BJGP OPEN

Characteristics of asthma patients overprescribed short-acting beta-agonist (SABA) reliever inhalers stratified by blood eosinophil count in North East London – a cross-sectional observational study

Pfeffer, Paul; Hajmohammadi, Hajar; Cole, Jim; Griffiths, Chris; Hull, Sally; De Simoni, Anna

DOI: https://doi.org/10.3399/BJGPO.2023.0020

To access the most recent version of this article, please click the DOI URL in the line above.

Received 31 January 2023
Revised 31 January 2023
Accepted 14 March 2023

Characteristics of asthma patients overprescribed short-acting beta-agonist (SABA) reliever inhalers stratified by blood eosinophil count in North East London – a cross-sectional observational study

Paul E. Pfeffer, Consultant Respiratory Physician, Barts Health NHS Trust, and Hon Senior Lecturer, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

Hajar Hajmohammadi, Senior Data Analyst, Wolfson Institute of Population Health, Queen Mary University of London, UK

Jim Cole, Quality Improvement Fellow, Wolfson Institute of Population Health, Queen Mary University of London, UK

Chris Griffiths, Professor of Primary Care Research, Wolfson Institute of Population Health, Queen Mary University of London, UK

Sally A Hull, Honorary Clinical Reader, Wolfson Institute of Population Health, Queen Mary University of London, UK

Anna De Simoni, Clinical Lecturer in Digital Health, Wolfson Institute of Population Health, Queen Mary University of London, UK

Corresponding Author: Dr Paul Pfeffer; Consultant Respiratory Physician, Department of Respiratory Medicine, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK; p.pfeffer@qmul.ac.uk

Word Count: 2771 words

Keywords: asthma, eosinophil, salbutamol, reliever

Characteristics of asthma patients overprescribed short-acting beta-agonist (SABA) reliever inhalers stratified by blood eosinophil count in North East London – a cross-sectional observational study

ABSTRACT

Background: Over-prescription of short-acting beta-agonist (SABA) inhalers and blood eosinophil count have strong associations with exacerbation risk in asthma. However, in our recent publication only a minority of SABA-overprescribed patients (≥6 inhalers in 12 months) were eosinophilic (≥0.3x10^9 cells/L).

Aim: To compare the characteristics of eosinophilic and non-eosinophilic SABA over-prescribed patients, and identify latent classes using clinical variables available in primary care.

Design & setting: Cross-sectional analysis of asthmatic patients in North East London using primary care electronic health record data.

Method: Unadjusted and adjusted multi-variate regression models and latent class analysis.

Results: Eosinophilia was significantly less likely in female patients, those with multiple mental health comorbidities and those with SABA on repeat prescription. Latent class analysis identified 3 classes of SABA over-prescribed patients representing those with classical Uncontrolled Asthma (oral-steroid requiring exacerbations, step 2-3 asthma medications, high probability of being eosinophilic), Mild Asthma (low exacerbation frequency, low asthma medication step, low probability of being eosinophilic), and Difficult Asthma (high exacerbation frequency despite high-strength preventer inhalers, low probability of being eosinophilic). The Mild Asthma class was the largest.

Conclusion: Many patients being over-prescribed SABA are non-eosinophilic with a low exacerbation frequency suggesting disproportionately high SABA prescription compared to other asthma control markers. Potential reasons for high SABA prescription in these patients include repeat prescription (being dispensed but not taken) and use of SABA for non-asthma breathlessness (e.g. breathing pattern disorders with anxiety). Further research is needed into management of SABA overuse in patients without other markers of uncontrolled asthma.

Keywords: asthma, eosinophil, salbutamol, reliever, breathlessness

How this fits in

Overuse of short-acting beta-agonist (SABA) reliever inhalers and peripheral blood eosinophilia are two risk factors both associated with increased risk of asthma exacerbations. Stepping-up inhaled corticosteroids is effective at reducing future exacerbations in eosinophilic patients, however this study showed most asthma patients over-prescribed SABA inhalers are not eosinophilic.

The characteristics of eosinophilic and non-eosinophilic SABA over-prescribed patients were found to be different. Lack of eosinophilia in an asthmatic patient with high SABA use should alert the clinician to look for other causes of overuse, such as inappropriate SABA use for other causes of breathlessness.

Through analysis of routinely collected clinical data, distinct patient subgroups overusing SABA are readily-identifiable by clinicians, potentially prompting different management approaches. More research is needed in this area.

Characteristics of asthma patients overprescribed short-acting beta-agonist (SABA) reliever inhalers stratified by blood eosinophil count in North East London – a cross-sectional observational study

INTRODUCTION

Overuse of short-acting beta-2-agonist (SABA) inhalers, such as salbutamol relievers, is an acknowledged indicator of uncontrolled asthma with increased risk of exacerbations and hospital admissions,[1] [2] yet remains highly prevalent.[3] [4] Indeed SABA overuse can paradoxically worsen asthmatic airways pathology and dampen response to SABA taken when appropriately needed.[5] [6] Additionally as most SABA inhalers are pressurised metred-dose inhalers (pMDIs) their use is associated with a major carbon footprint, harmful to the environment.[7] There is therefore a current focus on reducing patient SABA overuse and over-prescription.

For patients with frequent SABA use most asthma guidelines recommend that the clinician addresses potential poor adherence to preventer medications and inhaler technique, and then considers a step-up in asthma medications including higher-dose inhaled corticosteroids. Such approaches encourage a one-size-fits-all model in contrast to increasing conceptual understanding of asthma as a disease of treatable traits, and that not all 'asthma' symptoms are due to uncontrolled small airways inflammation.[8] Whilst uncontrolled asthma is associated with increased SABA usage, it is less certain whether most patients who overuse SABA have uncontrolled asthma, in terms of active small airways inflammation.

In a recent publication we investigated factors associated with SABA over-prescription in the North East London population, and identified an association with prescription type.[9] The objective of this further evaluation was to examine whether the characteristics of SABA overusing patients differ by presence of an eosinophilia or not, and by potential latent class analysis of SABA over-prescribed patients. Blood eosinophil counts, as a surrogate biomarker of airways Type 2 (T2) inflammation, are increasingly recognised as a marker of exacerbation risk in asthma and an indicator of patients likely to benefit from increased inhaled corticosteroids.[10] [11] Our findings suggest that there are different phenotypes of SABA

overusing patients that may need different approaches to manage their SABA overuse in primary care.

METHODS

Study Population

Patients over-prescribed SABA inhalers in the preceding 12 month period and with a full blood count measured in the last 2 years were selected from our previous evaluation of SABA prescription, using primary care data from over 30 000 patients aged 5-80 with asthma from North East London.[9] Primary care data, including all prescriptions for inhaled asthma medications and courses of oral corticosteroids in the preceding year, was extracted on secure N3 terminals from EMIS Web during October and November 2021. Data extracted on SABA prescriptions included prescribing modality (acute/automatic, repeat dispending, repeat prescribing). All participants had a coded diagnosis of asthma in their primary care electronic medical record. SABA over-prescription was defined as the prescription of 6 or more salbutamol 200-dose 100µg/dose equivalent inhalers in the preceding 12 months as previously described.[9] Potential selection bias was addressed by including all patients with asthma from all primary care practices in the region. Use of clinical data extracted from regional standard-of-care templates for clinical care addressed potential information bias.

Outcome and determinant variables

Blood eosinophil counts, undertaken as part of clinically-indicated full blood counts, were extracted from primary care medical records. Where patients had had more than one eosinophil count in the preceding 2 years, the count closest to the (evaluation) data extraction date was used. Characteristics were compared between those whose last eosinophil count was $<0.3 \times 10^9$ cells/L (no eosinophilia) and those $\geq 0.3 \times 10^9$ cells/L (eosinophilia).

Patient demographics (age, gender, ethnicity, BMI, smoking history) were extracted as most recently recorded in primary care records. Ethnic categories were based on the 18 categories of the UK 2011 census and were combined into four groups reflecting the study population. Asthma medication step was extracted from the patient's last annual asthma review. Courses oral corticosteroids in preceding year were determined from prescribing records. Medication

prescription refill for inhaled corticosteroids was calculated from prescription data as previously described.[9]

Co-morbidities data were extracted on 16 conditions that form part of the UK Quality and Outcomes Framework (QOF),[12] using the earliest recorded diagnostic code before the start of the study, supplemented by SNOMED codes (www.snomed.org) for chronic rhinitis and generalised anxiety.

Statistics

To compare the characteristics of eosinophilic and non-eosinophilic regression models were undertaken, both unadjusted and adjusted for other variables of interest as described below. Regression models were analysed in R version 4.0.4.

For the latent class analysis, we developed models with blood eosinophil count, courses of oral corticosteroids in preceding year, asthma medication step and SABA prescription type as indicator variables and other variables as covariates. We developed models with 2, 3 and 4 classes and then selected the best one based on Bayesian Information Criterion (BIC). Models with smaller values of BIC are preferred, with the use of additional parameters justified by sufficient improvement in the likelihood of the fitted model. This criterion provides a balance between improvement in fit (represented by increased log-likelihood) and model complexity (represented by the number of parameters used). Based on the BIC values (55394, 55239 and 55457 for 2, 3 and 4 classes), latent class analysis with 3 classes was selected. These analyses were run using package "poLCA" in R version 4.0.4.

Patient and Public Involvement

Input from Asthma UK Centre for Applied Research (AUKCAR) Patient and Public Involvement (PPI) representatives has informed this programme of work addressing SABA overuse,[13] and AUKCAR PPI have reviewed the results of the evaluation of which this publication forms part with their views informing our analysis of the ongoing asthma programme.

Data reporting and availability

This cross-sectional observational research is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. The data analysed

formed part of a service evaluation intrinsic to a regional quality improvement project and under this framework the dataset cannot be publicly released.

RESULTS

In our recent analysis of SABA prescribing in North East London, 10 081 of 30 694 patients with asthma were over-prescribed SABA inhalers (six or more salbutamol 100micrograms/dose (200 dose/inhaler) or equivalent inhalers in the preceding year). On their last blood eosinophil count, 3 507 SABA-overprescribed patients were eosinophilic and 4 375 not eosinophilic (no full blood count for remaining 2 199 patients).

In univariate analyses there were significant differences by eosinophil count in SABA over-prescribed patients in terms of patient characteristics and asthma medication usage. For example, there was an Odds Ratio (OR) of 0.85 for being eosinophilic as compared to non-eosinophilic for ex-smokers referenced to never smoked. In multivariate analysis, factors significantly associated with being eosinophilic included Asian ethnicity (OR 1.78; 95% CI [1.57-1.96]), being on Step 2 or 3 asthma medications (OR 1.28; CI [1.06-1.53]; and 1.30; CI [1.04-1.52]), having received three or more courses of oral steroids in preceding year (OR 1.20; CI [1.18-1.36]). Eosinophilia was less likely in female patients (OR 0.88; CI [0.78-0.95]), those with multiple mental health comorbidities (OR 0.58; CI [0.41-0.78]) or SABA issued through Repeat or Repeat Dispense prescription types (OR 0.81; CI [0.72-0.91]; and 0.69 CI [0.50-0.94]; Table 1).

Given the association with numbers of comorbidities, we further examined whether there might be associations with specific comorbidities (Table 2). Depression, anxiety, comorbid COPD, heart failure and GORD were associated with significantly decreased OR of being eosinophilic. Rhinitis was associated with significantly increased OR.

Given the significant differences in SABA over-prescribed patients by eosinophil count we next examined whether there might be latent subclasses of SABA over-prescribed patients by latent class analysis (LCA). Indicator variables of blood eosinophil count, courses of oral corticosteroids in preceding year, asthma medication step and SABA prescription type were chosen (Figure 1; Supplemental Table S1, Figure S1). A latent class analysis model with three classes was selected in preference to models with two or four classes based on Bayesian Information Criterion (BIC) values.

Class 1 comprised 456 patients and was relatively enriched for patients with an eosinophilia, one or more courses of oral steroids in the preceding year, and step 2 or 3 asthma medications. Classes 2 and 3, relative to Class 1, had lower probabilities for patients to be eosinophilic (in both the probability of a patient being eosinophilic was less than 50%) and higher probabilities for patients having a repeat prescription type for their SABA inhalers.
Class 2 comprised 6627 patients compared to 799 patients in Class 3. Comparing Class 2 and Class 3, those in Class 3 had much higher probabilities for having had courses of oral steroids in the preceding year despite patients in Class 3 having a higher probability of being on higher asthma step medications than patients in Class 2.

DISCUSSION

Summary

There are significant differences in the characteristics of eosinophilic and non-eosinophilic patients with asthma over-prescribed SABA inhalers in the North East London population, with the majority not eosinophilic on their last full blood count. In adjusted multivariate regression models we found eosinophilia in SABA over-prescribed patients to be associated with male gender, Asian ethnicity, multiple courses of oral steroids in preceding year, SABA not of repeat / repeat dispensing prescription modality, and absence of multiple mental health co-morbidities. In terms of specific co-morbidities, eosinophilia was positively associated with rhinitis, and negatively associated with anxiety, depression, gastro-oesophageal reflux, cardiac failure and co-morbid COPD. To further explore these differences, we conducted a latent class analysis with indicator variables of blood eosinophil count, courses oral corticosteroids in preceding year, asthma medication step and SABA prescription type. This identified three latent classes that correspond, as discussed below, to patients with classical eosinophilic Uncontrolled Asthma, those with Difficult Asthma and a class of 'Mild' Asthma patients with high SABA prescription discordant to other measures of asthma control.

Strengths and limitations

The strength of this analysis is the large size of the population studied and use of routine electronic health record data from primary care, reducing potential selection bias.

Furthermore, use of routine clinical data, together with the latent class methodology in particular, revealed patient subgroups readily-identifiable by clinicians in routine primary care practice, potentially prompting different management approaches.

A limitation of this analysis is that we were not able to include all SABA over-prescribed patients from the original evaluation as a minority of patients did not have a blood eosinophil count within the required timeframe. Although the relative sizes of the three latent classes identified may have been affected by that issue, it is unlikely that inclusion of 'missing' patients would have changed the characteristics of the identified latent classes. Although the relative proportions of patients within each latent class may vary geographically with differing healthcare systems and prescribing preferences, the three identified latent classes requiring different interventions are likely to be generalisable to other primary care asthma populations.

Comparison with existing literature

The associations identified in our regression studies are consistent with those reported in other populations. For example, the association between mental health comorbidities and SABA over-prescription in non-eosinophilic patients is consistent with previous studies showing an association between SABA overuse and mental health conditions,[14] but we extend the finding to show this association is a particular feature in non-eosinophilic patients. The association between eosinophilia and frequent exacerbations is well-described in poorly-controlled asthma.[8 10 11] The higher prevalence of eosinophilia in Asian patients with poorly-controlled asthma in this evaluation is consistent with reports of differences by ethnicity in characteristics of severe asthma patients in the UK.[15] Differences by gender have also been described in severe asthma, consistent with our findings in a broader population of asthma patients. For example, Eastwood and colleagues have recently reported poor symptom control with discordantly low biomarker levels is particularly a feature in female severe asthma patients.[16]

Our latent class analysis extends the published literature by identifying that the subgroup of eosinophilic, exacerbating asthma patients is a minority of the larger population of SABA over-prescribed asthma patients. Latent class analysis is a form of cluster analysis that can include categorical variables and is designed to identify latent clusters within a population. Cluster analyses have been conducted in asthma research before, but predominantly in severe

asthma. Haldar *et al.* did include a minority of primary care managed asthma patients in their cluster analysis of predominantly severe asthma patients, and interestingly reported a symptomatic female-predominant cluster with absent eosinophilic airway inflammation, a cluster with concordant symptoms and eosinophilic airway inflammation, and a cluster with few symptoms and absent eosinophilia.[17] Our research extends the understanding of SABA over-prescription in asthma patients by describing subgroups easily identifiable by routine clinical markers in primary care, including blood eosinophil count, and these have significant implications for clinical practice, as described below.

Implications for practice and research

The three latent classes identified correspond to distinct patient groups for which different approaches are required in primary care if their SABA over-prescription is to be safely addressed. Class 1 in the LCA was enriched for eosinophilic patients with uncontrolled asthma, who would likely respond to guideline-based review and increase in inhaled corticosteroids in primary care. We have therefore termed this class classical Uncontrolled Asthma. In these patients switching to a combined anti-inflammatory reliever may be a pragmatic approach to ensuring adequate inhaled corticosteroids to prevent future exacerbations.[18 19] However, these patients with classical Uncontrolled Asthma, that are the focus of most guidelines, were a minority of the entire population of patients over-prescribed SABA.

On the other side, many of the patients in Class 3 had been prescribed multiple courses of oral steroids despite being on higher-step asthma medications, identifying them as patients who may benefit from referral to specialist severe asthma services, as recommended in most guidelines – and we have therefore termed this class Difficult Asthma.[20] Many patients in Class 3 were not eosinophilic and potentially their symptoms and exacerbations might be secondary to other causes than asthma, for example inducible laryngeal obstruction and breathing pattern disorders.[21] However, the addition of Tezepelumab to the biologics armamentarium has extended the range of severe asthma patients who benefit from biologics to include those without current eosinophilia or other raised T2 biomarker, and the lack of raised inflammatory biomarkers should not dissuade primary care clinicians from referring these patients to regional Difficult Asthma services.[22]

Although a single eosinophil count cannot exclude uncontrolled T2 airways inflammation, the high proportion of patients who were not eosinophilic suggests many patients are being over-prescribed SABA despite controlled airway inflammation and low exacerbation risk as exemplified by patients in Class 2. We have termed this class Mild Asthma given the low medication step for most of these patients and low exacerbation frequency (despite discordant high SABA prescription).

The majority of patients in Class 2 were receiving their SABA inhalers under repeat prescription (or repeat dispensing) and may be receiving unwanted repeat prescriptions of SABA inhalers they are not using. Switching SABA prescription-type for these patients to as-requested acute prescriptions may significantly reduce over-prescription, and addressing SABA prescription-type should be included in future asthma guidelines.

However approximately 20% of Mild Asthma patients (Class 2) were receiving multiple SABA inhalers through acute prescriptions suggesting actual overuse despite a low proportion of these patients being eosinophilic. SABA inhalers may be being taken inappropriately for other causes of breathlessness, such as breathing pattern disorders and anxiety, which needs further research. Stepping up the strength of their inhaled corticosteroids in unlikely to be beneficial in these non-eosinophilic patients and may be associated with unwarranted inhaled corticosteroid side-effects. Alternative strategies for managing symptoms in these patients are needed.[23 24] How best to manage such patients is not a focus of most asthma guidelines despite these patients being in the majority in our latent class analysis. Importantly, frequent usage of SABA for complex breathlessness is likely associated with extra-pulmonary side-effects of excess B-adrenergic stimulation in addition to the complications of not actually treating the underlying pathology driving the breathlessness.[25 26]

Research is now needed in how to reduce SABA usage in those patients over-using despite control of underlying asthmatic airways inflammation. SABA reduction / withdrawal needs to be done with a safe approach but also in a manner that respects the complex health beliefs of many patients who over-use SABA inhalers.[27 28] Elements of an inpatient SABA withdrawal programme have been described,[29] but given the numbers of patients overusing SABA consideration needs to be given to how this can be safely done in the community.

Conclusions

There are significant characteristic differences amongst asthma patients over-prescribed SABA between those who are and are not eosinophilic. In a latent class analysis, in the largest class of patients (Class 2) only a minority were eosinophilic on their last blood eosinophil count. The lack of eosinophilia in many SABA over-prescribed patients raises concern that these patients are either collecting but not using the inhalers, or inappropriately using SABA inhalers for other causes of breathlessness. Research and guidelines are now needed on how to manage SABA over-use in patients inappropriately taking excessive doses despite controlled airways inflammation.

Figure Legends

Figure 1: Characteristics of latent classes of SABA-overprescribed patients

Radar plots for each Class showing the asthma medication step and number of oral steroids courses in preceding year of highest probability for members of that class (horizontal positive and negative spokes); ratio of (probabilities for) members having SABA on Repeat prescription vs other prescription type, and for an eosinophil count ≥0.3 vs $<0.3 \times 10^9$ cells/L (vertical positive and negative spokes). Variables in LCA analysed as categorical with levels for radar plot axis steps as per embedded table.

Funding: The project was funded by Barts Charity reference MGU0419 as part of the REAL-Health: REsearch Actionable Learning Health Systems Asthma programme.

Ethical Approval: These findings are from a service evaluation of the REAL-Health: REsearch Actionable Learning Health Systems Asthma programme, conducted by the programme team. Ethical approval was not required for this service evaluation as patient-level data were anonymised, and only aggregated patient data are reported in this study. All GPs in the participating East London practices consented to the use of their anonymised patient data for research and development for patient benefit.

Declarations of Interest: PEP has attended advisory board for AstraZeneca, GlaxoSmithKline and Sanofi; has given lectures at meetings with/without lecture honoraria supported by AstraZeneca and GlaxoSmithKline; has attended international conferences with AstraZeneca; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis and Sanofi; and is conducting research funded by GlaxoSmithKline for which his institution receives remuneration. None of these are directly relevant to the research in this publication.

Acknowledgments: The authors are grateful to the participating GPs for their cooperation without which such studies would be impossible. The authors wish to thank staff at the Clinical Effectiveness Group (CEG), QMUL, for supporting practices with guidance and data-entry tools that support this project.

361 **Table 1**

362

Adult patients (>=18)		Patients (n)		Univariate OR	Multivariate OD (95% CI)
		Eos < 0.3 n=4375	Eos ≥ 0.3 n=3507	Eos ≥ 0.3	Eos ≥ 0.3 x10^9 cells/L
Age	Adult (18-60)	3160	2591	ref	ref
	Older adult (>60)	1215	916	0.92	0.91 (0.81-1.02)
Sex	Male	1756	1521	ref	ref
	Female	2619	1986	**0.88**	**0.88** (0.78-0.95)
BMI	Normal	859	679	ref	ref
	Underweight	65	39	0.76	0.83 (0.55-1.27)
	Overweight	1136	988	1.10	1.10 (0.95-1.25)
	Obese	1608	1305	1.03	1.12 (0.97-1.26)
	Unknown	707	496	0.89	0.97 (0.83-1.14)
Ethnicity	White	1881	1167	ref	ref
	Mixed	147	107	**1.82**	0.88 (0.61-1.12)
	Asian or Asian British	1505	1714	**1.84**	**1.78** (1.57-1.96)
	Black	500	303	0.98	0.93 (0.79-1.10)
	Other/unclassified	342	216	1.02	0.99 (0.83-1.14)
IMD score	1 (least deprived)	600	458	ref	ref
	2	779	590	0.99	0.91 (0.76-1.07)
	3	973	804	1.08	0.93 (0.78-1.08)
	4	1035	878	1.11	0.99 (0.83-1.14)
	5 (most deprived)	988	777	1.03	0.95 (0.80-1.12)
Smoking	Never	2567	2166	ref	ref
	Current	829	632	0.90	1.03 (0.89-1.16)
	Ex	972	698	**0.85**	0.96 (0.84-1.07)
	Unknown	7	11	1.86	2.34 (0.64-6.27)
Asthma Medication Step	step 1	388	252	ref	Ref
	step 2	1689	1471	**1.34**	**1.28** (1.06-1.53)

	step 3	952	830	**1.34**	**1.30** (1.04-1.52)
	step 4+step5	185	133	1.11	1.15 (0.80-1.44)
	unknown	1161	821	1.09	1.15 (0.94-1.37)
Oral Steroid	zero	3256	2504	ref	ref
	1	596	526	**1.15**	1.12 (1.00-1.30)
	2	209	196	**1.22**	**1.20** (1.12-1.33)
	>=3	314	281	**1.16**	**1.20** (1.18-1.36)
Physical health	0	1110	806	ref	ref
	1	1499	1221	**1.12**	1.10 (0.97-1.24)
	2-3	1385	1190	**1.18**	1.11 (0.97-1.25)
	≥4	381	290	1.05	0.94 (0.76-1.13)
Mental health	0	2468	2146	ref	ref
	1	906	679	**0.86**	0.90 (0.79-1.25)
	2	878	623	**0.82**	0.89 (0.78-1.00)
	3	123	59	**0.55**	**0.58** (0.41-0.78)
MPR category	zero	306	196	ref	ref
	under use	885	712	**1.26**	1.17 (0.92-1.42)
	reasonable use	2175	1809	**1.30**	1.19 (0.94-1.42)
	over use	1009	790	**1.22**	1.11 (0.88-1.35)
Prescription Type	Acute+Automatic	737	707	ref	ref
	Repeat	3517	2725	**0.81**	**0.81** (0.72-0.91)
	Repeat Dispensed	121	75	**0.65**	**0.69** (0.50-0.94)

Table 1: Characteristics of patients with 6 or more short-acting beta-agonist (SABA) bronchodilator relievers prescribed over preceding year stratified by last blood eosinophil count.

Odds Ratios (OR) with p value significance < 0.05 in bold. MPR; medication prescription refill rate (categories as previously defined).[9] Multivariate analyses include adjustment for all other factors listed.

370

371 **Table 2**

372

Adult patients (>=18)		Patients with SABA >=6 (n)		Univariate OD	+ adjustment (95% CI)
		Eos < 0.3 n=4375	Eos ≥ 0.3 n=3507	Eos ≥ 0.3	Eos ≥ 0.3 x10^9 cells/L
Co-morbidities	Atrial Fibrillation	93	58	0.77	0.80 (0.57-1.12)
	Cancer	161	106	0.82	0.85 (0.65-1.09)
	CHD	244	237	**1.23**	1.09 (0.90-1.32)
	CKD	332	264	0.99	0.99 (0.83-1.17)
	COPD	15	5	**0.42**	**0.37** (0.12-0.97)
	Dementia	20	11	0.69	0.61 (0.28-1.28)
	Depression	1330	902	**0.79**	**0.85** (0.77-0.94)
	Diabetes	963	843	**1.12**	0.98 (0.88-1.09)
	Epilepsy	123	75	**0.76**	0.78 (0.588-1.06)
	Heart Failure	94	55	0.73	**0.71** (0.50-1.00)
	Hypertension	1390	1100	0.98	0.96 (0.87-1.06)
	Learning Disabilities	57	35	0.76	0.77 (0.49-1.17)
	Mental health	219	149	0.84	0.86 (0.69-1.07)
	Palliative care	26	16	0.77	0.69 (0.36-1.29)
	Peripheral Arterial Disease	29	22	0.95	0.94 (0.52-1.64)
	Stroke & TIA	109	78	0.89	0.90 (0.66-1.21)
	Anxiety	1482	1051	**0.84**	**0.89** (0.81-0.98)
	Gastro-oesophageal	846	633	0.92	**0.85** (0.76-0.96)
	Rhinitis	1945	1799	**1.32**	**1.22** (1.12-1.34)

373

374 **Table 2: Comorbidities in patients with 6 or more short-acting beta-agonist (SABA)**
375 **bronchodilator relievers over preceding year stratified by last blood eosinophil count.**
376 Odds Ratios (OR) with p value significance < 0.05 in bold. Univariate OR, and multivariate OR
377 after additional adjustment for sex, ethnicity, asthma medication step, oral steroid courses
378 and prescription type.

379

References

1. Quint JK, Arnetorp S, Kocks JWH, et al. Short-Acting Beta-2-Agonist Exposure and Severe Asthma Exacerbations: SABINA Findings From Europe and North America. *J Allergy Clin Immunol Pract*. Mar 29 2022;doi:10.1016/j.jaip.2022.02.047
2. Hull SA, McKibben S, Homer K, Taylor SJ, Pike K, Griffiths C. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. *NPJ Prim Care Respir Med*. Aug 18 2016;26:16049. doi:10.1038/npjpcrm.2016.49
3. Janson C, Menzies-Gow A, Nan C, et al. SABINA: An Overview of Short-Acting β. *Adv Ther*. Mar 2020;37(3):1124-1135. doi:10.1007/s12325-020-01233-0
4. Bloom CI, Cabrera C, Arnetorp S, et al. Asthma-Related Health Outcomes Associated with Short-Acting β. *Adv Ther*. 10 2020;37(10):4190-4208. doi:10.1007/s12325-020-01444-5
5. Taylor DR. The beta-agonist saga and its clinical relevance: on and on it goes. *Am J Respir Crit Care Med*. Jun 01 2009;179(11):976-8. doi:10.1164/rccm.200901-0055CC
6. Reisman RE. Asthma induced by adrenergic aerosols. *J Allergy*. Sep 1970;46(3):162-77. doi:10.1016/0021-8707(70)90095-x
7. Wilkinson A, Woodcock A. The environmental impact of inhalers for asthma: A green challenge and a golden opportunity. *Br J Clin Pharmacol*. Jul 2022;88(7):3016-3022. doi:10.1111/bcp.15135
8. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *The Lancet*. 2017;doi:10.1016/s0140-6736(17)30879-6
9. De Simoni A, Hajmohammadi H, Pfeffer P, Cole J, Griffiths C, Hull S. Reducing SABA overprescribing in asthma: lessons from a Quality Improvement prescribing project in East London. *British Journal of General Practice*. 2022;
10. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med*. Nov 2015;3(11):849-58. doi:10.1016/S2213-2600(15)00367-7
11. Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med*. 07 2020;8(7):671-680. doi:10.1016/S2213-2600(20)30053-9

12. NHS Digital Quality and outcomes framework. 2020. p. 21. https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2020-21 (accessed 23 June 2022).

13. McKibben S, Bush A, Thomas M, Griffiths C. "Tossing a coin:" defining the excessive use of short-acting beta. *NPJ Prim Care Respir Med*. Jul 18 2018;28(1):26. doi:10.1038/s41533-018-0096-4

14. Gerald JK, Carr TF, Wei CY, Holbrook JT, Gerald LB. Albuterol Overuse: A Marker of Psychological Distress? *J Allergy Clin Immunol Pract*. 2015;3(6):957-62. doi:10.1016/j.jaip.2015.06.021

15. Busby J, Heaney LG, Brown T, et al. Ethnic Differences in Severe Asthma Clinical Care and Outcomes: An Analysis of United Kingdom Primary and Specialist Care. *J Allergy Clin Immunol Pract*. Oct 07 2021;doi:10.1016/j.jaip.2021.09.034

16. Eastwood MC, Busby J, Jackson DJ, et al. A randomised trial of a T2-composite-biomarker strategy adjusting corticosteroidtreatment in severe asthma, a post- hoc analysis by sex. *J Allergy Clin Immunol Pract*. Jan 05 2023;doi:10.1016/j.jaip.2022.12.019

17. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. Aug 1 2008;178(3):218-24. doi:10.1164/rccm.200711-1754OC

18. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med*. May 17 2018;378(20):1865-1876. doi:10.1056/NEJMoa1715274

19. Kaplan A, Mitchell PD, Cave AJ, Gagnon R, Foran V, Ellis AK. Effective Asthma Management: Is It Time to Let the AIR out of SABA? *J Clin Med*. Mar 27 2020;9(4)doi:10.3390/jcm9040921

20. Redmond C, Heaney LG, Chaudhuri R, et al. Benefits of specialist severe asthma management: demographic and geographic disparities. *Eur Respir J*. Jul 01 2022;doi:10.1183/13993003.00660-2022

21. Hull JH. Not all wheeze is asthma: time for patients to exercise their rights. *Thorax*. Jan 2015;70(1):7-8. doi:10.1136/thoraxjnl-2014-206096

22. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *N Engl J Med*. May 13 2021;384(19):1800-1809. doi:10.1056/NEJMoa2034975

23. Lehrer PM, Karavidas MK, Lu SE, et al. Psychological treatment of comorbid asthma and panic disorder: a pilot study. *J Anxiety Disord*. May 2008;22(4):671-83. doi:10.1016/j.janxdis.2007.07.001

24. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*. 01 2018;6(1):19-28. doi:10.1016/S2213-2600(17)30474-5

25. Lai CC, Chen CH, Wang YH, Wang CY, Wang HC. The impact of the overuse of short-acting β2-agonists on the risk of sepsis and septic shock. *J Allergy Clin Immunol*. Jul 2022;150(1):75-81.e1. doi:10.1016/j.jaci.2021.11.029

26. Khan MA, Howell A, Pham T, Guzman N. Reverse Takotsubo Cardiomyopathy in the Setting of Acute Asthma Exacerbation. *Cureus*. Jun 2021;13(6):e15469. doi:10.7759/cureus.15469

27. Cole S, Seale C, Griffiths C. 'The blue one takes a battering' why do young adults with asthma overuse bronchodilator inhalers? A qualitative study. *BMJ Open*. 2013;3(2)doi:10.1136/bmjopen-2012-002247

28. Chan AHY, Katzer CB, Horne R, et al. SABA Reliance Questionnaire (SRQ): Identifying Patient Beliefs Underpinning Reliever Overreliance in Asthma. *J Allergy Clin Immunol Pract*. 2020;8(10):3482-3489.e1. doi:10.1016/j.jaip.2020.07.014

29. Taylor DR, Hannah D. Management of beta-agonist overuse: why and how? *J Allergy Clin Immunol*. Oct 2008;122(4):836-838. doi:10.1016/j.jaci.2008.07.025