers		
	Odds ratio	95% CI	p-value
Intercept	0.8083	0.1381–4.635	0.8120
Age	0.9750	0.9618–0.9883	0.0003***
Gender (male)	0.9132	0.6329–1.313	0.6252
BMI	1.056	1.020–1.094	0.0023**
Smoking habits			
Current smokers	2.013	1.284–3.148	0.0022**
Ex-smokers	1.531	0.9658–2.423	0.0689
Season, N (%)			
Autumn	0.6682	0.4077–1.094	0.1084
Winter	0.7833	0.4694–1.302	0.3468
Spring	0.8911	0.5389–1.472	0.6520
Exacerbations in previous 12 months (n·patient^{-1}·y^{-1})	1.313	1.195–1.446	<0.0001****
FEV_1, % predicted	0.9818	0.9694–0.9943	0.0045**
FEV_1/FVC, %	0.9773	0.9554–0.9992	0.0444*
BDR, % pred	1.003	0.9826–1.028	0.7763
F_{ENO}, ppb (n=2073)	1.003	0.9977–1.007	0.2756
Sputum eosinophils, %	1.020	1.007–1.033	0.0028**
Sputum neutrophils, %	1.003	0.9945–1.012	0.4777
Blood eosinophils, cells·µL^{-1}	0.5636	0.2909–1.005	0.0670
Blood neutrophils, cells·µL^{-1}	1.064	1.022–1.118	0.0068**
Total serum IgE, kUA·L^{-1}	1.000	1.000–1.000	0.1048

FIGURE 1 a) Patient characteristics in the whole asthma cohort according to the use of rescue bronchodilators. Results are expressed as mean±SD or median (interquartile range): * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 compared with non-users group and # p<0.05; ## p<0.01; ### p<0.001; #### p<0.0001 compared with moderate users group after unpaired t-test or Mann–Whitney according to the distribution. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BDR: bronchodilation response; $PC_{20}M$: provocative concentration of methacholine causing a 20% fall in FEV_1; F_{ENO}: exhaled nitric oxygen fraction. Seasons: Winter: December–January–February; Spring: March–April–May; Summer: June–July–August; Autumn: September–October–November. b) Factors predicting overuse of rescue medication after multivariable logistic regression in the whole cohort. * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001.

overusers. In addition, the fact that young age makes asthma patients feel more intensive chest tightness would explain why young age favours excessive reliever usage in the current study [11].

Limitation of our study to one week of observation precludes any conclusion on the long term use of β2 agonists, so we cannot exclude that patients classified as overusers the week they were investigated could have been in a state of heightened exacerbations [15] and have become non-users or moderate users a few weeks or months later. Conversely, some of our non or moderate users may have experienced later period with higher use of rescue bronchodilators. Another limitation concerns the potential non-adherence to maintenance treatment, as is often the case in real-life, even in severe asthma patients [16], and good adherence to ICS/LABA was found to reduce SABA over-dispensing [17].

We conclude that approximately 15% of asthma patients referred to a secondary/tertiary centre overuse rescue bronchodilators, a clinical situation which is associated not only with young age, smoking and overweight, but also with impaired spirometry and increased airway eosinophilic inflammation.

France Louis[1], Françoise Guissard[2], Virginie Paulus[2], Mare Sabbe[2], Geneviève Philippe[1], Renaud Louis[2] and Florence Schleich[2]

[1]Department of Pharmacy, University of Liège, Belgium. [2]Department of Pneumology, GIGAI3, University of Liège, Belgium.

Corresponding author: France Louis (france.louis@uliege.be)

Provenance: Submitted article, peer reviewed.

Ethics statement: The study was approved by the CHU Liège ethics committee. Signed informed consent was obtained from patients upon their entry into the asthma clinic at CHU Liège. They agreed to the use of their clinical data and the health outcomes they reported in the routine setting for research purposes.

Authors contributions: F. Louis, F. Schleich and R. Louis contributed to the conception of the study. F. Guissard, V. Paulus, M. Sabbe, F. Schleich and R. Louis contributed to data acquisition. F. Louis and R. Louis performed statistical analysis. F. Louis, G. Philippe, F. Schleich and R. Louis drafted and critically revised the work. All authors gave final approval of the manuscript.

Conflict of interest: Outside of this submitted work, R. Louis received unrestricted research grants from GSK, AstraZeneca, Sanofi and Chiesi, lecture or advisory board fees from GSK, AZ, Novartis and Sonafi and participation on a data safety monitoring board from AstraZeneca. Outside of this submitted work, F. Schleich received grants or contracts from GSK, AstraZeneca, Chiesi and Novartis, consulting fees from GSK, AstraZeneca, Chiesi and Novartis, and lectures for GSK, AstraZeneca, Chiesi and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

References

1 Cockcroft DW. Clinical concerns with inhaled β2-agonists. *Clin Rev Allerg Immunol* 2006; 31: 197–207.
2 Noorduyn SG, Qian C, Johnston KM, *et al.* SABA use as an indicator for asthma exacerbation risk: an observational cohort study (SABINA Canada). *ERJ Open Res* 2022; 8: 00140-2022.
3 Nwaru BI, Ekström M, Hasvold P, *et al.* Overuse of short-acting β2-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: 1901872.
4 Schleich FN, Chevremont A, Paulus V, *et al.* Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J* 2014; 44: 97–108.

5 Juniper EF, O'Byrne PM, Guyatt GH, *et al.* Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14: 902–907.
6 Bel EH, Zwinderman AH, Timmers MC, *et al.* The protective effect of a beta 2 agonist against excessive airway narrowing in response to bronchoconstrictor stimuli in asthma and chronic obstructive lung disease. *Thorax* 1991; 46: 9–14.
7 Patel M, Pilcher J, Reddel HK, *et al.* Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin Exp Allergy* 2013; 43: 1144–1151.
8 O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006; 368: 794–803.
9 Schatz M, Zeiger RS, Yang SJ, *et al.* Prospective study on the relationship of obesity to asthma impairment and risk. *J Allergy Clin Immunol Pract* 2015; 3: 560–565.e1.
10 Chaudhuri R, McSharry C, McCoard A, *et al.* Role of symptoms and lung function in determining asthma control in smokers with asthma. *Allergy* 2008; 63: 132–135.
11 Louis G, Pétré B, Sousa-Pinto B, *et al.* When patient-reported respiratory symptoms shed light on pathophysiology in adult asthma: a cross-sectional study. *Sci Rep* 2024; 14: 29997.
12 Holmes J, McGarvey LPA, Birring SS, *et al.* An observational study to determine the relationship between cough frequency and markers of inflammation in severe asthma. *Eur Respir J* 2022; 60: 2103205.
13 Schleich FN, Seidel L, Sele J, *et al.* Exhaled nitric oxide thresholds associated with a sputum eosinophil count ⩾3% in a cohort of unselected patients with asthma. *Thorax* 2010; 65: 1039–1044.
14 Verleden GM, Dupont LJ, Verpeut AC, *et al.* The effect of cigarette smoking on exhaled nitric oxide in mild steroid-naive asthmatics. *Chest* 1999; 116: 59–64.
15 Tattersfield AE, Postma DS, Barnes PJ, *et al.* Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999; 160: 594–599.
16 Gamble J, Stevenson M, McClean E, *et al.* The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180: 817–822.
17 Toh MR, Ng GXZ, Goel I, *et al.* Asthma prescribing trends, inhaler adherence and outcomes: a Real-World Data analysis of a multi-ethnic Asian asthma population. *NPJ Prim Care Respir Med* 2024; 34: 1.