BMJ Open Respiratory Research

Medication use of Canadians with chronic obstructive pulmonary disease: a cohort study

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To cite: Stickland MK, Martins KJB, Sharpe H, *et al*. Medication use of Canadians with chronic obstructive pulmonary disease: a cohort study. *BMJ Open Respir Res* 2023;**10**:e002083. doi:10.1136/bmjresp-2023-002083

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2023-002083).

Received 21 September 2023
Accepted 1 December 2023

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ABSTRACT

Objectives The objectives of this study were to describe medication use, treatment patterns and adherence, as well as acute exacerbations of chronic obstructive pulmonary disease (AECOPD) among adults living with COPD.

Methods A retrospective observational study using administrative data (linked by unique person-level personal health numbers) between 1 April 2007 and 31 March 2018 from Alberta, Canada was performed. Individuals aged ≥35 years who had been living with COPD ≥1 year on 1 April 2017 (index date) were identified. COPD-related medication use was determined on the index date (baseline), and medication use, treatment patterns, adherence and AECOPD were measured during the 1-year postindex observation period; descriptive statistics were applied.

Results Among the total cohort (n=192 814), 59% were not using a COPD-related medication at baseline; among those using medication, the most common (>10%) classes were short acting bronchodilators only (29%), dual inhaled corticosteroids/long acting beta$_2$ agonists (ICS/LABA, 27%), combined ICSs/LABA/long acting muscarinic antagonist (ICS/LABA/LAMA, 21%) and LAMA monotherapy (12%). During the observation period, those with baseline COPD medication use had low adherence (42% were adherent (medication possession ratio ≥0.80) to their baseline medication class) and AECOPD were common (13%–40%); 66% of those with ≥1 dispensation for an additional medication class had a step-up in therapy that was concordant with guideline recommendations.

Conclusions In this population-based study, the majority of individuals identified as living with COPD were not taking any COPD-related medication, while in those who were taking medication, adherence was low, deficits in alignment to guideline-recommended therapy were observed and many had AECOPD. Strategies for earlier identification of undertreatment, consideration of guideline-based knowledge transfer strategies and mechanisms to improve long-term medication adherence may improve outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ National and international guidelines provide evidence-based approaches to pharmacotherapy for the management of chronic obstructive pulmonary disease (COPD). Despite this, low medication adherence appears to be common in individuals living with COPD and is a risk factor for acute exacerbations of COPD, hospitalisations, and mortality.

WHAT THIS STUDY ADDS

⇒ This study demonstrated inconsistent application of guideline-based pharmacotherapy for COPD, and low adherence to prescribed regimens. Acute exacerbations of COPD were common among those with COPD-related medication use, suggesting undertreatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research into optimal care management for those living with milder COPD is warranted. Areas for future improvement may include considering approaches to facilitate earlier identification of undertreatment, guideline-based knowledge transfer strategies for healthcare providers, and promoting long-term medication adherence.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease with significant morbidity and is the third leading cause of death globally.[1] Over 300 million individuals have COPD worldwide, and in Canada, prevalence is estimated to be approximately 10%–16% among those ≥40 years of age.[2 3] Acute exacerbations of COPD (AECOPD) can accelerate disease progression and lead to hospitalisations, which account for the majority of healthcare costs related to COPD in Europe and Canada.[4 5] Appropriate management of COPD can reduce symptoms experience and healthcare utilisation.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Canadian Thoracic Society guidelines, management of COPD involves non-pharmacological strategies such as smoking cessation, receiving appropriate vaccinations, self-management education, and pulmonary

rehabilitation, as well as pharmacotherapy.[6 7] Inhaled short-acting bronchodilators (SABDs) provide acute relief of symptoms as needed; this rescue medication is recommended for all individuals living with COPD as an accompaniment to maintenance medications.[6 7] Maintenance pharmacotherapy includes the use of long-acting bronchodilators (LABDs) such as long-acting beta$_2$ agonists (LABA) and long-acting muscarinic antagonists (LAMA), either as mono or dual therapy; inhaled corticosteroids (ICS) are added to LABD therapy for individuals at increased risk of AECOPD or who have persistent symptoms despite dual LAMA/LABA therapy. Pharmacotherapy tends to begin with LABA or LAMA monotherapy, with a step-up to dual LABA/LAMA or ICS/LABA therapy, and then triple ICS/LABA/LAMA therapy, as necessary, to control symptoms and reduce the frequency and severity of AECOPD.[7] Alternative step-up medications that have been recommended for those who continue to exacerbate despite triple inhaled therapy include phosphodiesterase-4 (PDE-4) inhibitors (if they have the chronic bronchitic phenotype and regular macrolide antibiotics).[6 7] Despite the availability of pharmacological treatments, earlier studies report low medication adherence in individuals living with COPD, with poor adherence being a risk factor for AECOPD, hospitalisations and mortality.[8–11]

With the evolution of COPD pharmacotherapy, enhanced knowledge translation, and improvements in patient education, it would be expected that prescription patterns would better comply to guideline directed therapy with suitable patient adherence to prescription respiratory medication. Accordingly, the objectives of this study were to describe medication use, treatment patterns, and adherence, as well as AECOPD within the population of individuals living with COPD in the province of Alberta.

METHODS

Study design

This retrospective cohort study used administrative health data from Alberta between 1 April 2007 and 31 March 2018 without any intervention and was reported according to the Reporting of studies Conducted using Observational Routinely collected Data, an extension of the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[12] No participants were placed at risk as a result of the study, and a waiver of consent was applied.

Data source

A person-level data extract from the following listed databases was linked using personal health numbers (unique lifetime identifiers assigned to individuals eligible for Alberta Health Care Insurance Plan (AHCIP) coverage; all Alberta residents are eligible and over 99% participate[13]), then deidentified and provided to the researchers by the data custodians. Data from the National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD), Practitioner Claims, Pharmaceutical Information Network (PIN), Population Health, Population Registry, and the Alberta COPD Registry of Alberta (contains data elements from the DAD, Practitioner Claims, Population Health and Provincial Registry) were used in this study. NACRS and DAD include data on all individuals discharged from facility-based ambulatory care clinics and hospitals, respectively; a most responsible diagnostic field and secondary fields are included and use International Classification of Disease Version 10-Canadian Enhancement (ICD-10-CA) codes. Practitioner Claims includes information on fee-for-service, alternative payment plan billing and shadow billing; up to three ICD Version 9-Clinical Modification (ICD-9-CM; Alberta specific) diagnostic codes can be listed per visit. PIN contains information on dispensed prescription medications from all community pharmacies. Population Health contains information about specific populations. The Population Registry contains demographic information for all Albertans with AHCIP coverage. Records that were duplicates or contained an invalided or non-Alberta Personal Health Number were discarded. Variables were checked for missing data and inconsistencies; inconsistent data were corrected using data logic or information majority.

The COPD Registry of Alberta contains individuals who met a validated case definition for COPD (had ≥1 COPD physician code (ICD-9-CM 491, 492 or 496 within Practitioner Claims; from April 2001 onwards) or hospitalisation (ICD-10-CA J41-J44 in any diagnostic field within DAD; from April 2002 onwards) and were aged ≥35 years[14]), and had AHCIP coverage when the code occurred. This case definition was validated in Canada using medical records linked to administrative data. An expert panel of pulmonologists determined COPD and non-COPD cases based on gold-standard diagnoses (from the Canadian Thoracic Society, as opposed to primary care physician diagnosis), which surpassed the standards by which the majority of individuals with COPD are diagnosed. The case definition resulted in 85% sensitivity, 78% specificity, 58% positive predictive value, and 94% negative predictive value; according to the authors, these results indicate that this case definition accurately identified individuals living with COPD using administrative health data.[14] While some validated case definitions for COPD incorporate spirometry or COPD-related medications, Quint *et al*[15] showed that requiring these measures, in addition to diagnostic codes, only marginally improved the accuracy of identifying individuals living with COPD in administrative data.[15] Additionally, Greshon *et al* (2018) showed that when individuals had spirometry completed, there was a greater occurrence of underdiagnosis of COPD (no physician diagnostic code for COPD in administrative data, but COPD according to spirometry (GOLD definition)) than overdiagnosis of COPD (a physician diagnostic code for COPD in administrative data, but no COPD according to spirometry).[16]

Collectively, these findings suggest there is not a significant concern with the potential of identifying those who do not have the disease in the COPD Registry of Alberta.

Study population

From an extract of the COPD Registry of Alberta (data provided between 1 April 2012 and 31 March 2018), individuals who had been living with COPD for ≥1 year as of 1 April 2017 (index date) were selected as follows: (1) alive on 1 April 2017, (2) did not have a COPD incident date after March 2016 (defined as no hospitalisations or physician billing claims for COPD within 5 years before the first hospitalisation/physician billing claim date for COPD) so that baseline COPD-related medication use (or non-use) could be determined (based on prescription dispensations during the 1-year preindex period) and (3) had AHCIP coverage ≥2 years before and ≥1 year after the index date.

Measures

Characteristics on the index date included COPD-related medication use (termed 'baseline' medication use), age, sex, and urban/rural residence.[17] Clinical characteristics included the number of years living with COPD before the index date, and a Charlson Comorbidity Index score that was determined during the 2-year preindex period[18 19] (see online supplemental table 1) for details. Results are presented among all participants, and according to baseline COPD medication use (or non-use) that was determined based on prescription dispensations during the 1-year preindex period. Medications were categorised into classes that allowed for all participants using COPD-related medications in this study to be classified, and included SABD only (short-acting beta$_2$ agonist and/or short-acting muscarinic antagonist) and the maintenance therapy (±SABD) classes of monotherapy (LABA, LAMA), dual therapy (LABA/LAMA, ICS/LABA) and triple therapy (ICS/LABA/LAMA); ancillary medication classes were ICS only, ICS with methylxanthines and/or PDE-4 inhibitors (termed 'other') and/or SABD, and 'other' (±SABD). Single inhaler delivery for triple therapy was not available during the study time period. It was not feasible to discern drug delivery devices (such as metered dose inhaler, dry powder inhaler) used (see online supplemental table 2) for a list of drugs included in each medication class and the anatomical therapeutic chemical codes used to identify them.

COPD-related medication use, treatment patterns, and adherence, as well as AECOPD, were measured during the 1-year postindex observation period. Those who received ≥1 dispensation for a specific medication class, as well as additional medication classes relative to baseline use were reported. Adherence (prescription-based medication possession ratio ≥0.80) to the baseline COPD medication class was calculated by dividing the number of days of supply of the baseline COPD medication(s) by the number of days from the index date to the last refill date during the postindex observation period; SABDs were not included.[20] The baseline medication treatment patterns of discontinuation (a gap in baseline medication supply of ≥90 days, with no additional medication added), switch (change to a different medication class <90 days after the last day of supply of the discontinued baseline medication), and step-up (the addition of ≥1 drug class for ≥30 consecutive days, based on guidelines) were reported.[7 21] AECOPD included an emergency department visit or hospitalisation for COPD (severe exacerbation; ICD-10-CA J41-44 in the most responsible diagnostic field within NACRS or DAD, respectively), or a physician code for COPD (ICD-9-CM 491, 492 or 496 within Practitioner Claims) plus a prescription dispensation for short-course (≤21 days of supply) antibiotics and/or systemic corticosteroids within 7 days of the claim (moderate exacerbation)[22 23] (see online supplemental table 2) for a list of medications.

Statistical analyses

Descriptive statistics were reported using summary statistics. Continuous variables were reported using median and IQR, and categorical variables were reported using counts and percentages. Analyses were performed by using SAS V.9.4 software.

Patient and public involvement

Patient and public involvement did not occur in the design and implementation of this study.

RESULTS

Cohort selection

Figure 1 shows the selection and data linkage of the identified COPD cohort. Of the 2 388 107 individuals aged ≥35 years and living as Alberta residents on 1 April 2017, 264 604 were identified as living with COPD, and 192 814 were included in the cohort as they had been living with COPD for ≥1 year, and had the required AHCIP coverage.

Characteristics

Figure 2 shows baseline COPD medication use (or no use) of the total cohort. At baseline, 59% of the total cohort had no COPD-related medication use (83% did not have any dispensations for COPD medications and 17% discontinued their medication during the previous year), and 41% had use. Among those with medication use at baseline, the most common medication classes that individuals used were SABDs only (12% of the total cohort; 29% of those with baseline COPD medication use), and maintenance therapies (26% of the total cohort; 63% of those with baseline COPD medication use); ancillary medication classes were used by 3% of the total cohort and 7% of those with baseline COPD medication use.

Table 1 describes the characteristics of the total cohort, and according to the most common COPD medication use at baseline. Males and females each comprised

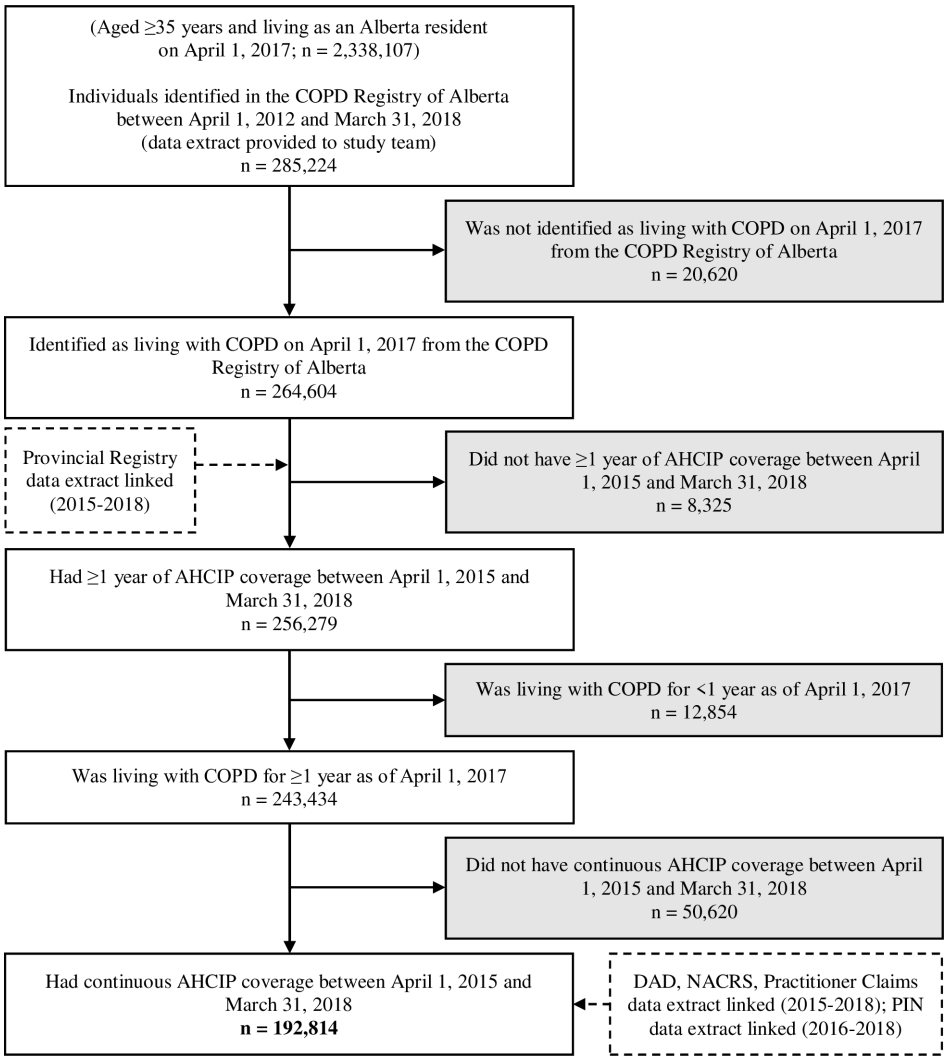

Figure 1 Participant selection (solid boxes and arrows) and data linkage (dashed boxes and arrows) flow diagram. ACHIP, Alberta Health Care Insurance Plan; COPD, chronic obstructive pulmonary disease; DAD, Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; PIN, Pharmaceutical Information Network.

approximately half of the cohort (51% and 49%, respectively), and 79% lived in urban areas. The median age of the total cohort was 66 (IQR 57–76) years; those with no COPD medication use at baseline (65 (IQR 56–75) years) or SABD only (63 (IQR 55–73) years) were more likely to be younger than those who received maintenance therapy (67 (58–77) to 72 (63–80) years). Individuals who received triple ICS/LABA/LAMA therapy at baseline (compared with those who did not) were more likely to have been living with COPD longer (a median of 8 (IQR 5–12) vs 6 (3–10) to 7 (4–11) years). Characteristics of those who received ancillary COPD-related medications at baseline are presented in online supplemental table 3.

Trajectory of medication use during the observation period

Medication use during the 1-year postindex observation period is presented in table 2; ancillary medication classes are detailed in online supplemental table 4. In total, 46% of individuals received ≥1 dispensation for a COPD medication during this time period. Among those with no COPD medication use at baseline, 17% received ≥1 dispensation for a COPD-related medication during the observation period and 88% of those classified as medication users at baseline received ≥1 dispensation. The addition of medication class(es) during the observation period was highest among the baseline defined SABD only and LABD monotherapy users (37%–45% received ≥1 dispensation for an additional drug class, respectively), and lowest among the triple ICS/LABA/LAMA therapy users (11% received ≥1 dispensation for an additional drug class).

Among those classified as COPD medication users at baseline, 42% were adherent to all drug component(s) contained within their baseline medication class for the length of time they received this medication class during the observation period; 54% were adherent to ≥1 drug component of the baseline medication class.

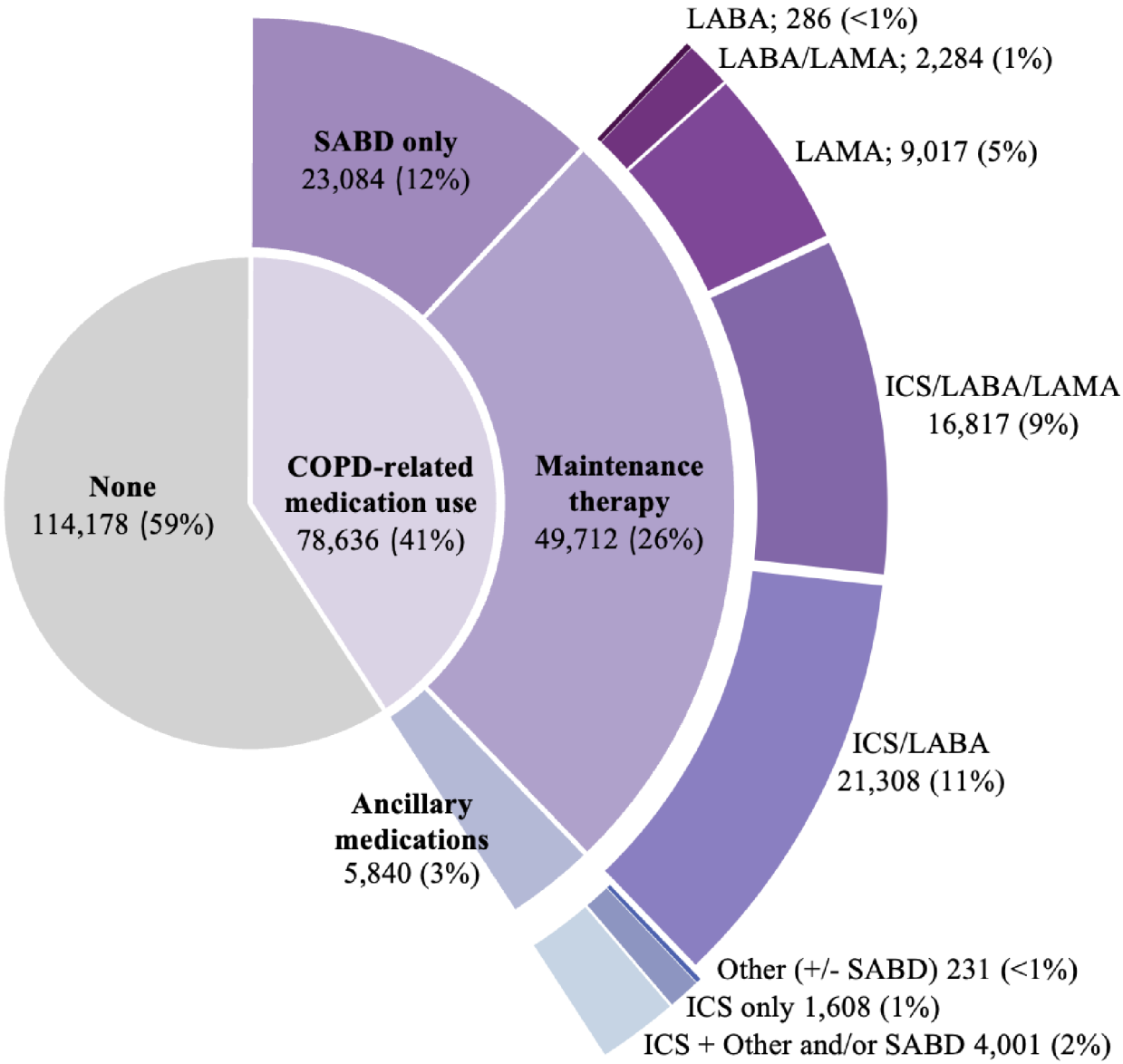

Figure 2 Baseline COPD-related medication use. 'Other' medications include methylxanthines and/or PDE-4 inhibitors. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta2 agonists; LAMA, long-acting muscarinic antagonists; SABD, short-acting bronchodilators.

In total, 52% discontinued their baseline medication class (not including SABD only) during the observation period. Discontinuation of baseline maintenance therapy ranged from 37% for dual LABA/LAMA users to 55% for dual ICS/LABA users. Regarding medication change, 14% of those with baseline COPD medication use (not including SABD only) discontinued their baseline medication class and switched to a different medication class during the observation period. Among those who had ≥1 dispensation for an additional medication class (21% of the total cohort), 66% had a step-up in therapy that was concordant with guideline recommendations.

AECOPD during the postindex observation period

In total, 11% of the cohort had ≥1 AECOPD during the observation period; 6% (51% of those with ≥1 AECOPD) had ≥1 severe exacerbation and 7% (66% of those with ≥1 AECOPD) had ≥1 moderate exacerbation (table 3). The proportion of those who had ≥1 AECOPD ranged from 4% (had no medication use at baseline) to 13%–40% (had SABD only or maintenance therapy at baseline). AECOPD among those who were in the ancillary medication classes are detailed in online supplemental table 5.

DISCUSSION

In this population-based retrospective cohort study that used administrative health data, COPD-related medication use, treatment patterns, and adherence, as well as AECOPD were described among adults aged ≥35 years who had been living with COPD for at least a year, in Alberta, Canada. At baseline, 59% of individuals living with COPD were not using any COPD-related medication;

Table 1 Baseline characteristics

	Total		Baseline COPD medication class													
			None		SABD only		Maintenance therapy (±SABD)									
							LABA		LAMA		LABA/LAMA		ICS/LABA		ICS/LABA/LAMA	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cohort size	192 814	100	114 178	59.2	23 084	12	286	0.1	9017	4.7	2284	1.2	21 308	11.1	16 817	8.7
Demographics																
Age, years																
Age, median (IQR)	66 (57–76)		65 (56–75)		63 (55–73)		72 (63–80)		71 (63–79)		70 (63–78)		67 (58–77)		71 (63–79)	
Category																
35–44	6400	3.3	4256	3.7	1096	4.8	<10	N/A	54	0.6	11	0.5	667	3.1	108	0.6
45–54	29 249	15.2	18 936	16.6	4560	19.8	26	9.3	541	6	117	5.2	2987	14	1105	6.6
55–64	53 860	27.9	33 076	29	6964	30.2	53	18.9	2044	22.7	546	24.1	5656	26.5	3804	22.6
65–74	49 878	25.9	28 155	24.7	5398	23.4	88	31.4	2879	31.9	784	34.6	5620	26.4	5492	32.7
75–84	35 264	18.3	19 210	16.8	3314	14.4	69	24.6	2363	26.2	628	27.7	4227	19.8	4438	26.4
85+	18 163	9.4	10 545	9.2	1752	7.6	>40	15.7	1136	12.6	198	8.7	2151	10.1	1870	11.1
Sex																
Male	97 795	50.7	53 650	47	12 947	56.1	134	46.9	4632	51.4	1248	54.6	9967	46.8	8632	51.3
Female	95 019	49.3	60 528	53	10 137	43.9	152	53.1	4385	48.6	1036	45.4	11 341	53.2	8185	48.7
Residence																
Urban	1,52,974	79.3	90 805	79.5	17 735	76.8	222	77.6	7282	80.8	1877	82.2	17 222	80.8	13 550	80.6
Rural	39 840	20.7	23 373	20.5	5349	23.2	64	22.4	1735	19.2	407	17.8	4086	19.2	3267	19.4
Clinical																
Years living with COPD																
Years, median (IQR)	6.6 (3.6–10.5)		6.5 (3.5–10.2)		6.2 (3.2–10.1)		6.8 (3.4–9.9)		6.2 (3.3–10.0)		6.8 (3.5–11.0)		6.8 (3.8–10.7)		8.2 (4.9–12.1)	
Category																
1–5	71 325	37	43 340	38	9281	40.2	115	40.2	3612	40.1	874	38.3	7665	36	4346	25.8
>5–10	68 536	35.6	40 985	35.9	7912	34.3	103	36	3158	35	740	32.4	7556	35.5	6075	36.1
>10–15	44 265	23	25 368	22.2	4976	21.6	56	19.6	1865	20.7	562	24.6	4972	23.3	5063	30.1
>15	8688	4.5	4485	3.9	915	4	12	4.2	382	4.2	108	4.7	1115	5.2	1333	7.9
Charlson Comorbidity Index																
Score, median (IQR)	1 (0–2)		0 (0–1)		1 (0–2)		1 (1–3)		1 (1–3)		1 (1–3)		1 (1–2)		1 (1–3)	
Category																
0	77 168	40	61 517	53.9	6908	29.9	38	13.3	1443	16	130	5.7	4338	20.4	1209	7.2

Continued

Table 1 Continued

	Total		Baseline COPD medication class											
			None		SABD only		Maintenance therapy (±SABD)							
							LABA		LAMA		LABA/LAMA		ICS/LABA		ICS/LABA/LAMA	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
1 February	84 783	44	39 121	34.3	11 770	51	169	59.1	5198	57.6	1496	65.5	12 958	60.8	10 828	64.4
3 April	19 466	10.1	8591	7.5	2581	11.2	55	19.2	1500	16.6	416	18.2	2680	12.6	2996	17.8
≥5	11 397	5.9	4949	4.3	1825	7.9	24	8.4	876	9.7	242	10.6	1332	6.3	1784	10.6

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$ agonist; LAMA, long-acting muscarinic antagonists; N/A, not applicable; SABD, short-acting bronchodilator.

among those who had medication use, the most common (>10%) classes that individuals used were SABD only (29%), dual ICS/LABA (27%), triple ICS/LABA/LAMA (21%), and LAMA (12%). During the 1-year observation period, 66% of those with ≥1 dispensation for an additional medication class had a step-up in therapy that was concordant with guideline recommendations. Additionally, those with baseline COPD medication use had low adherence (ie, 42%–54% of individuals maintained medication use for at least 80% of the days they received this medication class), and many had AECOPD (13%–40%) during the observation period. Combined, these results identify inconsistencies in the application of COPD guideline-recommended therapy and suboptimal medication adherence.

COPD is recognised as a heterogeneous condition, with a high degree of variation in the clinical presentation and rate of disease progression between individuals.[24–26] While we did not have clinical evaluative information on the severity of COPD, considering that 59% of individuals living with COPD in this study were not receiving any respiratory medication at baseline, and these individuals exhibited a low rate of AECOPD during the observation period, it could be argued that mild COPD was recognised, diagnosed, and managed appropriately with non-pharmacological strategies in a number of these individuals. On the other hand, while recommendations for pharmacotherapy are not clear for those with milder disease because of a lack of high-quality evidence,[27] it is possible that individuals with milder COPD could also benefit from pharmacotherapy. As an example, SABDs were found to improve pulmonary function, operating lung volumes, and dyspnoea among individuals with GOLD stage 1 COPD; although, exercise tolerance was not improved.[28 29] We also found that among those living with COPD who did not receive a respiratory medication at baseline, 4% experienced at least one AECOPD, which typically occurs in more advanced COPD[30] and 17% received a COPD-related medication over the observation period, likely representing a group who were undertreated and would benefit from respiratory medications earlier in the course of their COPD. It is also possible that some of the individuals who did not receive a COPD-related medication at baseline or during the observation period were previously misidentified as having COPD and included in the cohort. Although, this is less likely as a validated case definition was used to identify individuals living with COPD in this study (that reported a high sensitivity (85.0%; 95% CI 77.0% to 91.0%) and specificity (78.4%; 95% CI 73.6% to 82.7%)).[14]

Among those who were receiving a respiratory medication at baseline, this study identified areas of concordance with the 2017 recommendations for pharmacotherapy management of COPD,[31 32] along with potential areas for improvement. COPD guidelines promote pharmacotherapy based on lung function impairment as well as symptom burden and risk of future AECOPD.[6 7 31] Recommendations suggest step-up pharmacotherapy as

Table 2 Medication use, treatment patterns and adherence during the 1-year postindex observation period

			Baseline COPD medication class													
							Maintenance therapy (±SABD)									
	Total		None		SABD only		LABA		LAMA		LABA/LAMA		ICS/LABA		ICS/LABA/LAMA	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cohort size	1 92 814	100	1 14 178	59.2	23084	12	286	0.1	9017	4.7	2284	1.2	21308	11.1	16817	8.7
COPD-related medication use																
Received ≥1 dispensation during the observation period:																
Overall	88597	46	19367	17	16091	69.7	278	97.2	8630	95.7	2229	97.6	20104	94.4	16641	99
≥1 additional medication class	41136	21.3	19367	17	8636	37.4	129	45.1	3483	38.6	638	27.9	5407	25.4	1847	11
Adherence to baseline medication class																
All drug component(s)	21119	41.8	N/A	N/A	N/A	N/A	138	51.5	4705	56.2	1284	59.5	6830	35.7	6693	42.5
≥1 drug component	27119	53.6	N/A	N/A	N/A	N/A	138	51.5	4705	56.2	1397	64.8	7159	37.4	11990	76.2
Treatment patterns																
Discontinuation of baseline medication	28698	51.7	N/A	N/A	N/A	N/A	131	45.8	4015	44.5	845	37	11613	54.5	8249	49.1
Switch from baseline medication	7964	14.3	N/A	N/A	N/A	N/A	29	10.1	960	10.7	230	10.1	3032	14.2	2836	16.9
Among those who received ≥1 dispensation for an additional medication class																
Guideline-concordant step-up	27018	65.7	15402	79.5	5928	68.6	90	69.8	2413	69.3	328	51.4	2490	46.1	367	19.9

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$ agonist; LAMA, long-acting muscarinic antagonists; N/A, not applicable; SABD, short-acting bronchodilator.

Table 3 Acute exacerbations of COPD during the 1-year postindex observation period

	Total		Baseline COPD medication class											
			None		SABD only		Maintenance therapy (±SABD)							
							LABA		LAMA		LABA/LAMA		ICS/LABA	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Cohort size	1 92 814	100	1 14 178	59.2	23 084	12	286	0.1	9017	4.7	2284	1.2	21 308	11.1	16 817	8.7
Had ≥1 AECOPD:																
Overall	20 817	10.8	4250	3.7	2920	12.7	53	18.5	1891	21	678	29.7	3534	16.6	6639	39.5
Severe	10 658	51.2	1923	45.2	1439	49.3	27	50.9	965	51	299	44.1	1759	49.8	3788	57.1
Moderate	13 810	66.3	2608	61.4	1875	64.2	32	60.4	1233	65.2	501	73.9	2375	67.2	4624	69.6

AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$ agonist; LAMA, long-acting muscarinic antagonists; SABD, short-acting bronchodilator.

necessary, to control symptoms and reduce the frequency and severity of AECOPD.[7] In this study, only 66% of those with ≥1 dispensation for an additional medication class had a step-up in therapy that was concordant with guideline recommendations, suggesting potential practice variability or lack of clarity in guidelines. Recommendations also suggest that individuals with less symptomatic COPD (based on health status or dyspnoea) receive SABD, with LABA or LABA monotherapy added to reduce dyspnoea, improve exercise tolerance, and improve health status in individuals with stable COPD who become more symptomatic.[6 7] In the current study, 12% of individuals living with COPD were receiving SABD only at baseline, and 13% of these individuals experienced an AECOPD during the observation period. These data indicate that a number of these individuals may have been undertreated. In support of this, 37% received at least one additional medication class during the observation period. Collectively, these findings highlight the importance of guideline-based knowledge transfer strategies for healthcare providers, an integrated approach to care that includes ongoing monitoring of symptoms and quality of life, and evaluation of the risk of future AECOPD to support ideal evidence-based person-centred management of COPD.[6 7]

Long-term adherence to pharmacotherapy is an important component of COPD management. We found that 42% of individuals were adherent to all drug component(s) contained within their baseline medication class for the length of time they received this medication class during the observation period. Low medication adherence appears to be common in individuals living with COPD, and is associated with an increased risk of AECOPD, hospitalisations, and mortality.[8–11] Multiple factors contribute to adherence including knowledge, attitudes, and beliefs of the individual towards the medication, and cost of the medication; various strategies to improve and support medication adherence in COPD have been suggested such as strong patient–physician and patient–pharmacist communication, optimised coordination of care, patient education, confidence in inhaler technique, and single-inhalers for multiple medications.[6 33–35] To this end, Yu *et al*[36] conducted a retrospective study on 11 747 matched pairs of individuals living with COPD in the USA, and found that after adjusting for confounding factors, those who used multiple inhalers had significantly higher discontinuation rates and were less likely to be adherent compared with those who used single inhalers.[36] Our results are consistent with previous findings, showing that overall adherence to COPD-related medication was low, and a higher proportion of individuals were more likely to be adherent to one drug component (one inhaler) than to all drug components contained within a medication class (multiple inhalers, in most cases), suggesting a simplified drug regimen may be advantageous.

This study has several important strengths, including the large size and population-based design. However, this

study is also subject to a number of limitations that should be taken into consideration when interpreting results. Retrospective claims-based studies use administrative data as opposed to medical records, and therefore, there is a potential for misclassification of the study groups or measures. Although the case definition used to identify individuals living with COPD in the Alberta COPD Registry has been validated using Canadian administrative health data (from the province of Ontario) and resulted in 85% sensitivity, 78% specificity, 58% positive predictive value and 94% negative predictive value,[14] it is possible that some individuals who did not have COPD were included in the cohort, which would affect the calculation of proportion receiving therapy, but not calculations of medication adherence. The PIN database only provides information on prescription medication dispensations from community pharmacies. While over the counter medications are not captured in the PIN, SABDs are only available by prescription in Canada, and therefore, comprehensively included in the study. It is possible that some individuals would have received short-term medication while hospitalised, and these medications would not be reported; although this would likely be a small proportion of medications dispensed. Non-pharmacotherapy self-management techniques are not captured within provincial administrative data, and therefore, not reported.

CONCLUSIONS

Results of this study provide a snapshot into real world medication use and AECOPD among individuals living with COPD that can inform opportunities for optimised pharmacotherapy practices and improved contemporary management. The majority of individuals living with COPD were not using any COPD-related medication (59%), while in those who were taking medication, deficits in alignment to guideline-recommended therapy were observed, adherence was low (42%–54%) and many had AECOPD. These findings identify substantial gaps in COPD pharmacotherapy that may guide clinical care and future guideline development. Areas for improvement may include strategies for earlier identification of undertreatment, consideration of guideline-based knowledge transfer strategies for healthcare providers and mechanisms to improve long-term medication adherence.

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Contributors KJBM, NKV, SWK and MKS contributed to the study concept and design, NKV conducted the analyses, and HS prepared the initial manuscript with support from KJBM. All authors contributed to the interpretation of the data and critical revision of the manuscript for important intellectual content, as well as approved the final version to be published and agreed to be accountable for all aspects of the work ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved. SWK provided study supervision, and accepts full responsibility for the finished work and/or conduct of the study, had access to the data, and controlled the decision to publish.

Funding Funding for the study was provided by GlaxoSmithKline (study 212858) to Lawrence Richer.

Disclaimer The funder had no role in the study design, analysis, interpretation of the data, drafting of the manuscript, or in the decision to submit for publication.

Competing interests The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: KJBM, NKV, TW, LR and SWK are members of the Alberta Real World Evidence Consortium, an academic entity that conducts research including investigator-initiated industry-funded studies. MB and BLW have received research, speaking, and consultancy funds (from sources such as industry, non-profit organisations, and research groups). No other conflict of interest was declared. All authors of this study had complete autonomy over the content and submission of the manuscript, as well as the design and execution of the study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and ethics approval for this study was received from the University of Alberta institutional review board (Pro00093415). No participants were placed at risk as a result of the study, and a waiver of consent was applied.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The datasets analysed during the current study are not publicly available because the data custodians, Alberta Health Services and Alberta Health do not allow users of the data to publish the data. Please contact the corresponding author for requests related to the data used in this study.

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Supplementary Table 1. Diseases, and their associated codes and weights included in the Charlson Comorbidity Index.

Disease	ICD-9-CM codes	ICD-10-CA codes	Weight
Myocardial infarction	410, 412	I21, I22, I25.2	1
Congestive heart failure	398, 402, 425, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0	1
Peripheral vascular disease	440, 441, 443, 447, 557	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	430, 431, 432, 433, 434, 435, 436, 437, 438	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H34.0	1
Dementia	290, 294, 331	F00, F01, F02, F03, G30, F05.1, G31.1	1
Chronic pulmonary disease	416, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, I27.8, I27.9, J68.4, J70.1, J70.3	1
Connective tissue disease	446, 710, 714, 725	M05, M32, M33, M34, M06, M31.5, M35.1, M35.3, M36.0	1
Peptic ulcer disease	531, 532, 533, 534	K25, K26, K27, K28	1
Mild liver disease	070, 570, 571, 573	B18, K73, K74, K70.0, K70.1, K70.2, K70.3, K70.9, K71.7, K71.3, K71.4, K71.5, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4	1
Moderate/severe liver disease	456, 572	K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2	3
Diabetes (without complication)	250	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	1
Diabetes (with complication)	250	E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7, E14.2, E14.3, E14.4, E14.5, E14.7	2

Disease	ICD-9-CM codes	ICD-10-CA codes	Weight
Hemiplegia and paraplegia	334, 342, 343, 344	G81, G82, G04.1, G11.4, G80.1, G80.2, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9	2
Moderate or severe renal disease	403, 582, 583, 585, 586, 588, V56	N18, N19, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N25.0, I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2	2
Cancer	140-165, 170-172, 174-176, 179-195, 200- 208, 238	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90- C97	2
Metastatic Carcinoma	196, 197, 198, 199	C77, C78, C79, C80	6
HIV/AIDS	042, 043, 044	B20, B21, B22, B24	6

To be considered as having one of the listed diseases, an individual must have had ≥1 hospitalization (associated ICD-10-CA code listed in any diagnostic field) or ≥2 physician claims (associated ICD-9-CM codes listed in any diagnostic field) of the corresponding ICD within ≤2-years. Abbreviations: HIV/AIDS = Human immunodeficiency virus / acquired immunodeficiency syndrome; ICD-9-CM = International classification of diseases, ninth revision, clinical modification; ICD-10-CA = International classification of diseases, tenth revision, Canadian enhancement.

Supplementary Table 2. Drugs included in the COPD medication classes and those used to define acute exacerbations of COPD (AECOPD).

COPD medications	Active ingredient(s)	ATC classification
COPD treatment medications		
SABA	Salbutamol	R03AC02
	Terbutaline sulfate	R03AC03
	Fenoterol hydrobromide	R03AC04
SAMA	Ipratropium bromide	R03BB01
SABA / SAMA	Fenoterol hydrobromide / Ipratropium bromide	R03AL01
	Salbutamol / Ipratropium bromide	R03AL02
LABA	Salmeterol	R03AC12
	Formoterol	R03AC13
	Indacaterol	R03AC18
LAMA	Tiotropium	R03BB04
	Aclidinium bromide	R03BB05
	Glycopyrronium bromide	R03BB06
	Umeclidinium bromide	R03BB07
LABA / LAMA	Vilanterol / Umeclidinium	R03AL03
	Indacaterol / Glycopyrronium	R03AL04
	Formoterol / Aclidinium	R03AL05
	Olodaterol / Tiotropium	R03AL06
ICS	Fluticasone furoate	R01AD12
	Beclomethasone dipropionate	R03BA01
	Budesonide	R03BA02
	Fluticasone propionate	R03BA05
	Mometasone furoate	R03BA07
	Ciclesonide	R03BA08
ICS / LABA	Fluticasone / Salmeterol	R03AK06
	Budesonide / Formoterol	R03AK07
	Mometasone / Formoterol	R03AK09
	Fluticasone / Vilanterol	R03AK10
ICS / LABA / LAMA	Fluticasone / Vilanterol / Umeclidinium	R03AL08
Methylxanthines	Theophylline	R03DA04
	Aminophylline	R03DA05
	Oxtriphylline / Guaifenesin	R03DA54
PDE-4 inhibitors	Roflumilast	R03DX07
Antibiotics	Azithromycin (long-term use: >21 consecutive days of supply)	J01FA10
AECOPD medications (short-term use; ≤21 consecutive days of supply)		
Oral corticosteroids	Prednisone	H02AB07
Antibiotics	All antibiotics for systemic use	J01

Abbreviations: ATC - anatomical therapeutic chemical; COPD - chronic obstructive pulmonary disease; ICS - inhaled corticosteroid; LABA - long-acting beta$_2$ agonist; LAMA - long-acting muscarinic antagonists; PDE-4 - phosphodiesterase-4; SABA - short-acting beta$_2$ agonist; SAMA - short-acting muscarinic antagonists; AECOPD – acute exacerbations of COPD.

Supplementary Table 3. Characteristics of those who received ancillary medication classes at baseline.

	Baseline COPD medication class					
	ICS				Other (+/- SABD)	
	ICS only		ICS + Other and/or SABD			
	N	(%)	N	(%)	N	(%)
Cohort size	1,608	0.8	4,001	2.1	231	0.1
Demographics						
Age, years						
Age, median (IQR)	66 (57 - 75)		64 (56 - 75)		65 (59 - 71)	
Category						
35-44	47	2.9	152	3.8	<10	N/A
45-54	248	15.4	702	17.6	27	11.7
55-64	448	27.9	1,187	29.7	82	35.5
65-74	442	27.5	943	23.6	77	33.3
75-84	283	17.6	697	17.4	35	15.2
85+	140	8.7	320	8.0	<10	N/A
Sex						
Male	839	52.2	2,366	59.1	118	51.1
Female	769	47.8	1,635	40.9	113	48.9
Residence						
Urban	1,315	81.8	2,792	69.8	174	75.3
Rural	293	18.2	1,209	30.2	57	24.7
Clinical						
Years living with COPD						
Years, median (IQR)	6.8 (3.4 - 10.2)		6.9 (3.6 - 11.0)		9.7 (5.4 - 14.1)	
Category						
1 - 5	608	37.8	1,437	35.9	47	20.3
>5 - 10	575	35.8	1359	34.0	73	31.6
>10 - 15	353	22.0	977	24.4	73	31.6
>15	72	4.5	228	5.7	38	16.5
Charlson Comorbidity Index						
Score, median (IQR)	1 (0 - 1)		1 (1 - 2)		2 (1 - 3)	
Category						
0	668	41.5	882	22.0	35	15.2
1-2	749	46.6	2,366	59.1	128	55.4
3-4	129	8.0	471	11.8	47	20.4
≥5	62	3.9	282	7.1	21	9.1

Abbreviations: COPD - chronic obstructive pulmonary disease; ICS - inhaled corticosteroid; IQR - interquartile range; LABA - long-acting beta$_2$ agonist; LAMA - long-acting muscarinic antagonists; N/A - not applicable; SABD - short-acting bronchodilator.

Supplementary Table 4. Medication use, treatment patterns, and adherence during the 1-year post-index period among those who received ancillary medication classes.

	Baseline COPD medication class					
	ICS				Other (+/- SABD)	
	ICS only		ICS + Other and/or SABD			
	N	(%)	N	(%)	N	(%)
Cohort size	1,608	0.8	4,001	2.1	231	0.1
COPD-related Medication use						
Received ≥1 dispensation during the observation period:						
Overall	1,293	80.4	3,745	93.6	219	94.8
≥1 additional medication class	504	31.3	1,050	26.2	75	32.5
Adherence to baseline medication class						
All drug component(s)	333	27.3	1,015	29.2	121	56.8
≥1 drug component	333	27.3	1,276	36.8	121	56.8
Treatment patterns						
Discontinuation of baseline medication	1,171	72.82	2,567	64.16	107	46.32
Switch from baseline medication	70	4.35	789	19.72	18	7.79
Among those who received ≥1 dispensation for an additional medication class						
Guideline-concordant step-up	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: COPD - chronic obstructive pulmonary disease; ICS - inhaled corticosteroid; LABA - long-acting beta$_2$ agonist; LAMA - long-acting muscarinic antagonists; N/A - not applicable; SABD - short-acting bronchodilator.

Supplementary Table 5. AECOPD during the 1-year post-index period among those who received ancillary medication classes.

	Baseline COPD medication class					
	ICS				Other (+/- SABD)	
	ICS only		ICS + Other and/or SABD			
	N	(%)	N	(%)	N	(%)
Cohort size	1,608	0.8	4,001	2.1	231	0.1
Had ≥1 AECOPD						
Overall	76	4.7	743	18.6	33	14.3
Severe	31	40.8	404	54.4	23	69.7
Moderate	54	71.1	489	65.8	19	57.6

Abbreviations: AECOPD – acute exacerbations of COPD; COPD - chronic obstructive pulmonary disease; SABD - short-acting bronchodilator.