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ORIGINAL RESEARCH

A 4-Year Retrospective Claims Analysis of Oral Corticosteroid Use and Health Conditions in Newly Diagnosed Medicare FFS Patients with COPD

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Purpose: We analyzed population-level administrative claims data for Medicare fee-for-service (FFS) beneficiaries to provide insights on systemic oral corticosteroid (OCS) use patterns and associated health conditions and acute events among patients newly diagnosed with chronic obstructive pulmonary disease (COPD).

Background: COPD is a progressive inflammatory disease of the lungs, characterized by acute exacerbations that may lead to increased mortality. Short courses of systemic corticosteroids (SCS) are recommended to reduce recovery time from exacerbations, although SCS use has been associated with increased risk of adverse events.

Methods: This study used 2013–2019 Medicare 100% FFS research identifiable files, which contain all Medicare Parts A, B, and D paid claims incurred by 100% of Medicare FFS beneficiaries. Descriptive statistics for patients newly diagnosed with COPD were analyzed, including OCS use, select health conditions and acute events, and COPD exacerbations. Statistical models were used to analyze the relationship between the incidence of select health conditions and events and cumulative OCS dosage.

Results: Of Medicare FFS patients newly diagnosed with COPD, 36% received OCS in the 48 months following diagnosis, and 38% of OCS episodes lasted longer than the recommended 5–7 days. Patients had a variety of health conditions or acute events in the 24-month period prior to new COPD diagnosis, such as hypertension, depression/anxiety, type 2 diabetes, or osteoporosis, that could heighten the risks of OCS use. Patients treated with >1000 mg of prednisolone equivalent OCS in the 48 months following COPD diagnosis had a higher incidence of new conditions or events, including cardiovascular disease, heart failure, hypertension, obesity, dyspepsia, infections, and depression/anxiety, than patients with no OCS use.

Conclusion: These results highlight the potential risks of OCS in COPD treatment, including prolonged use among complex Medicare patients, and reinforce the importance of preventive treatment strategies and therapy optimization early in the disease course.

Keywords: chronic obstructive pulmonary disease, systemic corticosteroids, SCS, OCS, COPD exacerbations, claims analysis

Introduction

COPD is characterized by airflow limitation and caused by chronic exposure to inhaled noxious particles.[1] The prevalence of diagnosed COPD in the United States (US) in 2020 was estimated at 6.2%,[2] and the prevalence is projected to increase partly because of the aging population.[3] US healthcare costs attributable to COPD are sizeable; the medical cost burden of COPD in 2020 was estimated to be $49 billion dollars, which is 53% higher than 2010.[4]

Reducing the frequency and severity of exacerbations is an important goal of COPD treatment as these exacerbation events are associated with increased mortality.[5] Short courses of systemic corticosteroids (SCS), at a daily dose of 40 mg prednisolone equivalent for no more than 5–7 days, are recommended to shorten recovery time for exacerbations and the

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duration of hospitalizations.[6] However, in clinical practice, these bursts of SCS may be longer and larger than recommended.[7] Long-term SCS use has not been shown to reduce mortality, exacerbations, dyspnea, or hospital admissions.[7,8]

Among a broad sample of 18–64 year-olds from a large nationwide US insurer, even short courses of SCS were found to be associated with an increased risk of adverse events including sepsis, venous thromboembolism, and fractures.[9] Moreover, several recent publications have described the complications of SCS use specifically in asthma patients.[10–15] Specifically for COPD, a number of older studies demonstrated an association between SCS use and adverse effects including hyperglycemia, a reduction in bone mineral density, myopathy, hypertension, infection, psychiatric disturbances, and gastrointestinal bleeding.[8,16–18] While SCS are recommended treatments for COPD exacerbations, recent population-level information is not widely available on either the use of SCS in patients with COPD or the potential consequences of SCS exposure.[19] The availability of Medicare FFS administrative claims data yields an opportunity to study patients with COPD on a large scale in real-world settings. The purpose of this study was to analyze Medicare FFS administrative claims data to provide insights for providers, pharmacists, and health plans regarding oral SCS (OCS) use patterns and associated chronic health conditions and acute events among newly diagnosed Medicare FFS patients with COPD.

Materials and Methods

Study Population

The study population of newly diagnosed patients with COPD was identified from the Medicare 100% Research Identifiable Files of FFS beneficiaries for years 2013–2019; individuals may be eligible for Medicare due to age, disability, end-stage renal disease (ESRD), or amyotrophic lateral sclerosis (ALS).[20] Data was accessed through the Virtual Research Data Center under an Institutional Review Board agreement. The database contains Medicare Parts A, B, and D paid claims incurred by 100% of Medicare FFS beneficiaries, which provides all inpatient facility, outpatient facility, professional, and pharmacy claims for these patients.[20] The database consists of administrative claims only and does not include the additional clinical detail found in encounter data. To be identified as a patient with COPD, a diagnosis of COPD (ICD-9-CM: 491x, 492x, 496; ICD-10-CM: J41x, J42, J43x, J44x) was required in any diagnosis code position on at least one acute or non-acute inpatient, emergency department, or observation claim in 2015, or at least two outpatient visit claims on different dates of service at least 30 days apart in 2015. The earliest date in 2015 of a COPD diagnosis was defined as the index date. Patients were required to have continuous Medicare Parts A, B, and D coverage for the 24 months prior to the index date (baseline period) and at least 12 months after the index date. The baseline period was used to identify patient characteristics, background chronic health conditions, and acute events of interest, as well as parameters used to exclude patients from the study. Patients were followed for a minimum of 12 months and up to 48 months post-index.

Patients that met any of the following criteria were excluded from the study population: patients aged under 40 at index, patients with any COPD diagnosis in the baseline period (ie prevalent patients with COPD), patients with any claim for oral or injectable SCS (excluding intraarticular injections) in the baseline period, patients originally eligible for Medicare on the basis of ESRD, patients with any diagnosis of adrenal insufficiency or cancer (not including basal/squamous cell skin cancers) in the baseline period or within 12 months of the index date, patients with any claim for hormonal therapy of breast cancer in the baseline period or within 12 months of the index date, patients with diagnoses for conditions for which SCS may be commonly prescribed in the baseline period or within 12 months of the index date (so as to remove patients for whom SCS use may be associated with conditions other than COPD or associated exacerbation events), or patients with any diagnosis of history of transplant or history of cancer in the baseline period or at any point following the index date (see Table S-7 for these conditions).

The impact of these exclusions on the study population size can be found in Figure S-2. In order to include as much follow-up time as possible while excluding OCS use likely related to non-COPD conditions, patients who developed one of the exclusionary conditions more than 12 months after the index date were censored from the analysis as of the date of the excluded diagnosis or claim. Exposure and claims data occurring prior to these diagnoses or claims were included in the analysis.

Identification of OCS and Related Measures

OCS use in the post-index period was identified by Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes (NDCs) for oral betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone. The dosage for each prescription was converted to prednisolone equivalents (see Table S-8). Injectable SCS were not included in this study, as often these are administered in an inpatient setting and consequently detailed dosage and administration information is not available in the source database.

The percentage and number of patients receiving OCS prescriptions, as well as distribution of OCS fills during the post-index period and cumulative dosing, were examined. To further describe OCS use, OCS episodes were defined as periods of continuous OCS use (allowing for gaps in days supply of up to 14 days). The proximity of multiple scripts likely indicates continuous use with refills rather than separate prescriptions. Patients were grouped by the timing of their OCS episodes: (a) sporadic users with gaps of at least 365 days between episodes, (b) infrequent users with gaps of 182–364 days, (c) moderately infrequent users with gaps of 90–181 days, and (d) frequent users with gaps of 15–89 days. Patients with varying size gaps between episodes were considered mixed users.

Identification of Health Conditions and Events

Twenty-nine different chronic health conditions and acute events were examined in both the baseline period and post-index period, collectively termed potential adverse health outcomes of interest (see Table 1). Due to the limited evidence among COPD patients, the selection of these conditions and events was informed by existing literature on the impact of SCS use for asthma patients.[10–15] A chronic condition was considered incident in the post-index period if it was not also identified in the 24-month baseline period. For acute events, the first event in the post-index period was used as the date of the event. See Supplemental Materials for the identification algorithms for the 29 health conditions and events.

Treatment for COPD exacerbations were identified to provide further context on possible opportunities for OCS use and treatment patterns that may not be captured fully in pharmacy claims, particularly COPD hospitalizations where both

Table 1 Potential Adverse Health Conditions and Events of Interest

Chronic Conditions	Acute Events
Atrial fibrillation/flutter	Gastrointestinal bleeding/peptic ulcers
Avascular necrosis	Myocardial infarction
Cardiomyopathy	Osteoporotic fracture
Cardiovascular disease	Other infections that may be associated with immunosuppression
Cataracts	Sepsis
Chronic kidney disease	Stroke
Depression/anxiety	
Dyslipidemia	
Dyspepsia	
Glaucoma	
Heart failure	
Hypertension	
Metabolic syndrome/pre-diabetes	
Mycobacterium avium infection	
Non-healing extremity ulcer	

(*Continued*)

Table 1 (Continued).

Chronic Conditions	Acute Events
Obesity	
Osteoporosis	
Peripheral arterial disease	
Psychosis	
Sleep apnea	
Sleep disorders (non-apnea)	
Thromboembolism	
Type 2 diabetes	

OCS and injectable administration may be common. COPD hospitalizations were defined as acute inpatient hospital facility claims with a principal diagnosis of COPD or bronchiectasis; a principal diagnosis of an acute pulmonary condition, sepsis, or respiratory failure with a secondary diagnosis of COPD or bronchiectasis; or a principal diagnosis for select acute pulmonary conditions commonly diagnosed in the setting of COPD hospitalizations, such as acute bronchitis and unspecified pneumonia. Emergency department (ED) visit exacerbation events were identified as facility claims for ED or observation visits with a diagnosis code for COPD or bronchiectasis in any diagnosis code position with an accompanying pharmacy claim for a short course of OCS or antibiotic commonly used for respiratory infections (up to a 14-day supply) within 7 days (±) of the ED visit or a HCPCS code on the ED visit claim for an SCS or respiratory infection antibiotic injection/infusion. Ambulatory, non-ED COPD exacerbation events were identified as outpatient medical claims that met at least one of the following requirements: a principal diagnosis code specifically for a COPD acute exacerbation on a claim for an outpatient evaluation and management (E&M) visit or telephone assessment and management visit; or a diagnosis code of COPD or bronchiectasis in any position on a claim for an outpatient E&M or a telephone assessment and management encounter where an accompanying pharmacy claim for a short course of OCS or antibiotic (as defined earlier) is present.

With the exception of COPD hospitalizations events, only one exacerbation was attributed to a patient during any 14-day period. The exacerbation event of the most severe type (hospitalization, then emergency department, then ambulatory non-ED) during the period was assigned.

Descriptive and Statistical Analysis

OCS scripts, episodes, and prednisolone equivalent dose were analyzed for the 1–12, 1–24, 1–36, and 1–48 month post-index periods. Patient characteristics, COPD exacerbations, baseline chronic health conditions and events, and incident health outcomes post-index were summarized for the full study population and by cumulative OCS dose in the 1–48 months post-index.

Cox proportional hazards regression models with time-varying covariates were developed to analyze each of the 29 health conditions and events in the post-index period. Patients with one or more of the chronic conditions of interest identified in Table 1 in the baseline period were excluded from the regressions for those specific conditions so as to focus on the occurrence of new, incident diagnoses. Time-varying covariates were used for cumulative OCS prednisolone equivalent dosage. Before adjusting for patient characteristics, univariable regressions using OCS prednisolone equivalent dosage only were run to produce natural spline graphs to show initial risk and dose exposure relationships. For all multivariable regressions, dual-eligibility at index date, 2015 Centers for Medicare & Medicaid Services Hierarchical Condition Category (CMS-HCC) risk score,[21] race, residence in a Metropolitan Statistical Area,

and sex were included as independent variables. For acute events, the presence of the same event in the baseline period was also included as a covariate. For specific health outcomes, additional covariates for the presence of a clinically related health condition or event in the baseline period were included: osteoporotic fractures: presence of osteoporosis; type 2 diabetes: presence of metabolic syndrome/pre-diabetes or obesity; cataracts: presence of type 2 diabetes; gastrointestinal bleeding/peptic ulcers: presence of dyspepsia or atrial fibrillation; stroke: presence of atrial fibrillation; and sleep apnea: presence of type 2 diabetes, metabolic syndrome/pre-diabetes, or obesity. Additional regression models were also run to explore the relationship between COPD hospitalizations and the risk of the health outcomes of interest.

Because of the large number of health outcomes consisting of both new onset chronic health conditions and acute events, an aggregate measure of the total number of incident health outcomes for a patient in the 48 months post-index was developed; consequently, analysis of this outcome was limited to patients with the full 48 month post-index data availability. A linear regression analysis was performed that included covariates for the total cumulative OCS prednisolone equivalent dosage in the 48 months post-index, dual-eligibility at index date, 2015 CMS-HCC risk score, race, residence in a Metropolitan Statistical Area, and sex. This regression was performed for individual health conditions and events as well for comparison.

Patients with >0-<50 mg or >4000 mg of prednisolone equivalent OCS use over the 48 months post-index (0.9% of the study population) were excluded from the statistical analysis to avoid outliers deemed clinically implausible and to exclude potentially miscoded dosage data which could bias results.

All statistical analyses were performed using SAS® 9.4.

Results

Study Population

Out of 24.2 million Medicare FFS beneficiaries with Parts A, B, and D coverage, 183,637 patients met the criteria for the study population. A total of 142,852 patients (78%) had at least 24 months of post-index data availability, 111,577 patients (61%) had at least 36 months post-index of data availability, and 88,029 patients (48%) had at least 48 months post-index of data availability; average months of post-index enrollment was 37 months for the total study population (Table 2). The average age of the 183,637 patients newly diagnosed with COPD was 71.8 years at the time of diagnosis. Nearly a quarter of the patients were aged 40–64; these patients were eligible for Medicare on the basis of disability. Over half of the identified patients were female (55.3%). Almost half of the patients were eligible for the Medicare Part D low-income subsidy. The accompanying Table S-1 provides additional details for the demographics of the study population by post-index OCS exposure.

Table 2 Patient Characteristics for Total Study Population (N=183,637)

Characteristic	n	%
Age at index		
Aged 40–64	42,836	23.3%
Aged 65–69	27,724	15.1%
Aged 70–74	36,826	20.1%
Aged 75–79	28,544	15.5%
Aged 80+	47,707	26.0%
Mean age	71.8	
Median age	72	

(*Continued*)

Table 2 (Continued).

Characteristic	n	%
Sex		
Female	101,471	55.3%
Male	82,166	44.7%
Low Income Subsidy eligibility		
Non low-income subsidy eligible at index	95,663	52.1%
Low-income subsidy eligible at index	87,974	47.9%
Medicaid-Medicare dual eligibility		
Non dual-eligible at index	107,499	58.5%
Dual-eligible at index	76,138	41.5%
Metropolitan Statistical Area (MSA)		
Residence in an MSA	133,448	72.7%
Residence outside an MSA	50,189	27.3%
Race		
White	155,704	84.8%
Black	17,248	9.4%
Other	9,876	5.4%
Unknown	809	0.4%
Follow-Up Time in Study Population		
At least 12 months post-index	183,637	100.0%
At least 24 months post-index	142,852	77.8%
At least 36 months post-index	111,577	60.8%
At least 48 months post-index	88,029	47.9%
Mean follow-up post-index (months)	37	
Median follow-up post-index (months)	47	

OCS Use

Within the first 12 months following the index date, 19% of the study population (n=34,320) received at least one prescription for OCS; of these patients, 71% filled a single script, 18% filled two, and 11% filled at least three. In this 12-month period, 85% of patients receiving OCS had a cumulative prednisolone equivalent dose of 500 mg or less, 11% had between 500 and 1000 mg, and 4% had over 1000 mg (Table 3). By 48 months following initial COPD diagnosis, 36% of the study population (n=65,525) had received at least one OCS script. Of the patients receiving OCS during this period, 73% had a cumulative prednisolone equivalent dose of up to 500 mg, 17% had between 500 and 1000 mg, and 11% had over 1000 mg. The mean cumulative OCS over 48 months post-index was 526 mg, and the median was 300 mg (Table 3).

Over the 48 months post-index, 58% of patients who filled OCS prescriptions had a single OCS episode. Another 11% were sporadic users, 8% were moderately infrequent or infrequent users, 6% were frequent users with gaps of under three months, and the remaining 17% had varied spacing between episodes. Of note, 62% of episodes were within the

Table 3 OCS Use Patterns

OCS Use within Time Period	1–12 Months Post-Index		1–24 Months Post-Index		1–36 Months Post-Index		1–48 Months Post-Index	
	n/Mean	%/Median	n/Mean	%/Median	n/Mean	%/Median	n/Mean	%/Median
Patients included in analysis	183,637	100%	183,637	100%	183,637	100%	183,637	100%
Average patient months in period per patient	12		23		31		37	
Cumulative OCS Dose[a]								
0 mg	149,317	81%	133,854	73%	124,465	68%	118,112	64%
>0 to 500 mg	29,091	16%	39,400	21%	44,563	24%	47,612	26%
>500 to 1000 mg	3,752	2%	6,927	4%	9,249	5%	10,930	6%
>1000 to 1500 mg	784	0%	1,679	1%	2,557	1%	3,209	2%
>1500 mg	693	0%	1,777	1%	2,803	2%	3,774	2%
Mean/median mg among >0 mg patients	343	210	422	250	481	280	526	300
Number of OCS Prescriptions								
0	149,317	81%	133,854	73%	124,465	68%	118,112	64%
1 Fill	24,433	13%	30,807	17%	33,367	18%	34,658	19%
2 Fills	6,251	3%	10,435	6%	12,755	7%	14,222	8%
3 Fills	1,948	1%	4,040	2%	5,717	3%	6,870	4%
≥4 Fills	1,688	1%	4,501	2%	7,333	4%	9,775	5%
Pattern of OCS use								
No OCS use	149,317	81%	133,854	73%	124,465	68%	118,112	64%
Single episode	26,649	15%	33,627	18%	36,406	20%	37,819	21%
Sporadic episodes: *at least 365 days apart*	> 0	~0%	2,706	1%	5,128	3%	7,068	4%
Infrequent episodes: *182–364 days apart*	1,816	1%	3,055	2%	3,373	2%	3,450	2%
Moderately infrequent episodes: *90–181 days apart*	1,669	1%	2,164	1%	2,238	1%	2,263	1%
Frequent episodes: *15–89 days apart*	2,982	2%	3,596	2%	3,796	2%	3,855	2%
Mixed: *gaps between episodes are a mixture of the patterns listed above*	> 1,194	~1%	4,635	3%	8,231	4%	11,070	6%

Notes: Results may be approximated with ">" or "~" in accordance with the CMS data use agreement. [a]Cumulative OCS dose is standardized to prednisolone equivalents.
Abbreviations: OCS, oral corticosteroid; mg, milligram; CMS, Centers for Medicare & Medicaid Services.

maximal length of 7-days recommended by GOLD,[6] whereas nearly 38% of OCS episodes exceeded these recommendations (Figure 1). Among all OCS episodes, 10% lasted at least 20 days.

COPD Exacerbations

COPD exacerbations (as evidenced by claim patterns) provide further context on possible opportunities for OCS use and treatment patterns that may not be captured fully in pharmacy claims. Within 12 months of a new COPD diagnosis, 11%

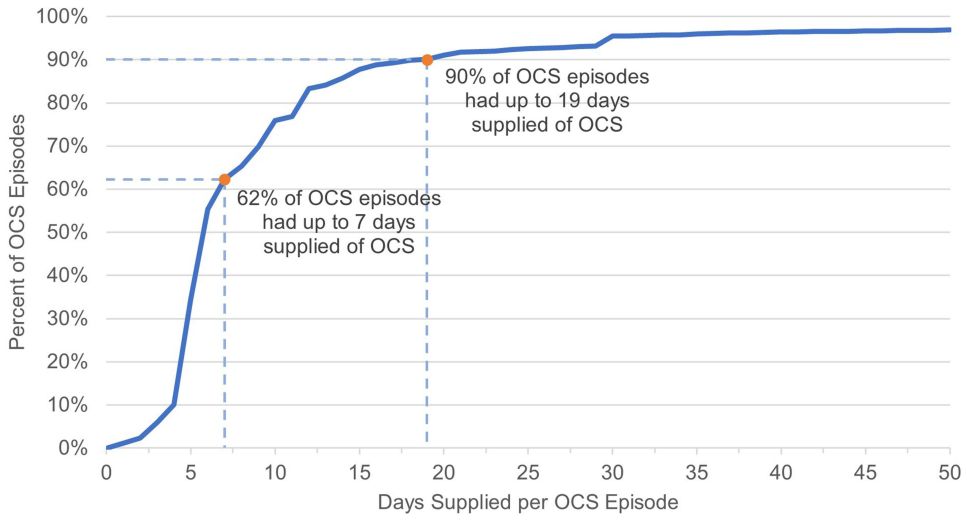

Figure 1 Cumulative distribution of OCS episodes by days supplied.
Abbreviation: OCS, oral corticosteroid.

of patients had at least one COPD hospitalization and 34% had at least one COPD hospitalization, emergency department, or ambulatory exacerbation. By 48 months after initial COPD diagnosis, 52% of patients had at least one COPD exacerbation (including hospitalization, emergency department, or ambulatory) identified by claim patterns (Table 4). The average number of COPD exacerbations per patient per year was 0.48 in the 12 month post-index period

Table 4 COPD Exacerbations by Severity for Initial 12-Month Period and by Cumulative Prednisolone Exposure Over 48-Month Period

% of Patients with COPD Exacerbations in the Specified Time Period	Months 1–12 Post-Index	Cumulative Prednisolone Equivalent OCS Use in Months 1–48 Post-Index					
	All Patients	All Patients	0 mg	>0-500 mg	>500-1000 mg	>1000-1500 mg	>1500 mg
Patients included in analysis	183,637	183,637	118,112	47,578	10,942	3,214	3,791
Average patient months in period per patient	12	37	36	39	41	41	41
COPD Hospitalizations							
% of patients with no exacerbations	89%	80%	85%	75%	67%	61%	53%
% of patients with 1 exacerbation	9%	14%	12%	18%	20%	22%	24%
% of patients with 2 exacerbations	1%	3%	2%	5%	7%	9%	11%
% of patients with at least 3 exacerbations	>0%	2%	1%	2%	5%	8%	13%
Hospitalization or ED COPD Exacerbations							
% of patients with no exacerbations	83%	72%	80%	61%	51%	46%	39%
% of patients with 1 exacerbation	14%	19%	15%	27%	26%	24%	25%
% of patients with 2 exacerbations	2%	5%	3%	8%	12%	14%	13%
% of patients with 3 exacerbations	1%	3%	1%	4%	11%	16%	23%

(*Continued*)

Table 4 (Continued).

% of Patients with COPD Exacerbations in the Specified Time Period	Months 1–12 Post-Index	Cumulative Prednisolone Equivalent OCS Use in Months 1–48 Post-Index					
	All Patients	All Patients	0 mg	>0-500 mg	>500-1000 mg	>1000-1500 mg	>1500 mg
Hospitalization, ED, or Ambulatory COPD Exacerbations							
% of patients with no exacerbations	66%	48%	60%	29%	17%	13%	13%
% of patients with 1 exacerbation	25%	26%	25%	32%	23%	17%	14%
% of patients with 2 exacerbations	6%	12%	9%	18%	19%	16%	12%
% of patients with at least 3 exacerbations	3%	14%	7%	20%	41%	54%	61%

Notes: Results may be approximated with ">" or "~" in accordance with the CMS data use agreement.
Abbreviations: COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroid; ED, emergency department; mg, milligram; CMS, Centers for Medicare & Medicaid Services.

and 0.37 in the 48 month post-index period. See Table S-2 for additional data on COPD exacerbation event frequency by severity and time period post-index.

As shown in Table 4, the incidence of COPD exacerbations increased with increasing use of OCS during the 48-month post-index period. Among the 7,005 patients with more than 1000 mg prednisolone equivalent OCS exposure in the 48-month period, 43% had at least one COPD hospitalization and 87% had an exacerbation of any type. In contrast, among the 118,112 patients with no OCS fills in the 48 months post-index, 15% had at least one COPD hospitalization and 40% had an exacerbation of any type (results at least 2.5 standard deviations away from 0); it is possible that many of these patients experienced SCS exposure in the inpatient or emergency department setting that is unaccounted for in the available outpatient prescription claims data.

Comorbidities and Potential Adverse Health Outcomes

Table 5 displays the baseline prevalence of the 29 chronic conditions and acute events, as well the new incidence of outcomes post-index that were not previously identified for these patients. Of the 29 chronic health conditions and acute events identified, there were an average of 4.7 chronic conditions or events identified per patient in the study population in the 24-month baseline period prior to index date. Overall, hypertension (67% of patients), dyslipidemia (60%), infections that may be associated with immunosuppression (47%), depression/anxiety (32%), dyspepsia (29%), cardiovascular disease (28%), type 2 diabetes (28%), and cataracts (28%) were the most common chronic conditions and acute events identified in the baseline period, indicating a heavy comorbidity burden and complexity that many of these patients have upon initial COPD diagnosis.

In the 48-month period following initial COPD diagnosis, patients in the study population had a mean of 3.5 new chronic conditions or acute events identified; 94% of patients had at least one new health outcome in the post-index period. For example, 84% percent of patients had at least one cardiovascular chronic condition or acute event in the baseline period, and 54% experienced at least one additional new cardiovascular outcome in the post-index period. On an individual basis, the most frequently occurring new health outcomes were infections (77%), cataracts (20%), and dyspepsia (20%).

Patients with no OCS use over the 48-month study period had 3.3 new health outcomes identified in the claims data, whereas patients with more than 1500 mg cumulative OCS use had 4.5 health outcomes (results at least 2.5 standard deviations away from 0) (Figure 2). Compared to those with 0 mg OCS exposure in the 48 months post-index, those with >1000 mg had a higher incidence of new conditions or events such as cardiovascular disease, heart failure, hypertension,

Table 5 Comorbidities and Potential Adverse Health Outcomes Identified in the Baseline and Post-Index Periods

Health Outcome	Patients with Chronic Health Condition or Acute Event in Baseline Period		Patients with Incident Health Outcome in 1–48 Months Post-Index	
	n	%	n	%
Health Conditions/Events Examined	**29**		**29**	
Cardiovascular	**153,722**	**83.7%**	**102,315**	**55.7%**
Chronic Condition	**153,639**	**83.7%**	**99,953**	**54.4%**
Atrial fibrillation/flutter	22,463	12.2%	20,641	11.2%
Cardiomyopathy	7,966	4.3%	8,904	4.8%
Cardiovascular disease	51,603	28.1%	28,061	15.3%
Dyslipidemia	109,808	59.8%	24,326	13.2%
Heart failure	17,865	9.7%	30,916	16.8%
Hypertension	123,904	67.5%	19,596	10.7%
Non-healing extremity ulcer	11,323	6.2%	14,859	8.1%
Peripheral arterial disease	26,813	14.6%	24,365	13.3%
Thromboembolism	5,837	3.2%	8,576	4.7%
Event	**5,046**	**2.7%**	**13,075**	**7.1%**
Myocardial infarction	2,349	1.3%	6,560	3.6%
Stroke	2,774	1.5%	6,880	3.7%
Metabolic	**67,953**	**37.0%**	**43,677**	**23.8%**
Chronic Condition	**67,953**	**37.0%**	**43,677**	**23.8%**
Metabolic syndrome/pre-diabetes	1,051	0.6%	4,566	2.5%
Obesity	32,182	17.5%	31,442	17.1%
Type 2 diabetes	50,571	27.5%	12,684	6.9%
Bone	**28,799**	**15.7%**	**36,992**	**20.1%**
Chronic Condition	**19,462**	**10.6%**	**18,122**	**9.9%**
Avascular necrosis	667	0.4%	1,099	0.6%
Osteoporosis	18,917	10.3%	17,192	9.4%
Event	**13,520**	**7.4%**	**24,599**	**13.4%**
Osteoporotic fracture	13,520	7.4%	24,599	13.4%
Renal	**25,542**	**13.9%**	**20,020**	**10.9%**
Chronic Condition	**25,542**	**13.9%**	**20,020**	**10.9%**
Chronic kidney disease	25,542	13.9%	20,020	10.9%
Gastrointestinal	**58,170**	**31.7%**	**50,400**	**27.4%**
Chronic Condition	**53,122**	**28.9%**	**36,722**	**20.0%**

(*Continued*)

Table 5 (Continued).

Health Outcome	Patients with Chronic Health Condition or Acute Event in Baseline Period		Patients with Incident Health Outcome in 1–48 Months Post-Index	
	n	%	n	%
Dyspepsia	53,122	28.9%	36,722	20.0%
Event	**11,034**	**6.0%**	**19,775**	**10.8%**
Gastrointestinal bleeding/peptic ulcers	11,034	6.0%	19,775	10.8%
Ophthalmological	**65,186**	**35.5%**	**43,686**	**23.8%**
Chronic Condition	**65,186**	**35.5%**	**43,686**	**23.8%**
Cataracts	51,819	28.2%	36,777	20.0%
Glaucoma	25,754	14.0%	12,094	6.6%
Sleep	**30,665**	**16.7%**	**24,108**	**13.1%**
Chronic Condition	**30,665**	**16.7%**	**24,108**	**13.1%**
Sleep apnea	16,987	9.3%	11,039	6.0%
Sleep disorders (non-apnea)	16,747	9.1%	14,918	8.1%
Infection	**86,987**	**47.4%**	**140,732**	**76.6%**
Chronic Condition	**> 170**	**~0%**	**338**	**0.2%**
Mycobacterium avium infection	> 170	~0%	338	0.2%
Event	**86,927**	**47.3%**	**140,696**	**76.6%**
Other infections that may be associated with SCS-related immunosuppression	86,482	47.1%	140,012	76.2%
Sepsis	7,205	3.9%	25,565	13.9%
Mental Health	**66,297**	**36.1%**	**35,173**	**19.2%**
Chronic Condition	**66,297**	**36.1%**	**35,173**	**19.2%**
Depression/anxiety	59,467	32.4%	27,284	14.9%
Psychosis	17,313	9.4%	10,658	5.8%

Notes: Results may be approximated with ">" or "~" in accordance with the CMS data use agreement.
Abbreviation: CMS, Centers for Medicare & Medicaid Services.

obesity, dyspepsia, infections that may be associated with immunosuppression, and depression/anxiety (results at least 2.5 standard deviations away from 0) (Table S-3).

Regression Analysis

Figure 3 presents univariate spline graphs for the examined cardiovascular conditions with the highest new incidence in the post-index period across all patients in the study population: heart failure (17%) and cardiovascular disease (15%). Increased risk with higher OCS dose is shown once the cumulative dose is above 400–500 mg for both heart failure and cardiovascular disease. Over 1000 mg of OCS is associated with a 20–30% higher risk of these new health outcomes versus no OCS. These potential inflection points of risk can vary considerably across the potential adverse conditions of interest; spline graphs for all health outcomes are available in Figure S-1.

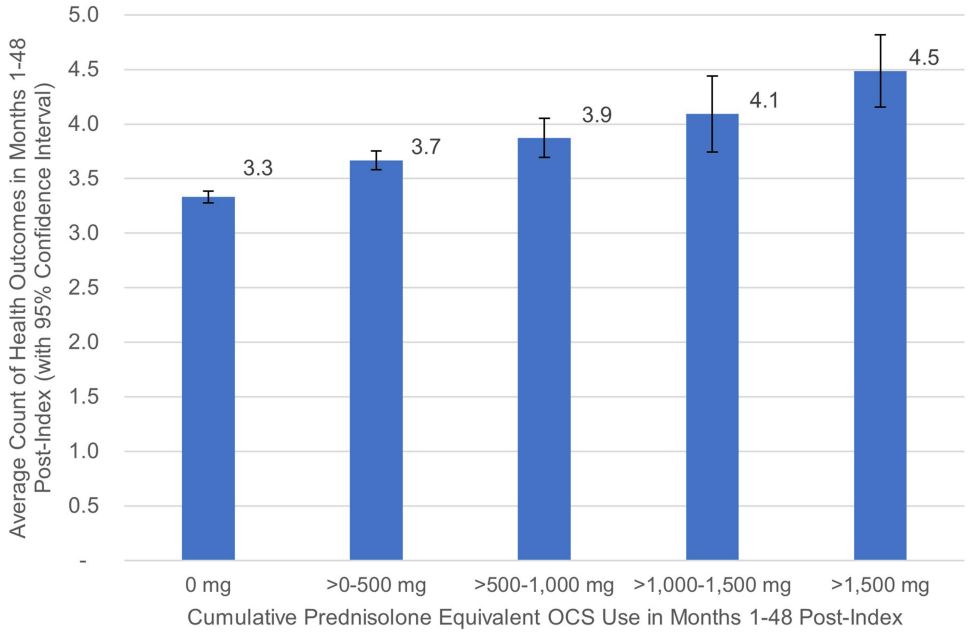

Figure 2 Potential adverse health outcomes in months 1–48 post-index by OCS exposure.
Abbreviations: OCS, oral corticosteroid; mg, milligram.

After controlling for underlying patient characteristics and other factors, higher risks for individual health outcomes with higher cumulative OCS dose observed in the descriptive analysis were still significant for many conditions as OCS exposure increased, particularly for amounts >1500 mg. For this newly diagnosed Medicare COPD population, the effects of patient demographics and underlying comorbidities also contributed greatly to the risk of the health outcomes analyzed in the four-year post-index period. Table 6 provides multivariable regression results for the 10 conditions with the highest new incidence in the post-index period; full multivariable regression results are provided in Tables S-4-S-6. An increase in risk can be seen from the lower to higher OCS exposure groupings. For several conditions, lower risks compared to those with 0 mg of OCS exposure were observed. These results could be related to underlying differences between the patient populations receiving 0 mg OCS vs >0-500 mg OCS. The 0 mg OCS group

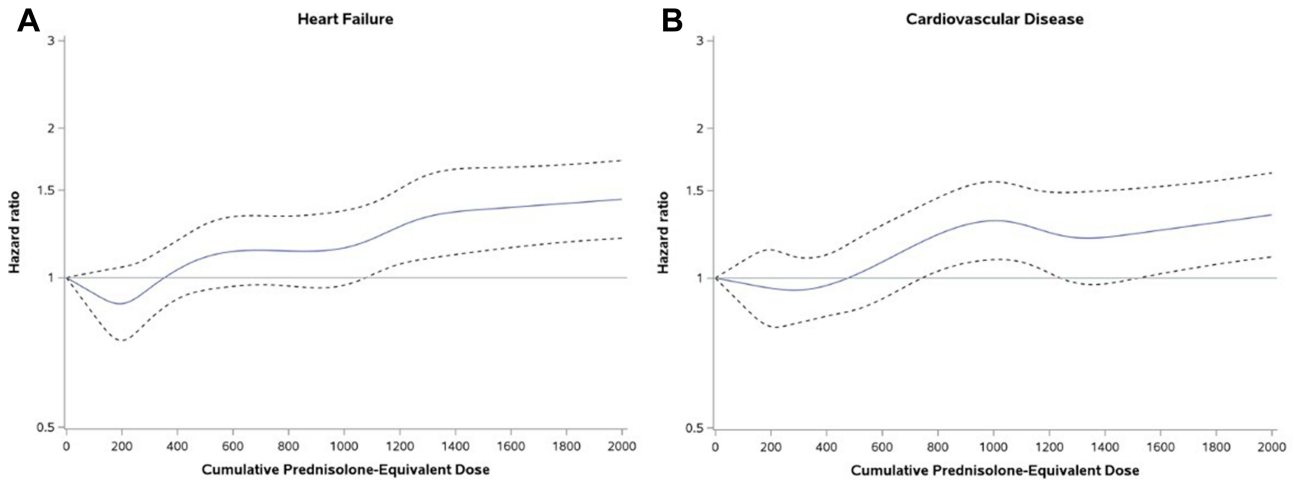

Figure 3 Hazard Ratios for univariate regressions by cumulative prednisolone equivalent OCS dose in mg (vs 0 mg) for (**A**) heart failure and (**B**) cardiovascular disease.[a]
Notes: [a]Dotted lines reflect 95% confidence interval.
Abbreviations: OCS, oral corticosteroid; mg, milligram.

Table 6 Multivariable Regression Results for Cumulative OCS Dose

Health Outcomes	Hazard Ratio					
	Cumulative Prednisolone Equivalent OCS Dose Grouping (vs 0 mg)					
	>0-250 mg	>250-500 mg	>500-750 mg	>750-1000 mg	>1000-1500 mg	>1500 mg
Cardiovascular disease	0.897*	0.895*	*1.040*	*1.102*	*1.155*	1.497*
Heart failure	0.884*	*0.986*	1.108*	*1.116*	1.259*	1.531*
Peripheral arterial disease	0.863*	0.850*	*0.899*	*0.838*	*0.917*	*1.070*
Obesity	*1.013*	1.126*	1.196*	1.201*	1.195*	1.311*
Osteoporotic fracture	*0.977*	*1.006*	*1.058*	*0.975*	*1.086*	1.341*
Dyspepsia	0.929*	*1.015*	*1.089*	*1.029*	1.443*	1.462*
Cataracts	*1.009*	1.068*	1.093*	1.160*	1.209*	1.334*
Other infections that may be associated with SCS-related immunosuppression	1.034*	1.061*	1.185*	1.207*	*1.099*	1.443*
Sepsis	0.936*	*1.005*	*0.997*	*1.098*	*1.140*	1.808*
Depression/anxiety	0.876*	*0.935*	*1.070*	*0.950*	*1.186*	1.282*

Notes: *at least 2.5 estimated standard deviations away from a 1.0 hazard ratio. Numbers in italics are less than 2.5 estimated standard deviations away from a 1.0 hazard ratio.
Abbreviations: OCS, oral corticosteroid; mg, milligram.

was older on average, which could increase the risk of these health outcomes and possibly impact OCS prescribing decisions.

The systemic inflammatory response from exacerbations, particularly severe events, may also lead to increased risk of cardiac conditions.[22] As a sensitivity analysis, the regression analysis was repeated on the subpopulation of patients with no COPD hospitalizations in the post-index period (80% of the full study population) to remove hospitalizations as a complicating factor. This model resulted in a positive association between the highest OCS exposures and the incidence of obesity, dyspepsia, cataracts, and infections, but no significant association for the other outcomes, as seen in Table 7.

Table 7 Multivariable Regression Results for Cumulative OCS Dose – Excluding Patients with COPD Hospitalizations in the 48 Months Post-Index (Includes 80% of Study Population)

Patient Count	Cumulative Prednisolone Equivalent OCS Dose Grouping (vs 0 mg)					
	>0-250 mg	>250-500 mg	>500-750 mg	>750-1000 mg	>1000-1500 mg	>1500 mg
Full Study Population	118,112	47,578	7,186	3,756	3,214	3,791
No COPD Hospitalizations	100,733	35,575	4,915	2,469	1,952	2,008
% in Subpopulation	85%	75%	68%	66%	61%	53%
Health Outcomes	**Hazard Ratio**					
Cardiovascular disease	0.871*	0.865*	*0.942*	*1.059*	*0.947*	*0.879*
Heart failure	0.856*	0.894*	0.843*	*0.933*	*0.872*	*1.101*
Peripheral arterial disease	0.851*	0.823*	0.797*	*0.864*	*0.843*	*0.793*

(*Continued*)

Table 7 (Continued).

Patient Count	Cumulative Prednisolone Equivalent OCS Dose Grouping (vs 0 mg)					
	>0-250 mg	>250-500 mg	>500-750 mg	>750-1000 mg	>1000-1500 mg	>1500 mg
Obesity	*1.049*	1.138*	1.216*	1.289*	*1.238*	*1.216*
Osteoporotic fracture	*0.963*	*0.983*	*1.049*	*0.914*	*1.009*	*1.213*
Dyspepsia	*0.978*	*0.986*	*1.040*	*1.025*	1.336*	*1.207*
Cataracts	*1.015*	1.073*	*1.098*	*1.147*	1.252*	1.356*
Other infections that may be associated with SCS-related immunosuppression	1.071*	1.070*	1.178*	1.194*	*0.961*	1.377*
Sepsis	0.840*	0.770*	0.615*	0.574*	*0.691*	*1.016*
Depression/anxiety	0.884*	0.909*	*1.040*	*0.884*	*1.155*	*1.156*

Notes: *at least 2.5 estimated standard deviations away from a 1.0 hazard ratio. Numbers in italics are less than 2.5 estimated standard deviations away from a 1.0 hazard ratio.
Abbreviations: COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroid; mg, milligram.

Notably (and as expected), the portion of the study population with no COPD hospitalizations had lower OCS exposure than the full study population, which could also contribute to these results. As part of this sensitivity analysis, an additional regression model on the full study population was developed to include the cumulative number of COPD hospitalizations as a covariate (Table S-6). Of note, the inclusion of COPD hospitalizations in the regression model resulted in a negative association between OCS exposure and the incidence of certain conditions such as heart failure and peripheral arterial disease, possibly as an artifact of the collinearity between OCS use and COPD hospitalizations. There was a strong positive association between the COPD hospitalizations and the incidence of all conditions except avascular necrosis, cataracts, and glaucoma. Further analysis would be needed to separate the associations of OCS use and COPD hospitalizations.

After controlling for underlying patient characteristics, a cumulative prednisolone equivalent OCS dose of >1000 mg over the 48 months post initial COPD diagnosis was associated with a modest increase of 0.7 more health outcomes in aggregate (2.5% of the 29 outcomes) compared to 0 mg of OCS. These results appear to be driven by the relationship between OCS dose and infections, obesity, heart failure, sleep apnea, and dyspepsia (Figure 4). A slight negative association was seen between >1000 mg OCS dose and the development of stroke; 7 outcomes did not appear have a statistically significant relationship with >1000 mg OCS dose individually or on an aggregate basis.

Discussion

This study was intended to give prescribers, pharmacists, and health plans a detailed view into Medicare patients newly diagnosed with COPD, including their OCS treatment and health outcomes. Unlike asthma and other chronic conditions, real-world data examining OCS use among the COPD population is not widely available nor have the risks of potential adverse health outcomes been examined broadly. The use of the Medicare FFS administrative claims database allowed for the examination of these outcomes in a population where COPD is prevalent.

This study demonstrated that among the newly diagnosed COPD Medicare population, 19% received at least one script for OCS in the 12 months after COPD diagnosis, and 36% received at least one script in the 48 months post-index. Furthermore, despite recommendations made by GOLD that SCS courses should last no more than 5–7 days,[6] 38% of OCS episodes lasted over 7 days and 30% of OCS episodes lasted at least 10 days. As even short courses of SCS have been associated with increased risks of some adverse events, it is important to describe the real-world length of these episodes so that potential risks associated with prolonged OCS exposures can be better understood.

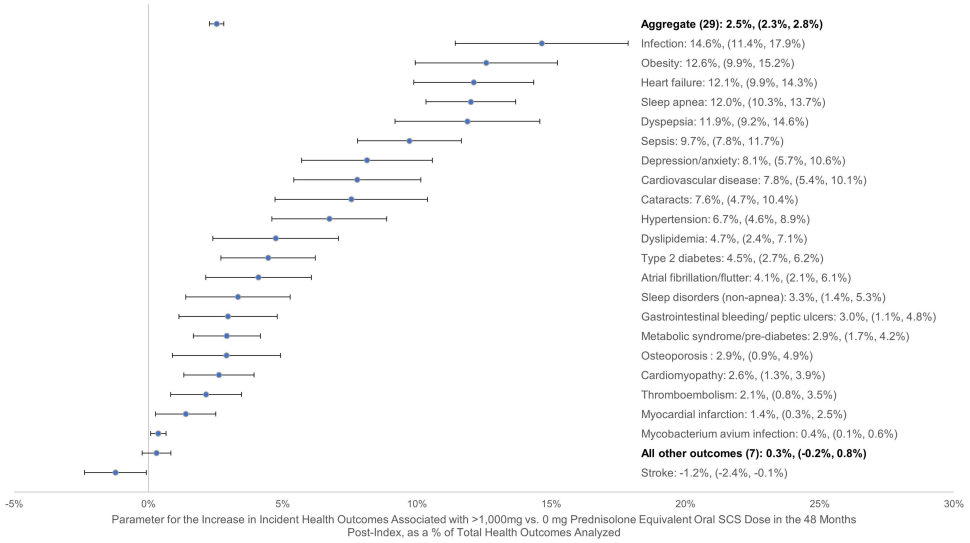

Figure 4 Parameter (as percent of the total number of outcomes analyzed) and 95% confidence interval for the increase in specified health outcomes associated with >1000 mg vs 0 mg prednisolone equivalent OCS dose in the 48 months post-index.
Abbreviations: OCS, oral corticosteroid; mg, milligram.

It is important to note that in this study of newly diagnosed patients with COPD there was an average of 4.7 chronic health conditions and acute events (out of the 29 investigated) identified in the two years before initial COPD diagnosis. Hypertension, dyslipidemia, infections that may be associated with immunosuppression, depression or anxiety, dyspepsia, cardiovascular disease, type 2 diabetes, and cataracts each were found in over a quarter of the study population before their COPD diagnosis. These Medicare patients experience complex comorbidities prior to their initial COPD diagnosis, including multifactorial conditions that have elsewhere been shown to be associated with SCS exposure, among other factors. Therefore, potential SCS-related risks of condition incidence experienced by this population with COPD are likely different than for patients with other respiratory conditions, such as asthma, where the patients are younger on average. The prevalence of underlying conditions is also likely to be lower in younger asthma patients due to their other demographic risk characteristics, making associations between OCS use and multifactorial health outcomes more apparent. While many of the potential adverse conditions and events of interest may occur as COPD progresses and patients age, prescribers should be aware of their existence before prescribing SCS or further escalating exposure that may increase health risk as these existing conditions could be complicated by these exposures.

On a descriptive level, patients with higher OCS exposure after their index COPD diagnosis experienced more new conditions or events post-index. Compared to those with 0 mg OCS exposure in the 48 months post-index, those with >1000 mg had a higher incidence of new conditions or events such as cardiovascular disease, heart failure, hypertension, obesity, dyspepsia, infections, and depression or anxiety. The association of higher risks for specific health outcomes with higher cumulative OCS dose observed in the descriptive analysis was also seen in the regression analysis. The effects of patient demographics and underlying comorbidities also contributed to the risk of adverse health outcomes in the four-year post-index period. COPD hospitalizations may also contribute to increased risk of certain health outcomes, but the collinearity of COPD hospitalizations and OCS exposure and the impact on health outcomes suggests further research. Treatment of COPD exacerbations often involves OCS or injectable SCS use, but these exacerbation events may also independently increase the risk of certain conditions like myocardial infarction and stroke, accelerate lung function decline, impair quality of life, and increase risk of mortality due to the systemic inflammatory response.[22,23] Cardiovascular conditions in particular are an important comorbidity of COPD, with shared risk factors and mechanisms. Research has highlighted the increased risk of hospitalizations among patients with COPD and cardiovascular conditions,[24] which would in turn increase the risks of systemic inflammatory responses. Therefore, the observed association of OCS use with the identification of new cardiovascular conditions is likely multifactorial. Maintenance treatment for COPD, such as inhaled corticosteroids, may impact the frequency of COPD hospitalizations and can have

some systemic adverse effects. We did not include these treatments in the study, but their addition would be unlikely to have a major impact on the analysis results for most of the systemic adverse effects studied.

The observed effects of OCS in this study were not as strong or clear as those reported for younger asthma populations.[10–15] While Medicare patients with COPD are older and have greater general morbidity which can place them at high risk for many of the conditions and events observed, the full role of OCS exposure may be more complex in this population than can be identified through secondary data sources such as administrative claims. For example, this study only looked for the incidence of health outcomes; it is possible that the identified OCS exposures could have aggravated several of the existing conditions these patients had prior to their COPD diagnosis and resulted in more severe events or prolonged episodes of care for those conditions.

An additional limitation is that this study only captured OCS scripts occurring in the outpatient setting and did not include SCS exposures in an inpatient hospital setting, thereby likely underestimating the total SCS exposure. A noticeable portion of patients experienced COPD hospitalizations and emergency department exacerbations without any corresponding OCS exposure identifiable in claims data. As SCS is recommended to treat COPD exacerbations, it is likely that many of the patients with COPD hospitalizations and emergency department exacerbations received oral or injectable SCS not captured in the data used for this study; therefore, the true SCS exposure may have been higher than the OCS metrics suggest. Furthermore, while the Medicare FFS database includes all scripts filled at outpatient pharmacies it cannot determine whether the patients actually took the medications as prescribed. Consequently, it is possible that the observed exposure-related risks could have occurred at lower actual exposure amounts.

Furthermore, given the aforementioned complexities of COPD patients, this study purposely focused on newly diagnosed patients with COPD with no recent history of SCS exposure so that the context of the results could be more clearly understood. The goal was to better understand OCS patterns that would more likely be related to the initial treatment of COPD and not related to the treatment of other chronic conditions. In real-world practice, many patients with COPD excluded from our study could have had underlying chronic conditions commonly treated with SCS and, therefore, would be expected to have cumulative exposures of SCS prior to their initial COPD diagnosis that could contribute to the risks for experiencing additional adverse health outcomes from COPD-related SCS treatment. This study also relied on administrative claims data, which does not include the additional clinical detail found in encounter data, making the determination of the timing of COPD onset and COPD severity difficult. Thus, while direct generalizability to all patients newly diagnosed with COPD may be limited from this analysis, the results still offer valuable insights into the real-world OCS treatment patterns, patient complexities, and potential risks of OCS treatment.

Lastly, patients in this study were followed up for an average of 37 months after their initial COPD diagnosis. While this study did find associations with the number of new conditions and events among those with 48 months of available data, it's possible that longer exposure time is needed in order to observe statistically significant increased risks associated with several of these potential adverse health outcomes and events of interest. In addition, it is possible that a different methodology, data source, or time period for analysis could produce different results. The fragmented nature of healthcare data in the United States along with the shorter life expectancy among patients with COPD further complicate the examination of some long-term outcomes within this population.[25,26] Nonetheless, while this study contributes to the understanding of real-world OCS use, additional research is needed to more robustly assess OCS treatment patterns and associations with potential adverse health outcomes.

Conclusion

Over a third of Medicare FFS patients with newly diagnosed COPD received OCS prescriptions in the 48 months after their diagnosis. Over a third of OCS episodes lasted longer than the GOLD recommendations for COPD exacerbations (5–7 days).[6] Compared to those with 0 mg prednisolone equivalent OCS exposure in the 48 months post-diagnosis, those with >1000 mg had a higher incidence of new conditions or events that may be OCS-related, including cardiovascular disease, heart failure, hypertension, obesity, dyspepsia, infections, and depression or anxiety. Medicare FFS patients newly diagnosed with COPD were also found to be complex, with many underlying health conditions that could be further aggravated by prolonged exposure to OCS. This analysis was complicated by the underlying multimorbidity of

the population and collinearity with OCS exposure and COPD hospitalizations; further research is needed to investigate the connection between OCS use and the incidence or worsening of health outcomes in the COPD population. These results suggest the need for prescriber, pharmacist, health plan, and patient awareness of the potential risks of OCS in the treatment of COPD, reinforcing the importance of preventive treatment strategies and therapy optimization early in the disease course that may contribute to avoiding COPD exacerbations and corresponding SCS exposures.

Ethics Considerations

Use of the data for this study was obtained through an application approved by the Western Institutional Review Board (IRB Report ID 1887351), which is an independent review board. The patient data accessed from the Medicare 100% Research Identifiable Files complied with a Data Use Agreement (DUA) with CMS and the DUA was reviewed by CMS's Privacy Board to ensure that the beneficiary's privacy was protected and only the minimum data necessary was requested and justified. All data and summaries used for this report were reviewed by the CMS Chronic Condition Warehouse Analytical Review Team for compliance with CMS requirements to protect the privacy of Medicare beneficiaries' data.

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Disclosure

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