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ORIGINAL RESEARCH

Disease Burden of Asthma Patients Utilizing Short-Acting Beta-2 Agonist-Only Inhalers as Rescue in the United States

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Purpose: We aimed to describe the disease burden of asthma and examine relationships between short-acting beta-2 agonist (SABA) use and asthma exacerbations.

Patients and Methods: This retrospective cohort study used geographically diverse Premier Healthcare Database (PHD) and linked insurance claims (10/01/2021-09/30/2022) for US patients aged ≥18 years with a SABA-only prescription and a history of asthma exacerbation within 12 months before index date (the earliest SABA prescription date). Three asthma control groups were defined based on SABA usage: well controlled-low (0–1 prescriptions), not well controlled-medium (2–3 prescriptions), very poorly controlled-high (≥4 prescriptions). Four asthma severity groups were defined using asthma medication usage: intermittent, mild persistent, moderate persistent, and severe persistent.

Results: A total of 12,692 patients were included: mean age 38.7 years, 73% female, 54% white, 31% Black, and 70% Medicaid patients. During the 12-month post-index period, 31% (n = 3,889) experienced an exacerbation at a mean rate 0.51 (SD 1.05) per patient. The percentage of patients with low, medium, and high SABA-only prescriptions were 42%, 21%, and 37%, respectively. A greater proportion of high-SABA users had an asthma exacerbation (41%) versus medium- (32%) or low- (20%) SABA users (both $p < 0.0001$). The proportion of patients with asthma maintenance controller use was the highest (71%) among high-SABA users, followed by medium- (56%), and low- (35%) SABA users (all $p < 0.0001$). Mean rates of asthma exacerbation during 12-month post-index period were 0.34 (SD 0.75) in the intermittent, 0.43 (SD 0.87) in the mild persistent, 0.43 (SD 0.82) in the moderate persistent, and 0.73 (SD 1.37) in the severe persistent groups ($p < 0.0001$). Almost a quarter (24%) of patients with intermittent asthma experienced an exacerbation during this period.

Conclusion: Patients with greater use of SABA-only rescue inhalers experienced higher rates of exacerbations, despite having greater asthma controller use. New rescue therapy approaches are needed to decrease the burden of illness in asthma patients.

Plain Language Summary: Inappropriate use of short-acting beta-2 agonist (SABA) among patients with mild asthma is associated with increased risk of progressing to more severe disease. The results of this study show that patients with uncontrolled asthma (ie, greater use of SABA rescue inhaler) experienced higher rates of exacerbations, despite having greater use of maintenance therapy, underscoring the importance of new rescue therapy approaches to decrease the burden of asthma exacerbation among patients with high SABA-only rescue inhaler use.

Keywords: asthma, burden, SABA inhaler, albuterol, rescue therapy

Introduction

Asthma affects approximately 25 million (8%) of the United States (US) population and is associated with significant disease burden.[1] Patients with asthma are at risk of experiencing severe exacerbations which can contribute to asthma

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morbidity and hospitalizations.[2–5] Roughly half of patients with asthma of all severities experience at least one exacerbation in a given year.[6] It is well established that airway inflammation is the main culprit leading to symptoms and unpredictable asthma exacerbations.[7–9] While short-acting beta-2 agonist (SABA)-only inhalers can relieve symptoms, they do not treat the underlying processes of inflammation; anti-inflammatory medications play a vital role in the treatment of asthma and preventing severe exacerbations.[10] SABA-only over-reliance persists as an issue in asthma management, and while guidelines recommend limiting SABA utilization, patients may overuse SABA inhalers to relieve symptoms. There has been a growing body of evidence demonstrating that higher SABA usage is associated with a higher rate of exacerbations.[10–13]

Guidelines have previously focused on symptom management over treating underlying processes in recommending SABA-only inhalers as rescue therapy for all severities of asthma.[10] In 2019, the Global Initiative for Asthma (GINA) published new recommendations that no longer recommends SABA-only rescue therapy for adolescents and adults with asthma.[9] The decision represented a significant change in asthma management and resulted from evidence supporting the incorporation of inhaled corticosteroid (ICS) along with a long-acting beta agonist (LABA) or SABA as optimal rescue therapy to reduce symptoms and exacerbations. This change was also driven by data showing that SABA-only treatment puts patients at an increased risk of worse outcomes and asthma-related death.[14] However, only one ICS-containing rescue therapy became available in the US in 2023, and majority of US patients continue to use SABA-only rescue therapy.[15,16]

The disease burden of asthma patients using SABA-only inhalers as rescue across different asthma severity and control levels is not well understood. The purpose of this study is to assess asthma exacerbation rates across patients with different asthma severity levels and asthma control levels. We also aim to describe treatment patterns, healthcare resource use, and healthcare cost of asthma patients using SABA-only inhalers as rescue.

Materials and Methods

Data Source and Study Design

We performed a retrospective observational cohort study using the Premier Healthcare Database (PHD) and linked closed insurance claims database.[17] The PHD is an all-payer hospital administrative database for geographically diverse inpatient and outpatient visits from more than 1,400 hospitals. The PHD includes more than 86 million yearly outpatient visits in the US since 2012. PHD patients are tracked within the same hospital or hospital system using a unique identifier. The standard hospital discharge files include demographic characteristics, disease states, and a time-stamped log of billed items (eg, procedures, medications, laboratory services, and diagnostic services) at the patient-level, and geographic location, rural/urban populations served, teaching status, and bed capacity at the hospital-level. The linked closed claims data included medical claims such as diagnoses and procedures for exact dates of service, and pharmacy claims such as prescribed medications, prescription date, days of supply, and quantity dispensed.

Institutional review board approval for this study was not required, based on US Title 45 Code of Federal Regulations, Part 46. The PHD has been certified as deidentified and is not considered human subjects research. Study data and recorded information could not be identified directly or through identifiers linked to individuals. No informed consent was pursued. All data were compliant with the Health Insurance Portability and Accountability Act (HIPAA).[18] No permission or license was required to use the PHD data by the Premier research team.

Study Population

Adults (aged ≥ 18 years) who had an outpatient visit with diagnoses of asthma and one or more paid claims for SABA-only inhalers between October 1, 2021, and September 30, 2022, were included in the study. The earliest SABA-only inhaler prescription date was considered as "index" date. Patients were included if they: 1) had one or more asthma exacerbation episode (as defined below) during 12-month pre-index period and 2) had continuous coverage for medical and pharmacy benefits during 12-month pre-index and 12-month post-index periods. Patients were excluded if they: 1) had a history of major respiratory diagnoses including chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, interstitial lung disease, pulmonary hypertension, and tuberculosis during 12-month pre-index period, 2) had

a history of malignancy (except non-melanoma neoplasms of skin) during 12-month pre-index period, or 3) had evidence of pregnancy during 12-month post-index period.

Definition of Asthma Exacerbation

Asthma exacerbation was defined[2,19] if the patient had one of the following: 1) Inpatient admission with a primary diagnosis of asthma or 2) emergency department or urgent care visit with a primary or secondary diagnosis of asthma + filled systemic corticosteroids (defined as oral corticosteroid with at least 3-day supply or a single injection corticosteroid) ± 7-days from the date of visit or 3) office outpatient or telehealth visit with a primary or secondary diagnosis of asthma and filled systemic corticosteroid (as defined above) ± 7-days from the date of visit.

Treatment Stratifications

Asthma control level has been described previously[2,6] and was based on the number of SABA inhaler prescriptions during 12-month post-index period, excluding the index prescription: 1) well-controlled (low SABA use): 0–1 prescription; 2) not well-controlled (medium SABA use): 2–3 prescriptions; and 3) very poorly controlled (high SABA use): ≥4 prescriptions (Table 1a).

Asthma severity level was classified using the National Asthma Education and Prevention Program 2007 steps (intermittent, mild persistent, moderate persistent, and severe persistent) based on asthma maintenance treatment prescriptions in pharmacy claims during the 12-month pre-index period (Table 1b).[2]

Table 1 Study-Specific Treatment Criteria and Corresponding Categorizations for Asthma Control and Severity Levels

a. Asthma control level

Asthma Control	**SABA Categorization**	**Study-Specific Treatment Criteria**
Well-controlled	Low SABA use	0-1 SABA canister prescription
Not well-controlled	Medium SABA use	2–3 SABA canister prescriptions with or without evidence of maintenance prescriptions
Very poorly controlled	High SABA use	≥4 SABA canister prescriptions with or without evidence of maintenance prescriptions

a. Asthma severity level

Asthma Severity	**NAEPP Steps**	**Study-Specific Treatment Criteria**
Intermittent	Step 1	SABA-only, OR with <32 days of maintenance therapy
Mild Persistent	Step 2	Use of SABA/ICS combination, ORonly an LTRA, OR low-dose ICS, OR xanthine
Moderate Persistent	Step 3	Use of a low-dose ICS/LABA, OR both a LTRA and a low-dose ICS, OR a low-dose ICS and xanthine, OR a medium-high-dose ICS only
Severe Persistent	Step 4-6	Use of a medium-high-dose ICS/LABA, OR a medium-high-dose ICS and either a LTRA or xanthine, OR a biologic, OR a chronic corticosteroid user

Abbreviations: NAEPP, National Asthma Education and Prevention Program; SABA, Short-acting beta$_2$-agonist; ICS, Inhaled corticosteroid; LABA, Long-acting beta$_2$-agonist; LTRA, Leukotriene receptor antagonist.

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Patient, Hospital, and Clinical Characteristics, and Healthcare Cost

Baseline patient demographics (ie, age, sex, race, ethnicity, primary payer type) and hospital characteristics including geographical region (ie, Midwest, Northeast, South, or West), hospital size, urbanicity of served population (rural vs urban) and teaching status were provided by the hospitals. Baseline clinical conditions including allergic rhinitis, eczema or atopy, anxiety disorders, chronic rhinosinusitis with or without nasal polyps, depressive disorders, diabetes mellitus, gastroesophageal reflux disease, obstructive sleep apnea, osteoporosis, and pneumonia were identified during any visit within 12 months pre-index period using International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure codes.

Asthma maintenance controllers included inhaled corticosteroid (ICS), long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), dual therapy (ie, ICS + LABA), triple therapy (ie, ICS + LABA + LAMA), leukotriene receptor antagonists (LTRA), xanthines, and respiratory biologics. Asthma-related OCS use was identified in pharmacy claims if prednisone equivalent prescriptions were filled within ± 7 days from any visit with primary or secondary diagnosis of asthma. Non-prednisone OCS doses were converted to prednisone OCS doses.

Asthma exacerbation-related medical and pharmacy cost included the sum of all allowed amounts for visits and prescriptions related to asthma exacerbation episodes during 12-month post-index period. Asthma-related medical and pharmacy cost included the sum of all allowed amounts for visits with primary or secondary diagnosis of asthma and asthma-related prescriptions during 12-month post-index period. Cost variables were set to 90% winsorization (ie, all observations were set to have a maximum value at 95th percentile and a minimum value at 5th percentile). All costs were adjusted to 2022 US dollars based on the Consumer Price Index.[20]

Statistical Analysis

Descriptive statistics were used to present baseline patient and hospital characteristics of asthma patients and their outcomes. Continuous variables were reported as mean (standard deviation) or median (1^{st} quartile, 3^{rd} quartile), and categorical variables were reported as counts and percentages. For descriptive analyses across stratified groups, Kruskal–Wallis rank sum test was used for continuous measures, as indicated, and Pearson's χ^2 test or Fisher's exact test was used for categorical measures. For multiple comparisons across stratified groups, q-values for false discovery rate are shown in addition to p-values. All analyses and figures were performed and generated using R v.3.6.3 or higher (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 12,692 adult asthma patients were identified as meeting the study inclusion criteria (Supplementary Figure 1). Mean age was 38.7 years, 73% were women, 1.5% were Asian, 31% were Black, 54% were white, and 75% were non-Hispanic (Table 2). Most common insurance payer was Medicaid (70%), followed by commercial insurance (22%). Most common comorbid condition was anxiety (40%), followed by depression (35%), gastroesophageal reflux disease (30%), and allergic rhinitis (29%).

Among the 12,692 eligible patients, 42% (n = 5,383) of patients were characterized as well-controlled, 21% (n = 2,603) not well-controlled, and 37% (n = 2,706) had very poorly controlled asthma during 12-month post-index period (Table 2 and Supplementary Table S1). Overall, 40% (n = 5,101) were categorized as intermittent, 5.4% (n = 682) as mild persistent, 17% (n = 2,209) as moderate persistent, and 37% (n = 4,700) as severe persistent during 12-month pre-index period (Table 2 and Supplementary Table S2). Almost half (42%) of patients classified as intermittent did not have well-controlled asthma during 12-month post-index date period (Figure 1).

Asthma Control Level

A higher percentage (75%) of patients with very poorly controlled asthma (ie, needed 4+ SABA inhaler prescriptions) had Medicaid than patients with well-controlled asthma (67%, $p < 0.001$, Table 2). Patients with very poorly controlled asthma were more likely to visit a large (ie, 500+ beds), teaching hospital in the Northeast compared to patients with well-controlled asthma.

Table 2 Demographics, Hospital Characteristics, and Baseline Clinical Characteristics of Asthma Patients Requiring the Use of Rescue Therapy, Stratified by Asthma Control and Severity Levels

Characteristics	Overall	Asthma Control Level*			Asthma Severity Level**			
	N = 12,692	Well-Controlled, N = 5,383	Not Well-Controlled, N = 2,603	Very Poorly Controlled, N = 4,706	Intermittent, N = 5,101	Mild Persistent, N = 682	Moderate Persistent, N = 2,209	Severe Persistent, N = 4,700
Patient Demographics								
Age								
Mean ± SD	38.7 ±13.7	37.4 ±13.9	39.4 ±13.8	39.9 ±13.2	36.0 ±12.8	40.1 ±13.6	39.3 ±14.4	41.2 ±13.7
Sex, n (%)								
Male	3,403 (27)	1,404 (26)	686 (26)	1,313 (28)	1,486 (29)	150 (22)	611 (28)	1,156 (25)
Female	9,289 (73)	3,979 (74)	1,917 (74)	3,393 (72)	3,615 (71)	532 (78)	1,598 (72)	3,544 (75)
Race, n (%)								
White	6,858 (54)	2,992 (56)	1,388 (53)	2,478 (53)	2,706 (53)	398 (58)	1,199 (54)	2,555 (54)
Black	3,912 (31)	1,608 (30)	820 (32)	1,484 (32)	1,660 (33)	158 (23)	660 (30)	1,434 (31)
Asian	190 (1.5)	76 (1.4)	38 (1.5)	76 (1.6)	62 (1.2)	11 (1.6)	41 (1.9)	76 (1.6)
Other	1,355 (11)	549 (10)	272 (10)	534 (11)	526 (10)	101 (15)	226 (10)	502 (11)
Unknown	377 (3.0)	158 (2.9)	85 (3.3)	134 (2.8)	147 (2.9)	14 (2.1)	83 (3.8)	133 (2.8)
Type of Insurance, n (%)								
Medicare	658 (5.2)	251 (4.7)	148 (5.7)	259 (5.5)	169 (3.3)	37 (5.4)	147 (6.7)	305 (6.5)
Medicaid	8,902 (70)	3,600 (67)	1,786 (69)	3,516 (75)	3,882 (76)	429 (63)	1,484 (67)	3,107 (66)
Commercial insurance	2,746 (22)	1,344 (25)	585 (22)	817 (17)	918 (18)	182 (27)	511 (23)	1,135 (24)
Uninsured	75 (0.6)	23 (0.4)	21 (0.8)	31 (0.7)	24 (0.5)	6 (0.9)	11 (0.5)	34 (0.7)
Other/Unknown	311 (2.5)	165 (3.1)	63 (2.4)	83 (1.8)	108 (2.1)	28 (4.1)	56 (2.5)	119 (2.5)
Hospital Characteristics								
Urbanicity of Served Population, n (%)								
Rural	1,434 (11)	639 (12)	260 (10.0)	535 (11)	635 (12)	99 (15)	216 (9.8)	484 (10)
Urban	11,258 (89)	4,744 (88)	2,343 (90)	4,171 (89)	4,466 (88)	583 (85)	1,993 (90)	4,216 (90)
Geographic Location, n (%)								
Midwest	4,068 (32)	1,757 (33)	844 (32)	1,467 (31)	1,549 (30)	219 (32)	751 (34)	1,549 (33)
Northeast	1,836 (14)	645 (12)	343 (13)	848 (18)	628 (12)	72 (11)	372 (17)	764 (16)
South	3,913 (31)	1,787 (33)	820 (32)	1,306 (28)	1,689 (33)	251 (37)	481 (22)	1,492 (32)
West	2,875 (23)	1,194 (22)	596 (23)	1,085 (23)	1,235 (24)	140 (21)	605 (27)	895 (19)

(*Continued*)

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Table 2 (Continued).

Characteristics	Overall	Asthma Control Level*			Asthma Severity Level**			
	N = 12,692	Well-Controlled, N = 5,383	Not Well-Controlled, N = 2,603	Very Poorly Controlled, N = 4,706	Intermittent, N = 5,101	Mild Persistent, N = 682	Moderate Persistent, N = 2,209	Severe Persistent, N = 4,700
***Baseline Clinical Characteristics*, n (%)**								
Allergic Rhinitis	3,699 (29)	1,389 (26)	823 (32)	1,487 (32)	820 (16)	286 (42)	667 (30)	1,926 (41)
Anxiety	5,104 (40)	2,053 (38)	1,117 (43)	1,934 (41)	1,900 (37)	299 (44)	857 (39)	2,048 (44)
Depression	4,442 (35)	1,797 (33)	975 (37)	1,670 (35)	1,633 (32)	251 (37)	782 (35)	1,776 (38)
Gastroesophageal Reflux Disease	3,822 (30)	1,480 (27)	861 (33)	1,481 (31)	1,139 (22)	249 (37)	649 (29)	1,785 (38)
Obstructive Sleep Apnea	1,668 (13)	643 (12)	373 (14)	652 (14)	394 (7.7)	106 (16)	278 (13)	890 (19)

Notes: *See Supplementary Table S1 for additional details and p values. **See Supplementary Table S2 for additional details and p values.

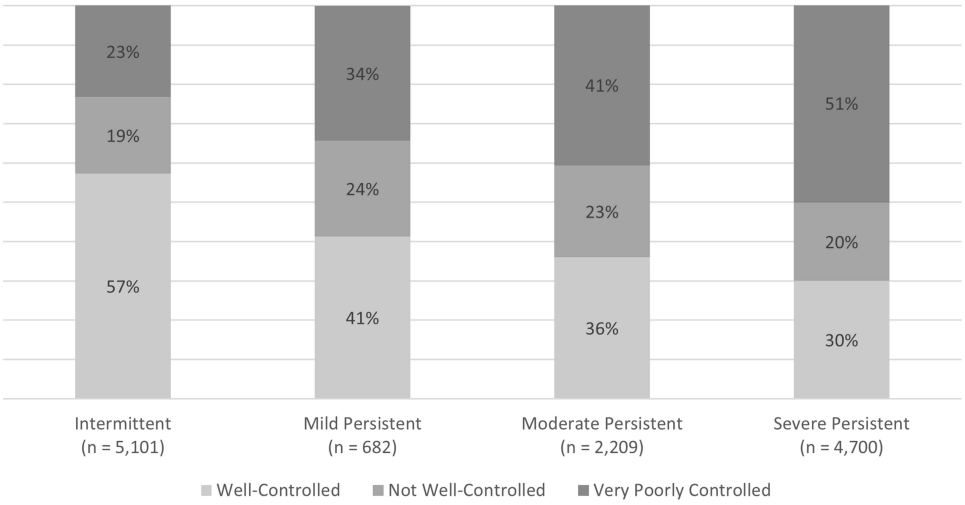

Figure 1 Relationship between asthma control level and asthma severity level.

Significantly higher proportions of patients with very poorly controlled asthma (41%) and not well-controlled asthma (32%) experienced exacerbations during 12-month post-index period compared to well-controlled asthma patients (20%, $p < 0.001$, Table 3). The mean number of asthma exacerbations per year per patient was also significantly higher among very poorly controlled asthma (0.78) and not well-controlled asthma (0.49) patients compared to well-controlled asthma (0.27) patients ($p < 0.001$). Similarly, the mean number of office visits per year per patient due to asthma exacerbation was the highest among very poorly controlled asthma (0.29) and not well-controlled asthma (0.19) compared to well-controlled asthma (0.12) patients ($p < 0.001$).

Up to 42% of patients with very poorly controlled asthma needed OCS for asthma exacerbation, and 10% of these patients received 1,000 mg or more OCS within 1 year. Over two-thirds of patients with very poorly controlled asthma were on asthma maintenance controllers (71%). Most frequently used asthma controllers were LTRA (46%), followed by dual therapy (ICS/LABA) (28%) in this group.

The mean cost of care for asthma among very poorly controlled asthma patients ($3,270) was higher than the cost of care for patients with well-controlled ($2,778) or not well-controlled asthma ($2,851) ($p < 0.001$, Table 3).

Asthma Severity Level

Patients with intermittent (ie, treated with SABA inhaler only) asthma were younger (mean age 36 years) than patients with persistent asthma (mean age 39–41 years, Table 2). A higher percentage (76%) of patients with intermittent asthma had Medicaid than patients with persistent asthma (63–66%). Compared to patients with mild persistent asthma, patients with intermittent asthma were less likely to have allergic rhinitis (16% vs 42%), anxiety (37% vs 44%), gastroesophageal reflux disease (22% vs 37%), and obstructive sleep apnea (8% vs 16%).

Mean number of asthma exacerbations during 12-month post-index period was the lowest in the intermittent group (0.34), but it was still comparable to mild persistent (0.43) and moderate persistent (0.43) groups ($p < 0.001$, Table 4). The proportion of patients with exacerbations was similar amongst the intermittent group and mild persistent group (24% and 27%, respectively) during the 12-month post-index period. The mean number of office visits per year per patient due to asthma exacerbation was the highest in severe persistent group (0.33, $p < 0.001$) and similar between mild persistent (0.19) and moderate persistent (0.16) groups ($p = 0.17$). One in five patients in the intermittent group received OCS for asthma exacerbation during the 12-month post-index period with 14% of these patients receiving 500 mg or greater doses of OCS.

Less than a quarter of patients with intermittent asthma received any maintenance controller during the 12-month post-index period. The mean cost of care for asthma among patients in the intermittent group was $2,470 comparable to $2,446 among patients in the mild persistent group (Table 4).

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Table 3 Asthma-Related Medication, HCRU, and Healthcare Cost Among Asthma Patients Requiring the Use of Rescue Therapy, Stratified by Asthma Control Levels

Characteristic	Overall, N = 12,692	Well-Controlled, N = 5,383	Not Well-Controlled, N = 2,603	Very Poorly Controlled, N = 4,706
Asthma exacerbation-related HCRU during 12-month post-index period*				
Number of asthma exacerbation per patient (times/year)				
Mean ± SD	0.51 ±1.05	0.27 ±0.68	0.49 ±0.87	0.78 ±1.38
Number of patients with asthma exacerbation, n (%)	3,889 (31)	1,101 (20)	843 (32)	1,945 (41)
Hospitalization	526 (4.1)	95 (1.8)	111 (4.3)	320 (6.8)
ED visit	1,921 (15)	518 (9.6)	426 (16)	977 (21)
Urgent care visit	51 (0.4)	8 (0.1)	12 (0.5)	31 (0.7)
Office visit	1,828 (14)	522 (9.7)	369 (14)	937 (20)
Telehealth visit	195 (1.5)	40 (0.7)	43 (1.7)	112 (2.4)
Asthma-related medication use during 12-month post-index period*				
Asthma exacerbation-related oral corticosteroid (OCS) use, n (%)				
Any	3,774 (30)	972 (18)	829 (32)	1,973 (42)
≥500 mg (% among any)	870 (23)	123 (13)	160 (19)	587 (30)
≥1,000 mg (% among any)	265 (7.0)	37 (3.8)	40 (4.8)	188 (9.5)
Asthma maintenance controller use, n (%)				
ICS alone	1,864 (15)	532 (9.9)	417 (16)	915 (19)
ICS + LABA	2,555 (20)	696 (13)	524 (20)	1,335 (28)
ICS + LABA + LAMA	459 (3.6)	96 (1.8)	89 (3.4)	274 (5.8)
LTRA	4,109 (32)	1,073 (20)	879 (34)	2,157 (46)
Xanthines	24 (0.2)	5 (<0.1)	1 (<0.1)	18 (0.4)
Respiratory biologics	379 (3.0)	105 (2.0)	67 (2.6)	207 (4.4)
Any asthma maintenance controller use, n (%)	6,658 (52)	1,878 (35)	1,452 (56)	3,328 (71)
Asthma-related healthcare cost during 12-month post-index period (allowed amount in 2022 USD)*				
Total asthma exacerbation-related medical and pharmacy claims cost				
N	3,018	840	687	1,491
Mean ± SD	$770 ±$1,244	$612 ±$1,119	$715 ±$1,189	$885 ±$1,323
Total asthma-related medical and pharmacy claims cost				
N	6,021	2,091	1,353	2,577
Mean ± SD	$3,005 ±$5,174	$2,778 ±$5,030	$2,851 ±$5,222	$3,270 ±$5,254

Notes: *All p-values and q-values were <0.001. For p-values, Kruskal–Wallis rank sum test, Pearson's Chi-squared test, and Fisher's exact test were used as appropriate. For q-values, false discovery rate correction was used for multiple testing.

Discussion

This retrospective observational study demonstrated that patients with uncontrolled asthma (ie, greater use of SABA rescue inhaler) experienced higher rates of exacerbations, despite having greater use of asthma controllers. Furthermore, a significant proportion of patients who were treated as having intermittent asthma had uncontrolled asthma and were not free from asthma exacerbations or OCS use.

Almost 60% of the patients in our study cohort had filled 2 or more SABA inhalers, indicating uncontrolled asthma. Amongst those filling 2 or more SABA inhalers, 32–41% of these patients experienced asthma exacerbations and required OCS prescriptions. This is consistent with a previous retrospective observational study using large employer Commercial insurance and Medicare advantage claims database, where exacerbation risk increased with increasing SABA prescriptions.[6] Even with minimized cost barrier, Lugogo et al found that exacerbations requiring the use of systemic corticosteroid were common, especially among patients with medium to high SABA

Table 4 Asthma-Related Medication, HCRU, and Healthcare Cost Among Asthma Patients Requiring the Use of Rescue Therapy, Stratified by Asthma Severity Levels

Characteristic	Overall, N = 12,692	Intermittent, N = 5,101	Mild Persistent, N = 682	Moderate Persistent, N = 2,209	Severe Persistent N = 4,700
Asthma exacerbation-related HCRU during 12-month post-index period*					
Number of asthma exacerbation per patient (times/year)					
Mean ± SD	0.51 ±1.05	0.34 ±0.75	0.43 ±0.87	0.43 ±0.82	0.73 ±1.37
Number of patients with asthma exacerbation, n (%)	3,889 (31)	1,216 (24)	187 (27)	659 (30)	1,827 (39)
Hospitalization, n (%)	526 (4.1)	156 (3.1)	24 (3.5)	91 (4.1)	255 (5.4)
ED visit, n (%)	1,921 (15)	705 (14)	91 (13)	315 (14)	810 (17)
Urgent care visit, n (%)	51 (0.4)	13 (0.3)	2 (0.3)	9 (0.4)	27 (0.6)
Office visit, n (%)	1,828 (14)	415 (8.1)	97 (14)	287 (13)	1,029 (22)
Telehealth visit, n (%)	195 (1.5)	47 (0.9)	5 (0.7)	32 (1.4)	111 (2.4)
Asthma-related medication use during 12-month post-index period*					
Asthma exacerbation-related oral corticosteroid (OCS) use, n (%)					
Any	3,774 (30)	1,078 (21)	191 (28)	648 (29)	1,857 (40)
≥500 mg (% among any)	870 (23)	155 (14)	35 (18)	111 (17)	569 (31)
≥1,000 mg (% among any)	265 (7.0)	37 (3.4)	5 (2.6)	22 (3.4)	201 (11)
Asthma maintenance controller use, n (%)					
ICS alone	1,864 (15)	414 (8.1)	76 (11)	660 (30)	714 (15)
ICS + LABA	2,555 (20)	380 (7.4)	84 (12)	370 (17)	1,721 (37)
ICS + LABA + LAMA	459 (3.6)	67 (1.3)	6 (0.9)	50 (2.3)	336 (7.1)
LTRA	4,109 (32)	576 (11)	508 (74)	662 (30)	2,363 (50)
Xanthines	24 (0.2)	4 (<0.1)	2 (0.3)	3 (0.1)	15 (0.3)
Respiratory biologics	379 (3.0)	22 (0.4)	6 (0.9)	12 (0.5)	339 (7.2)
Any asthma maintenance controller use, n (%)	6,658 (52)	1,186 (23)	534 (78)	1,367 (62)	3,571 (76)
Asthma-related healthcare cost during 12-month post-index period (allowed among in 2022 USD) *					
Total asthma exacerbation-related medical and pharmacy claims cost					
N	3,018	969	153	515	1,381
Mean ± SD	$770 ±$1,244	$540 ±$996	$611 ±$1,152	$846 ±$1,328	$921 ±$1,350
Total asthma-related medical and pharmacy claims cost					
N	6,021	2,111	338	1,056	2,516
Mean ± SD	$3,005 ±$5,174	$2,470 ±$4,827	$2,446 ±$4,717	$3,011 ±$5,062	$3,526 ±$5,500

Notes: *All p-values and q-values were <0.001. For p-values, Kruskal–Wallis rank sum test, Pearson's Chi-squared test, and Fisher's exact test were used as appropriate. For q-values, false discovery rate correction was used for multiple testing.

prescriptions.[6] Pollack et al[2] also found that each increase in SABA prescription was associated with a 26% increased incidence of an asthma exacerbation episode.

An observational, retrospective study by Lanz et al[19] found that 16% of patients 12 years and older treated as intermittent or mild persistent asthma experienced one or more exacerbation events within a 12-month period. In our cohort of adult asthma patients, the proportions of patients experiencing an asthma exacerbation episode were higher, at 24% for patients with intermittent asthma, and 27% for patients with mild persistent asthma.

We identified that the mean number of asthma exacerbations, number of patients with asthma exacerbations, and asthma-related OCS use were comparable between patients with intermittent vs mild persistent asthma. However, between the two groups of patients, 88% (n = 5,101) were treated as intermittent asthma and did not receive maintenance controllers while

only 12% (n = 682) were treated as mild persistent asthma. Lugogo et al[21] also found that in their study cohort of 533,679 patients with intermittent and mild persistent asthma, 70% (n = 373,471) were treated as intermittent asthma. Because 70% of our study cohort were Medicaid patients and the proportion of Medicaid was the highest among patients with intermittent asthma (76%) compared to those with mild, moderate, or persistent asthma (63–67%), greater access barrier to maintenance controller may have been present for patients with intermittent asthma. From the perspective of entire study cohort, mild persistent asthma group had the least number of patients (n = 682, 5.4%), compared to intermittent asthma (n = 5,101, 40%), moderate persistent asthma (n = 2,209, 17%) and severe persistent asthma (n = 4,700, 37%) groups, indicating further that patients with mild persistent asthma may be identified poorly in the US. In addition, our study suggests that many patients with intermittent asthma could have benefited from more optimized guideline directed medical therapy such as utilization of ICS/LABA or ICS/SABA as their rescue regimen or improved controller therapy as a significant proportion (43%) of these patients had uncontrolled asthma during 12-month post-index period.

Lanz et al[19] reported that in their cohort of patients with intermittent or mild persistent asthma, 81% did not fill anti-inflammatory therapies and instead had greater SABA prescriptions in the 30 days prior to an asthma exacerbation. Many of these patients filled their maintenance controllers after the exacerbation episode, but this reactive approach did not prevent 13% of these patients with subsequent asthma exacerbation episodes. A growing body of evidence supports the need for incorporation of ICS along with LABA or SABA as part of an asthma rescue regimen prior to the exacerbation episode to reduce the disease burden of asthma, regardless of asthma severity levels and asthma control levels. Considering that 70–80% of patients with mild asthma in the US do not have anti-inflammatory therapies, a new approach to rescue therapy, such as concomitant use of SABA and ICS, can be especially beneficial for patients with intermittent asthma.

Limitations

This study has several limitations. First, this was a secondary data analysis using a hospital and claims administrative database. Many clinical conditions were captured by ICD-10 diagnosis or procedure codes or National Drug Codes. Potential coding errors may affect the accuracy of patient identification and stratification. Furthermore, because of the cyclical nature of the relationship between SABA use and asthma symptoms, patients could have used more SABA-only inhaler because they were having more symptoms and exacerbations, not the other way around. Because we used PHD-claims linked dataset, all patients have had at least one visit (inpatient or outpatient) to the hospital or hospital system in the past. This may bias the study population towards patients with more comorbidities compared to asthma patients without any visits to hospitals. The findings may not be generalizable to the broader asthma population because the study required patients with a history of exacerbation(s). We were not able to assess medication adherence and presumed that the medications were taken as instructed when they were filled. Asthma severity levels and control levels were proxied using presence and numbers of filled prescriptions, and this could have resulted in misclassifications.

Conclusions

Patients with greater use of SABA-only rescue inhaler experienced higher rates of exacerbations, despite having greater asthma controller use. The need to implement anti-inflammatory therapy earlier in the patient's asthma journey (ie, prior to an asthma exacerbation) was evidenced by comparable asthma exacerbation rates between patients with intermittent and mild persistent asthma. The delay in implementing guideline recommendations of using ICS with SABA or LABA as rescue therapy may put patients at a higher risk of asthma exacerbations.

Abbreviations

ICS, inhaled corticosteroid; ICD-10, International Classification of Diseases, Tenth Revision; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonists; PHD, Premier Healthcare Database; SABA, short-acting beta-2 agonist; US, United States.

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