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Trajectory Analyses of Adherence Patterns in a Real-Life Moderate to Severe Asthma Population

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What is already known about this topic? When asthma is uncontrolled with combinations of high-dose inhaled corticosteroid/long-acting β -agonist (ICS/LABA), additional Global Initiative for Asthma (GINA) step 5 therapies (eg, oral corticosteroids, biologics, long-acting muscarinic antagonists) can be considered. It is recommended that adherence to ICS/LABA be optimized before such add-on therapy.

What does this article add to our knowledge? This article provides insights into real-world GINA step 5 add-on patterns after ICS/LABA initiation and their association with adherence to initial ICS/LABA.

How does this study impact current management guidelines? Four percent of patients with asthma initiating ICS/LABA receive additional GINA step 5 therapies, mainly maintenance oral corticosteroids. However, over 80% of patients commencing additional GINA-5 therapies had poor adherence to ICS/LABA. Objective adherence assessment and tailored interventions may reduce the oral corticosteroid burden.

BACKGROUND: Global Initiative for Asthma step 5 therapies (GINA-5), other than inhaled corticosteroids and long-acting β -agonists in fixed dose combinations (ICS/LABA FDC), often entail more expensive (eg, monoclonal biologics) or less safe (eg, maintenance oral corticosteroids [OCS]) treatments. It is therefore important to assess poor inhaler adherence as a possible cause of suboptimal response to ICS/LABA FDC before additional GINA-5.

OBJECTIVE: To determine rates of, and time to, additional GINA-5 after first-year ICS/LABA FDC use, and their association with inhaler adherence.

METHODS: Patients initiating ICS/LABA FDC between 2013 and 2017 were identified from Australian national dispensing data. Group-based trajectory modeling was used to estimate

medication adherence patterns. Multivariable Cox proportional hazards models were used to examine the association between adherence trajectories and GINA-5 addition during 2-year follow-up.

RESULTS: In total, 3062 new ICS/LABA FDC users were identified, of whom 120 (3.9%) received additional GINA-5 (OCS: 89; long-acting muscarinic antagonists: 39; biologics: <3). Mean time to commencing additional GINA-5 was 705.2 (standard deviation, 1.7) days. Adherence trajectories were nonpersistent use (20%), seasonal use (8%), poor adherence (58%), and good adherence (13%). Although poor adherence was associated with longer time to additional GINA-5 (adjusted hazard ratio: 0.58; 95% confidence interval: 0.35-0.95), over 80% of additional GINA-5 was commenced in poorly adherent

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Abbreviations used

CI- Confidence interval
 FDC- Fixed dose combination
 GBTM- Group-based trajectory modeling
 GERD- Gastroesophageal reflux disease
 GINA- Global Initiative for Asthma
 GP- General practitioner
 HR- Hazard ratio
 ICS- Inhaled corticosteroid
 IQR- Interquartile range
 LABA- Long-acting β -agonist
 LAMA- Long-acting muscarinic antagonist
 OCS- Oral corticosteroid
 PBS- Pharmaceutical Benefits Scheme
 SABA- Short-acting β -agonist
 SD- Standard deviation

patients. Use of ≥ 2 OCS/antibiotic courses also predicted additional GINA-5.

CONCLUSIONS: Almost 1 in 20 people with asthma commenced additional GINA-5 after ICS/LABA initiation, most of whom (>80%) were poorly adherent to inhaled preventers. There is a substantial unmet need for inhaler adherence to be addressed before prescribing additional GINA-5. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1961-9)

Key words: Asthma; Medication adherence; Biologics; Oral corticosteroids; Inhaler; Pharmacoepidemiology; Compliance; Persistence; Guidelines

International treatment guidelines recommend a stepwise approach in the management of asthma.¹ The Global Initiative for Asthma (GINA) 2019 guidelines recommend that in patients who remain uncontrolled despite high-dose inhaled corticosteroids/long-acting β -agonists (ICS/LABA), additional GINA step 5 (GINA-5) therapies can be initiated.¹ These include monoclonal antibody therapy (eg, anti-IgE, anti-IL-5, anti-IL4/13), maintenance oral corticosteroids (OCS), or long-acting muscarinic antagonists (LAMA).

Because of its local action and availability of generic equivalents, ICS/LABA therapy is relatively safe and affordable.² In contrast, additional GINA-5 therapy increases costs (eg, biologics³) and/or the risk of substantial side effects (eg, maintenance OCS⁴) and should therefore be preceded by careful clinical and behavioral evaluation. Medication adherence is an integral part of this behavioral evaluation. Although it is highly recommended that medication adherence to ICS/LABA be optimized, especially when considering biological therapy,^{1,5} the extent to which this recommendation is followed in clinical practice is unknown.

It can be challenging for busy clinicians to objectively assess medication adherence during routine consultations.⁶ Self-reported adherence and clinicians' judgment of adherence are often overestimated.^{7,8} Promising adherence advances on the clinical horizon include digital solutions⁹ and biochemical measures.¹⁰ However, until they find their way into routine clinical practice, pharmacy dispensing data remain one of the most objective measures of adherence in large populations.⁷ In particular, novel analytic techniques such as group-based

trajectory modeling (GBTM) provide granular insights into patients' longitudinal patterns of real-world drug utilization.¹¹ Although already applied in other chronic diseases, GBTM has not been used to assess asthma medication adherence.

The aim of this study was to assess the rates of, and time to, additional GINA-5 therapy in people with asthma initiating ICS/LABA in fixed dose combinations (ICS/LABA FDC), and to examine the impact of different adherence trajectories. We hypothesized that adherent patients would receive less additional GINA-5 therapy compared with poorly adherent patients. A secondary objective was to identify other clinical and demographic predictors for additional GINA-5 therapy initiation, including disease severity and specific comorbidities.

METHODS

Study design

This was a retrospective cohort study of people with asthma initiating ICS/LABA FDC in Australia subsidized via the national Pharmaceutical Benefits Scheme (PBS). A 1-year preindex period to assess inclusion and exclusion criteria was followed by a 1-year postindex period to assess adherence trajectories and other predictors for additional GINA step 5 medications (Figure 1). The outcome was assessed by estimating the time to whichever occurred earliest: additional GINA step 5 medication dispensed, death, or the end of the study period (August 2018). The study was registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS28437) and reported according to STROBE Strengthening the Reporting of Observational Studies in Epidemiology guidance (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).¹² An overview of the study design is presented in Figure 1.

Data, data source, and setting

Dispensing data for the period July 1, 2012, to August 31, 2018, were extracted from a 10% random sample of the Australian PBS database.¹³ The PBS subsidizes the costs of medications for Australian citizens, permanent residents, and foreign visitors from countries with reciprocal health care agreements. Medication in Australia is subject to a copayment of which the cost to patients varies depending on whether or not a patient has a concession card (eg, pensioners, people with low income, war veterans). In the PBS database, data on dispensing from all community pharmacies and private hospitals are included. Data are also included on hospital outpatient and discharge dispensing from public hospitals in all Australian states and territories except New South Wales and the Australian Capital Territory. The Australian Bureau of Statistics has validated the 10% random sample of the PBS population to be representative of the total Australian population. The use of PBS data in research has been described previously,¹³ and data have been widely used in previous studies.¹⁴

Study population

New users initiating ICS/LABA FDC between July 1, 2013, and June 30, 2017, were included in the cohort. A new user of ICS/LABA FDC was defined as an individual filling an ICS/LABA FDC prescription with no prescriptions from that medication class during the preceding year. The date of the first filled prescription for ICS/LABA FDC during the study period was denoted the *index date*. Each person was required to have 1 or more additional dispensing episodes of ICS/LABA FDC within 365 days after the *index date* to minimize inclusion of people being treated once-off

FIGURE 1. Overview of study design. *FDC*, Fixed dose combination; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *LABA*, long-acting β -agonists.

for seasonal/thunderstorm asthma. Patient demographic and clinical characteristics (age, gender, asthma severity, relevant comorbidities) were captured at or in the year after the *index date*. Precise definitions are provided in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org).

Inclusion and exclusion criteria

To maximize the specificity and sensitivity for selecting patients with moderate-to-severe asthma (ie, excluding mild and seasonal asthma) who initiated ICS/LABA FDC as maintenance therapy, and to allow sufficient follow-up, the following inclusion criteria (based on previously validated algorithms¹⁵⁻¹⁷) were applied:

- (1) New user with a dispensed prescription of an ICS/LABA FDC product (defined as no dispensings of ICS/LABA FDC during 1 year before *index date*).
- (2) At least 2 other respiratory dispensings¹⁵ (not being ICS/LABA FDC or other GINA step 5 treatments) during 1 year before *index date* (ie, any dispensing episodes of short-acting β -agonists [SABA], short-acting muscarinic antagonists, ICS, cromones, xanthines, or leukotriene antagonists). This limits the possibility that ICS/LABA FDC is prescribed as *pro re nata* or maintenance and reliever therapy.
- (3) At least 1 year of data available after the *index date*.

To avoid the inclusion of preteenage children (where different asthma stepup guidelines apply), minimize inclusion of patients with chronic obstructive pulmonary disease (>45 years old), and allow the outcome to only occur after a minimum of 1-year ICS/LABA FDC adherence assessment, the following exclusion criteria were applied:

- (1) Patients <12 years and ≥ 45 years old at *index date*.^{16,17}
- (2) Patients using LABA 1 year before or after *index date*.
- (3) Patients using GINA step 5 treatments that are the outcome of this study 1 year before *index date* to 1 year after *index date*.

Exposure

The exposure of interest was adherence to ICS/LABA FDC defined by the trajectory of dispensed monthly prescriptions over a 1-year period after *index date*, that is, a combined measure of implementation and persistence.⁸ Reported adherence to ICS/LABA for at least 12 months is a key stated criterion for reimbursement of biologics by the PBS (www.pbs.gov.au). ICS/LABA FDCs

reimbursed in Australia during study duration were fluticasone propionate/salmeterol, budesonide/formoterol, fluticasone furoate/vilanterol, and fluticasone propionate/formoterol (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Study outcomes

The primary outcome of this study was the percentage of patients initiating ICS/LABA FDC who received additional GINA step 5 treatment during a maximum follow-up time of 2 years after 1-year adherence assessment. This was defined as any dispensing of either (1) low dose maintenance OCS: 1 or 5 mg prednisone or prednisolone; (2) biologics: omalizumab, mepolizumab, benralizumab; or (3) LAMA. The total number of additional GINA step 5 medications and the types dispensed over the complete follow-up period were analyzed. Secondary outcomes were the time to initiation of first additional GINA step 5 treatment and its predictors.

Statistical analyses

The asthma cohort initiating ICS/LABA FDC was characterized using descriptive statistics. Categorical variables were described by frequencies and percentages. Continuous variables were described using mean ($\pm$ standard deviation [SD]) for normally distributed data or median and interquartile range (IQR) for skewed distributions.

Adherence to ICS/LABA FDC was estimated using GBTM over a 1-year period from the *index date*. GBTM identifies clusters of individuals with similar trajectories (ie, dispensing patterns) by using the maximum likelihood method.¹¹ Dispensing dates were used to define medication availability in each month of follow-up. Adherence trajectories allowed for switching among different ICS/LABA FDCs, and this was not considered as discontinuation. Multiple models to identify 2 to 5 groups using either quadratic, cubic, or quartic terms were tested, and final model selection was made based on both clinical and statistical considerations (specified in Table E3, available in this article's Online Repository at www.jaci-inpractice.org). ICS/LABA FDC users were assigned to trajectory groups to which they had the highest membership probability.

Hazard ratios (HRs) for time to first additional GINA step 5 therapy and corresponding 95% confidence intervals (CIs) were assessed using Cox proportional hazards models. The trajectory group with good adherence to ICS/LABA FDC was considered the reference category, and time from start of follow-up (*index date* + 1 year) to first GINA step 5 add-on therapy was the outcome. Analyses were adjusted for (age at *index date*: 12-19 vs 20-29; 30-39; 40-44 years),

FIGURE 2. Flow diagram of patient selection from the Australian Pharmaceutical Benefits Scheme data. *COPD*, Chronic obstructive pulmonary disease; *FDC*, fixed dose combination; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *LABA*, long-acting β -agonists; *LAMA*, long-acting muscarinic antagonists; *OCS*, oral corticosteroids.

concessional status at index date, prior comorbidities¹⁸ such as eczema/nasal polyps, gastroesophageal reflux disease (GERD), anxiety, and depression, asthma severity indicators such as ≥ 2 OCS short courses and ≥ 2 antibiotic dispensing episodes (specified in Table E2, available in this article's Online Repository at www.jaci-inpractice.org) in the previous year. Kaplan-Meier plots were examined to check the fulfillment of the proportional hazards assumption. After that, follow-up time was restricted to a maximum of 2 years.

Sensitivity analyses

To assess the consistency of the results, a sensitivity analysis was performed that only included low dose maintenance OCS treatment as GINA step 5 outcome.

Ethics

The analysis plan and manuscript were approved by the Australian Government Department of Human Services (External Request Evaluation Committee number RMS0418). Of note, to minimize patient traceability, the department requested patient numbers lower than 3 to be reported as <3. The study was approved by the Monash University Human Research Ethics Committee.

RESULTS

Patient population

After applying inclusion and exclusion criteria, 3062 people who commenced ICS/LABA FDC were included in the final study cohort (Figure 2).

TABLE I. Baseline patient and clinical demographics (N = 3062)

Characteristic	Total
General characteristics	
Gender, N (% female)	1827 (59.7)
Age at index date, mean (SD)	28.2 (10.2)
Concessional status, % yes	1704 (55.7)
Prescriber of index medication (% GP)	2450 (80.0)
Asthma severity characteristics	
OCS short courses, median (IQR)	0 (0-1)
≥2 OCS short courses, N (%)	244 (8.0)
Antibiotic dispensings, median (IQR)	1 (0-3)
≥2 antibiotic dispensings, N (%)	1335 (43.6)
≥2 OCS short courses and/or antibiotic dispensings, N (%)	1516 (49.5)
SABA dispensings*, median (IQR)	2 (0-4)
Medication use, N (%)	
SABA*	2273 (74.2)
SAMA	121 (4.0)
ICS	201 (6.6)
LTRA	73 (2.4)
Xanthines	5 (0.2)
Cromones	22 (0.7)
Asthma-related comorbidities, N (%)	
Cough	52 (1.7)
Eczema/nasal polyps	459 (15.0)
GERD	556 (18.2)
Oral thrush	52 (1.7)
Other chronic comorbidities, N (%)	
Anxiety	361 (11.8)
Depression	789 (25.8)
Diabetes	133 (4.3)
IBS	9 (0.3)

GERD, Gastroesophageal reflux disease; GP, general practitioner; IBS, irritable bowel syndrome; ICS, inhaled corticosteroid; IQR, interquartile range; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

*Excluding over-the-counter SABA.

The characteristics of the total cohort are provided in Table I. Overall, 59.7% were female, mean age (SD) was 28.2 (10.2) years, 8.0% had 2 or more short courses of OCS within the 1 year after starting ICS/LABA FDC, and most common comorbidities were GERD, anxiety/depression, and nasal polyps/eczema. Over 92% of people started on medium (51%) or high (41%) dose ICS/LABA FDC,¹⁹ with fluticasone propionate/salmeterol being the most common (61%) FDC. General practitioners (GPs) were the most common (80.0%) prescribers (Table I). During the first year after *index date*, approximately 3 quarters of people had a SABA dispensed. Of note, in Australia, SABA is available as both prescription and over-the-counter. Allergic rhinitis is treated mostly using over-the-counter medications and therefore could not be reliably captured. Also, influenza vaccination is not captured in PBS data.

Additional GINA step 5 treatment

Among the 3062 new ICS/LABA FDC users, 120 (3.9%) received 1 or more additional GINA step 5 therapies (OCS: 89; LAMA: 39; biologics: <3) during the median follow-up of 730 (IQR: 497-730) days after first year of ICS/LABA FDC use. This

resulted in an incidence rate of 2.36 (95% CI: 2.32-2.41) per 100 person-years. Mean time to first GINA-5 add-on was 705.2 (SD: 1.7) days and this was either OCS (N = 85, 2.8%) or LAMA (N = 35, 1.1%). Biologics were only prescribed after a period of OCS or LAMA usage, in line with guideline recommendations.

Adherence trajectories

Four distinct adherence trajectories were identified (Table E4, available in this article's Online Repository at www.jaci-inpractice.org, and Figure 3). Group 1 can be characterized as "nonpersistent users" (20.4%, blue line), group 2 as either seasonal users or reinitiators, termed "seasonal users" (8.3%, red line), group 3 as persistent users with poor implementation, termed "poor adherers" (58.1%, green line), and group 4 as persistent users with good implementation, termed "good adherers" (13.2%, orange line). Characteristics of the different adherence subgroups are specified in Table E5 (available in this article's Online Repository at www.jaci-inpractice.org).

Additional GINA step 5 treatment by adherence trajectories

In total, 22 of the 120 GINA step 5 add-ons (18%) occurred in patients with "good adherence." In the good adherence group, 3.44 (95% CI: 3.30-3.59) patients per 100 person-years received any additional GINA step 5 therapy with a mean time to add-on of 446.9 (SD: 3.1) days (Table II). In the other 3 groups (nonadherent), mean time to GINA-5 add-on was 704.8 (SD: 3.9) days for nonpersistent users, 581.1 (SD: 5.0) days for seasonal users, and 690.0 (SD: 2.0) days for poor adherers. On the other hand, patients with poor adherence had significantly longer time to (adjusted HR: 0.58; 95% CI: 0.35-0.95) receiving additional GINA-5 compared with patients with good adherence (Table II). The sensitivity analysis that only included low dose maintenance OCS treatment as the outcome (N = 85) showed similar patterns, but no statistically significant difference in HR was observed in poor adherers (adjusted HR: 0.70; 95% CI: 0.39-1.25). In Figure 4, the time to additional GINA-5 therapy is plotted per adherence trajectory.

Other predictors for additional GINA step 5 treatment

The HRs for other significant predictors are presented in Figure 5, and detailed results of all predictors (including nonsignificant ones) are provided in Table E6 (available in this article's Online Repository at www.jaci-inpractice.org). In unadjusted analyses, women, patients aged 40 to 44 years, patients with anxiety, ≥2 dispensings of high-dose OCS, and ≥2 dispensings of antibiotics had increased risk of receiving additional GINA-5 treatment. In adjusted analyses, only ≥2 dispensings of high-dose OCS (HR: 1.80, 95% CI: 1.09-2.98) and ≥2 dispensings of antibiotics (HR: 1.52, 95% CI: 1.04-2.21) were associated with higher risk of initiating additional GINA step 5 treatment.

DISCUSSION

Main findings

On average, 4% of patients who initiated ICS/LABA FDC were prescribed additional GINA step 5 therapy during study follow-up. The majority of patients received maintenance low-dose OCS or LAMA, and a small proportion of patients

FIGURE 3. Trajectories of adherence to ICS/LABA FDC in patients with asthma in year after initiation (N = 3062). *FDC*, Fixed dose combination; *ICS*, inhaled corticosteroids; *LABA*, long-acting β -agonists.

TABLE II. Detailed results of subgroup analyses: additional GINA-5 dispense

	Person-years	Events	Incidence rate (95% CI)	Unadjusted hazard ratio (95% CI)	P value	SE*	Adjusted hazard ratio (95% CI)	P value	SE*
Any additional GINA-5									
Group 4: good adherers, n = 405	638.68	22	3.44 (3.30-3.59)	1.00			1.00		
Group 3: poor adherers, n = 1780	2963.25	57	1.92 (1.87-1.97)	0.56 (0.34-0.92)	.0219	0.2511	0.58 (0.35-0.95)	.0316	0.2530
Group 2: seasonal users, n = 253	435.85	13	2.98 (2.82-3.14)	0.88 (0.44-1.74)	.7039	0.3499	0.86 (0.43-1.72)	.6734	0.3513
Group 1: early discontinuers, n = 624	1037.73	28	2.70 (2.60-2.80)	0.79 (0.45-1.38)	.4042	0.2850	0.81 (0.46-1.42)	.4633	0.2869
Add oral corticosteroids only									
Group 4: good adherers, n = 405	647.7	15	2.32 (2.20-2.43)	1.00			1.00		
Group 3: poor adherers, n = 1780	2972.28	48	1.61 (1.57-1.66)	0.70 (0.39-1.25)	.2268	0.2958	0.72 (0.40-1.28)	.2610	0.2979
Group 2: seasonal users, n = 253	442.28	6	1.36 (1.25-1.47)	0.59 (0.23-1.52)	.2737	0.4831	0.59 (0.23-1.51)	.2679	0.4843
Group 1: early discontinuers, n = 624	1046.03	20	1.91 (1.83-2.00)	0.83 (0.42-1.62)	.5803	0.3416	0.83 (0.43-1.64)	.5986	0.3437

CI, Confidence interval; GINA, Global Initiative for Asthma.

*SE is the standard error of the log(HR) estimate.

progressed to biological therapy. Patients with good adherence had the highest likelihood of receiving additional step 5 therapy. The other strong predictor was the need for 2 or more OCS short courses or antibiotic dispensing episodes. Our trajectory analyses of ICS/LABA FDC use indicated that only 13% of patients overall had good adherence. Even among patients commencing additional GINA step 5 treatment, those with good adherence remained in the minority. Nonadherent patients represented over 80% of patients being prescribed additional step 5 therapies. This included a group with early discontinuation and seasonal or intermittent users and a group with persistent use but poor adherence, of which the latter had a significantly lower relative risk for receiving additional GINA-5 compared with those with good adherence.

Interpretation

This study is among the first to quantify high rates of prior poor adherence to inhalers in people receiving non-ICS/LABA GINA step 5 therapies, adding to the expanding body of literature documenting high rates of poor adherence in general in patients with asthma.^{20,21} Definitions of poor adherence in the literature vary widely making direct comparisons difficult. A

small recent Australian study using electronic monitoring devices (N = 69) found that 50% to 59% of patients potentially eligible for step-up to GINA step 5 were identified as poorly adherent to their ICS/LABA FDC.⁷ A study looking at ICS/LABA initiators in a US population database found that adherence was equally low with only minor absolute differences between type of ICS/LABA.²⁰ Our finding of high numbers of patients not refilling prescriptions soon after initiation parallels other data from the United States, where between 14% and 20% did not refill their first prescription and the mean proportion of days covered of ICS/LABA was 25%.²¹

The finding that the likelihood of receiving additional GINA step 5 therapies is lower in poorly adherent patients was contrary to our hypothesis. One of the possible explanations could be reverse causality. More severely affected patients may have more symptoms (eg, shortness of breath), maximize their inhaled preventer use, and meet requirements for additional therapies more quickly. Such a chain of events would be consistent with the recent association found between good refill adherence and higher exacerbation rates and uncontrolled asthma.²² Although the likelihood of receiving additional GINA step 5 therapy was lower in poorly adherent patients, the

FIGURE 4. Kaplan-Meier curve showing the time to additional GINA step 5 treatments in patients with asthma adherent (group 4) and poorly adherent (groups 1-3) to ICS/LABA FDC. *FDC*, Fixed dose combination; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *LABA*, long-acting β -agonists.

FIGURE 5. Forest plot showing the hazard ratios for significant predictors of additional GINA step 5 therapy. *CI*, Confidence interval; *GINA*, Global Initiative for Asthma; *OCS*, oral corticosteroid. *Adjusted for adherence trajectory, age, sex, concessional status, coexisting atopy indicators (eg, eczema/nasal polyps), gastroesophageal reflux disease, anxiety, depression, ≥ 2 dispensing episodes of OCS short courses, and ≥ 2 dispensings of antibiotics.

absolute magnitude of the poor-adherence problem at a population level calls for concerted efforts to objectively measure and optimize adherence through educational and behavioral interventions.²³ The finding that being female, older age, and anxiety were all associated with increased risk of additional

therapy is interesting. All these factors were only significant in unadjusted analyses, but lost significance in adjusted analyses. We speculate that these individual risk factors are all correlated and relate to intermediate factors such as higher exacerbation risk, as has been recently shown.²⁴

Real-life population-based estimates of patterns of GINA step 5 therapies are scarce. Yet, the 4% of patients receiving additional GINA step 5, indicative of a severe asthma phenotype, were almost identical to population-based estimates of severe asthma prevalence in recent Swedish and Dutch studies, ranging from 3.6% to 6.1%.^{25,26} The findings of multiple OCS and antibiotic courses as strong predictors confirm that these are good markers for exacerbations and uncontrolled asthma. The slow uptake of biological therapies was to be expected under the Australian PBS reimbursement criteria: reported adherence to high-dose ICS/LABA for at least 12 months, Asthma Control Questionnaire-5 score ≥ 2 , a severe exacerbation, and at least 6 weeks' daily chronic OCS use or at least 500 mg prednisolone equivalent in the past 12 months. In addition, mepolizumab and benralizumab were not available under the PBS for the majority of the study period.

Strengths and limitations

To our knowledge, this is the first population-based study of asthma adherence using trajectory modeling to distinguish the different longitudinal adherence behaviors, thereby mirroring real clinical practice. Previous studies have generally classified patients as either adherent or nonadherent using a threshold (eg, $<80\%$) of medication refill to define nonadherence. This however does not provide details regarding the type of nonadherence (eg, early discontinuation, continuous low intake, discontinuation, and subsequent reinitiation). Our use of GBTM overcomes this limitation and provides granular insights into actual longitudinal patterns of time-varying medication intake reflecting real-world patient behavior. Another strength was the use of a robust longitudinal national database that is representative of the total Australian population, contributing to the generalizability of the results. Although a database cannot provide the detailed day-to-day usage patterns that electronic monitors can provide, the PBS captures complete population data providing an objective measure of poor adherence using dispensing records (regardless of region or health insurance type) and several years of longitudinal follow-up.

We should also acknowledge some study limitations. First, not all dispensed medications were necessarily administered and dispensing data do not permit assessment of the patient inhaler technique. Yet, although actual adherence is difficult to confirm, poor adherence is relatively certain if no medication is dispensed at all. Thus, the actual adherence estimated for each individual in our study could be an overestimate rather than an underestimate. Although GBTM assigned individuals to the trajectories to which they had the highest membership probability, not all individuals do follow the exact pattern of their group as described in Figure 3. Therefore, there is possibility of exposure misclassification in the outcome analyses. A further limitation is that the PBS database does not include health care utilization (eg, GP visits and hospitalizations), clinical data (eg, body mass index, smoking, patient-reported asthma control), and relevant over-the-counter medication (eg, allergic rhinitis medications). To overcome this limitation, it would be of interest to link with recently established Australian monoclonal antibody registries, yet these links are currently not in place. Of note, in Australia, SABAs are available both on prescription and over-the-counter. Their use—although reported in baseline characteristics—was therefore not included as either a predictor or outcome variable in our proportional hazard models. A final limitation of our

design is that we focused only on adherence in the first year of treatment. This may have resulted in missing possible reinitiation episodes in patients in the “early discontinuation” and “seasonal use” groups, but is likely of a minor impact on the poor adherers with persistent use.

Implications for clinical practice, future research, and policy

The SYGMA studies and the 2019 GINA guideline update may put less emphasis on adherence in the initial phase of (mild) asthma treatment.^{1,27} Yet, with the increasing evidence on the impact of OCS adverse effects, and the expected rise in the use of biologics, the need for proper adherence assessment at the more severe end of the asthma spectrum, where our study focused on, seems more evident than ever. This study highlights and reinforces the need for careful and objective assessment of adherence before initiating additional GINA step 5 therapy.^{28,29} Our results suggest that the majority of patients may be stepped up to high-risk OCS therapy without adequate assessment of medication adherence and/or interventions to enhance adherence to initial therapies. This probably represents a less favorable risk-to-benefit ratio than encouraging adherence to initial inhaled therapies. Ideally in daily practice, validated and objective adherence measurement, such as electronic inhaler monitoring, should be performed before making the decision to prescribe step-up therapy.³⁰⁻³³ These electronic devices are becoming increasingly available and affordable and are expected to slowly find their way into clinical practice.³⁰ If no routine access to electronic monitoring is available, at a minimum, validated adherence questionnaires should be used or dispensing data should be accessed, for example, by contacting the pharmacy of the patient.

In summary, our results demonstrate that 4% of ICS/LABA FDC initiators receive additional GINA step 5 therapies. A considerable proportion of poorly adherent patients were potentially inappropriately receiving additional GINA step 5 treatment. Given the potential medication-related adverse effects and cost implications, there is a pressing need for reliable and objective adherence assessment before asthma treatment escalation.

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ONLINE REPOSITORY

TABLE E1. STROBE statement—checklist of items that should be included in reports of cohort studies

	Item no.	Recommendation	Reported on page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than 1 group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	8
		(d) If applicable, explain how loss to follow-up was addressed	8
		(e) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	9
		(b) Give reasons for nonparticipation at each stage	NA
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarize follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-12
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(b) Report category boundaries when continuous variables were categorized	8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarize key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15

(continued)

TABLE E1. (Continued)

	Item no.	Recommendation	Reported on page
Generalizability	21	Discuss the generalizability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the websites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

*Give information separately for exposed and unexposed groups.

TABLE E2. Definitions of asthma severity, comorbidities, and medication use

Asthma severity indicators
In year (365 days) after index date:
<ul style="list-style-type: none"> • Annual number of OCS short courses defined as dispensings of 25 mg prednisone or prednisolone (ATC codes: H02AB06 and H02AB07) • Annual number of dispensings of antibiotics (ATC codes: J01AA [tetracyclines], J01C [beta-lactams], J01DA [cephalosporins], J01FA [macrolides]) • Annual number of SABA dispensings (ATC codes: R03AC02 and R03AC03)
Comorbidities
<ul style="list-style-type: none"> • Asthma-specific comorbidities defined as at least 1 dispensing (ATC code) within 1 y after index date: <ul style="list-style-type: none"> ○ Cough (R05) ○ Eczema/nasal polyps (topical steroids: D07, ointment with an immunosuppressant: D11) ○ GERD (proton pump inhibitors and others: A02BA01-A02BX05, excluding A02BD) ○ Oral thrush (nystatin: A01AB11; amphotericin B: A01AB04, miconazole: A01AB09) • Other <i>chronic</i> comorbidities, possibly affecting ICS use (diabetes/osteoporosis/glaucoma: long-term side effects of ICS/OCS; anxiety/depression: risk for nonadherence; irritable bowel syndrome [IBS]: other indication for OCS use), present in year before initiation (defined by proxy, as specified below). Patients need to have at least 1 dispensing within 1 y after index date, with ATC codes based on previously used Rx proxies^{E1}: <ul style="list-style-type: none"> ○ Anxiety (N05BA01-N05BA12, N05BE01) ○ Depression (N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX18, N06AX21-N06AX26) ○ Diabetes (A10AA01-A10BX99) ○ IBS (A07EC01-A07EC04, A07EA01-A07EA02, A07EA06, L04AA33)
Medication
<ul style="list-style-type: none"> • Asthma medication used in year after index date defined as the presence of at least 1 prescription of: <ul style="list-style-type: none"> ○ SABA (R03AC02, R03AC03, R03CC02, R03CC03) ○ SAMA (R03BB01) ○ SABA/SAMA (R03AK04) ○ ICS (R03BA) ○ Cromo (R03BC) ○ Xanthines (R03DA) ○ LTRA (R03DC)

ATC, Anatomical Therapeutic Chemical; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β -agonist; SAMA, short-acting muscarinic antagonist.

TABLE E3. Adherence trajectory model selection procedure

Group-based trajectory modeling background information
Adherence to ICS/LABA FDC was identified using group-based trajectory modeling (GBTM) ^{E2} over a 12-mo period after ICS/LABA FDC initiation. ICS/LABA FDC available (with ATC code) in Australia during the study period included fluticasone propionate/salmeterol (R03AK06), budesonide/formoterol (R03AK07), fluticasone furoate/vilanterol (R03AK10), and fluticasone propionate/formoterol (R03AK11). GBTM attempts to identify clusters of individuals with similar trajectories (ie, dispensing patterns) by using the maximum likelihood method. The binary monthly indicators of ICS/LABA FDC dispensings were modeled as a longitudinal response in a logistic GBTM. ^{E3} Models were tested using 2-5 groups using either quadratic, cubic, or quartic terms with “Proc Traj,” a free downloadable add-on package, in SAS version 9.4 (SAS Institute Inc., Cary, NC). ICS/LABA FDC users were assigned to trajectory groups to which they had the highest membership probability.
Model selection criteria
<ul style="list-style-type: none"> • Bayesian information criterion (BIC) • The estimated size of trajectory groups (at least 5%) • The average of the posterior probabilities for a given group of individuals assigned to that group (at least 0.7 for all groups)^{E2} • Correspondence between the model estimate of a group’s probability and the proportion of individuals classified in the group (should be close correspondence)^{E2} • Convergence • Clinical meaningfulness of the trajectory groups
Final model
None of the models fulfilled all the criteria (Table E4). A cubic trajectory model with 4 groups was determined to have the best overall model fit and the groups seemed to be most clinically meaningful. We further tested 4-group models by mixing quadratic, cubic, and quartic terms. However, none of the models were better than the cubic model.

ATC, Anatomical Therapeutic Chemical; FDC, fixed dose combination; ICS, inhaled corticosteroid; LABA, long-acting β -agonist.

TABLE E4. BIC values and estimated group sizes for group-based trajectory models with 2-5 groups using quadratic, cubic, and quartic terms

No. of groups (terms [‡])	BIC	Estimated group sizes, % (proportion classified in group*, average posterior probability [§])				
		Group 1	Group 2	Group 3	Group 4	Group 5
2 (2 2)	−19,126.18	84.0 (85.1, 0.962)	16.0 (14.9, 0.857)			
3 (2 2 2)	−19,097.23	19.6 (17.0, 0.767)	77.3 (80.2, 0.925)	3.2 (2.9, 0.798)		
4 (2 2 2 2)	−19,113.28	19.6 (17.4, 0.760)	71.4 (79.7, 0.858)	5.8 (0.0)	3.2 (2.9, 0.798)	
5 (2 2 2 2 2)	−19,126.73	19.2 (17.1, 0.741)	2.3 (1.7, 0.610)	74.2 (80.0, 0.890)	2.8 (0.0)	1.4 (1.2, 0.698)
2 (3 3)	−18,469.83	83.8 (85.0, 0.962)	16.2 (15.0, 0.863)			
3 (3 3 3)	−18,307.08	17.9 (16.6, 0.691)	64.6 (67.8, 0.854)	17.5 (15.6, 0.872)		
4 (3 3 3 3)	−18,238.19	18.4 (20.4, 0.630)	8.2 (8.3, 0.713)	59.0 (58.1, 0.833)	14.4 (13.2, 0.852)	
5 (3 3 3 3 3) [§]						
2 (4 4)	−17,945.72	84.2 (85.0, 0.965)	15.8 (15.0, 0.855)			
3 (4 4 4)	−17,848.17	12.6 (11.3, 0.673)	70.6 (73.6, 0.887)	16.8 (15.1, 0.876)		
4 (4 4 4 4)	−17,871.98	10.3 (6.9, 0.752)	0.0 (0.0)	72.9 (78.0, 0.890)	16.8 (15.2, 0.874)	
5 (4 4 4 4 4)	−17,840.56	0.0 (0.0)	11.2 (6.8, 0.776)	21.2 (18.6, 0.765)	63.8 (71.2, 0.833)	3.8 (3.4, 0.827)
4 (3 3 3 2)	−18,261.47	19.5 (20.5, 0.683)	25.5 (23.9, 0.774)	51.2 (52.1, 0.806)	3.8 (3.6, 0.830)	
4 (3 3 2 3)	−18,247.18	18.9 (20.0, 0.644)	8.8 (8.3, 0.734)	12.6 (11.6, 0.854)	59.7 (60.2, 0.831)	
4 (3 2 3 3)	−18,323.13	17.9 (16.6, 0.691)	0.0 (0.0)	64.6 (67.8, 0.854)	17.5 (15.6, 0.872)	
4 (2 3 3 3)	−18,433.00	1.6 (1.4, 0.696)	17.6 (15.2, 0.768)	77.9 (80.9, 0.929)	2.8 (2.5, 0.799)	
4 (3 3 2 2)	−18,319.32	16.7 (11.6, 0.723)	68.0 (74.7, 0.850)	1.3 (0.9, 0.780)	14.0 (12.8, 0.869)	
4 (3 2 2 3)	−18,319.32	16.7 (11.6, 0.723)	1.3 (0.9, 0.780)	14.0 (12.8, 0.869)	68.0 (74.7, 0.850)	
4 (2 2 3 3) [§]						
4 (2 3 3 2)	−18,430.73	1.7 (1.4, 0.705)	17.5 (15.5, 0.777)	78.3 (81.0, 0.932)	2.5 (2.1, 0.825)	
4 (3 2 3 2) [§]						
4 (2 3 2 3) [§]						
4 (3 2 2 2)	−19,117.29	0.0 (0.0)	77.3 (80.2, 0.925)	19.6 (17.0, 0.767)	3.2 (2.9, 0.798)	
4 (2 3 2 2) [§]						
4 (2 2 3 2) [§]						
4 (2 2 2 3) [§]						

BIC, Bayesian information criteria.

Bold indicates final model used in analysis.

*There should be close correspondence between the model estimate of a group's probability and the proportion of individuals classified in the group (based on the maximum posterior probability assignment rule).

†The average of the posterior probabilities for a given group of individuals assigned to this group by the maximum posterior probability assignment rule. This average should be at least 0.7 for all groups.

‡2 = quadratic; 3 = cubic; 4 = quartic.

§Error: singular convergence.

TABLE E5. Specification of adherence subgroups

	Total N = 3062 n (%)	Group 1 (early discontinuers) N = 624 n (%)	Group 2 (seasonal users) N = 253 n (%)	Group 3 (poor adherers) N = 1780 n (%)	Group 4 (good adherers) N = 405 n (%)
Mean age (SD)	28.2 (10.2)	27.5 (10.2)	28.4 (10.0)	28.3 (10.2)	28.9 (10.1)
% female	1827 (59.7)	373 (59.8)	148 (58.5)	1074 (60.3)	232 (57.3)
Concessional status, % yes	1704 (55.7)	385 (61.7)	145 (57.3)	974 (54.7)	200 (49.4)
Prescriber of index medication (% GP)*	2450 (81.3)	500 (82.2)	200 (79.7)	1429 (81.4)	321 (80.5)
Initial dose of ICS ^{E4}					
Low dose	231 (7.5)	53 (8.5)	17 (6.7)	133 (7.5)	28 (6.9)
Medium dose	1562 (51.0)	307 (49.2)	136 (53.8)	896 (50.3)	223 (55.1)
High dose	1269 (41.4)	264 (42.3)	100 (39.5)	751 (42.2)	154 (38.0)
Initial ICS/LABA combination					
Fluticasone/salmeterol	1867 (61.0)	390 (62.5)	164 (64.8)	1081 (60.7)	232 (57.3)
Budesonide/formoterol	1018 (33.3)	205 (32.9)	81 (32.0)	609 (34.2)	123 (30.4)
Fluticasone furoate/vilanterol	103 (3.4)	14 (2.2)	3 (1.2)	53 (3.0)	33 (8.2)
Fluticasone/formoterol	74 (2.4)	15 (2.4)	5 (2.0)	37 (2.1)	17 (4.2)
Asthma severity characteristics					
≥2 OCS short courses	244 (8.0)	45 (7.2)	27 (10.7)	133 (7.5)	39 (9.6)
≥2 antibiotic dispensings	1335 (43.6)	284 (45.5)	120 (47.4)	767 (43.1)	164 (40.5)
≥2 OCS short courses and/or antibiotic dispensings	1516 (49.5)	321 (51.4)	136 (53.8)	874 (49.1)	185 (45.7)
Medication use					
SABA [†]	2273 (74.2)	474 (76.0)	206 (81.4)	1322 (74.3)	271 (66.9)
SAMA	121 (4.0)	22 (3.5)	13 (5.1)	70 (3.9)	16 (4.0)
ICS [‡]	201 (6.6)	51 (8.2)	15 (5.9)	97 (5.5)	38 (9.4)
LTRA	73 (2.4)	15 (2.4)	3 (1.2)	44 (2.5)	11 (2.7)
XAN	5 (0.2)	<3 (<0.5)	0 (0.0)	4 (0.2)	0 (0.0)
CROMO	22 (0.7)	5 (0.8)	<3 (<1.2)	12 (0.7)	3 (0.7)
Asthma-specific comorbidities					
Cough	52 (1.7)	13 (2.1)	5 (2.0)	29 (1.6)	5 (1.2)
Eczema/nasal polyps	459 (15.0)	81 (13.0)	52 (20.6)	257 (14.4)	69 (17.0)
GERD	556 (18.2)	113 (18.1)	47 (18.6)	313 (17.6)	83 (20.5)
Oral thrush	52 (1.7)	14 (2.2)	3 (1.2)	26 (1.5)	9 (2.2)
Other chronic comorbidities					
Anxiety	361 (11.8)	74 (11.9)	27 (10.7)	204 (11.5)	56 (13.8)
Depression	789 (25.8)	176 (28.2)	65 (25.7)	431 (24.2)	117 (28.9)
Diabetes	133 (4.3)	23 (3.7)	13 (5.1)	83 (4.7)	14 (3.5)
IBS	9 (0.3)	<3 (<0.5)	<3 (<1.2)	4 (0.2)	<3 (<0.7)

FDC, Fixed dose combination; GERD, gastroesophageal reflux disease; GP, general practitioner; IBS, irritable bowel syndrome; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

*Excluding those with specialty missing (n = 49).

†Excluding over-the-counter SABA.

‡Use of single ICS (without LABA) was higher in year before initiation of ICS/LABA FDC (34.6% in total cohort, in good adherers 55.1%, in poor adherers 34.6%, in seasonal users 21.3%, and in nonpersistent users 26.8%).

TABLE E6. Other predictors for additional dispensing of any GINA step 5 treatment

	Person-years	Events	Incidence rate (95% CI)	Unadjusted hazard ratio (95% CI)	P value	SE*	Adjusted hazard ratio (95% CI) [†]	P value	SE*
Female	3007.12	82	2.73 (2.67-2.79)	1.00			1.00		
Male	2068.38	38	1.84 (1.78-1.90)	0.68 (0.46-0.99)	.0455	0.1963	0.74 (0.50-1.10)	.1410	0.2007
Age 12-19 y	1392.21	30	2.15 (2.08-2.23)	1.00			1.00		
Age 20-29 y	1242.63	22	1.77 (1.70-1.84)	0.82 (0.48-1.43)	.4871	0.2807	0.71 (0.40-1.24)	.2261	0.2861
Age 30-39 y	1493.66	31	2.08 (2.00-2.15)	0.97 (0.58-1.59)	.8891	0.2561	0.79 (0.47-1.33)	.3760	0.2680
Age 40-44 y	947.0	37	3.91 (3.78-4.03)	1.81 (1.12-2.93)	.0156	0.2457	1.47 (0.88-2.45)	.1392	0.2608
General beneficiary	2225.79	42	1.89 (1.83-1.94)	1.00			1.00		
Concessional beneficiary	2849.71	78	2.74 (2.68-2.80)	1.46 (1.00-2.12)	.0501	0.1914	1.25 (0.85-1.85)	.2626	0.2001
No depression	3762.69	80	2.13 (2.08-2.17)	1.00			1.00		
Depression	1312.8	40	3.05 (2.95-3.14)	1.44 (0.98-2.10)	.0621	0.1937	1.08 (0.71-1.66)	.7114	0.2182
No anxiety	4492.11	97	2.16 (2.12-2.20)	1.00			1.00		
Anxiety	583.39	23	3.94 (3.78-4.10)	1.83 (1.16-2.88)	.0095	0.23194	1.35 (0.81-2.25)	.2504	0.2603
No eczema/nasal polyps	4298.84	98	2.28 (2.23-2.32)	1.00			1.00		
Eczema/nasal polyps	776.66	22	2.83 (2.71-2.95)	1.25 (0.79-1.98)	.3507	0.2359	1.09 (0.68-1.74)	.7303	0.2398
No GERD	4153.9	90	2.17 (2.12-2.21)	1.00			1.00		
GERD	921.6	30	3.26 (3.14-3.37)	1.50 (0.99-2.27)	.0532	0.2108	1.09 (0.70-1.69)	.709	0.2257
<2 OCS short courses	4673.83	101	2.16 (2.12-2.20)	1.00			1.00		
≥2 OCS short courses	401.66	19	4.73 (4.52-4.94)	2.19 (1.34-3.57)	.0018	0.2501	1.80 (1.09-2.98)	.0229	0.2580
<2 antibiotic dispensings	2863.7	50	1.75 (1.70-1.79)	1.00			1.00		
≥2 antibiotic dispensings	2211.8	70	3.16 (3.09-3.24)	1.81 (1.26-2.61)	.0013	0.1852	1.52 (1.04-2.21)	.0309	0.1930

CI, Confidence interval; GINA, Global Initiative for Asthma; OCS, oral corticosteroid.

*SE is the standard error of the log(HR) estimate.

†Adjusted for trajectory group, age, sex, concessional status, eczema/nasal polyps, gastroesophageal reflux disease (GERD), anxiety, depression, ≥2 OCS short courses, and ≥2 dispensings of antibiotics.

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