Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

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ABSTRACT

OBJECTIVE

To determine the frequency of prescriptions for short term use of oral corticosteroids, and adverse events (sepsis, venous thromboembolism, fractures) associated with their use.

DESIGN

Retrospective cohort study and self controlled case series.

SETTING

Nationwide dataset of private insurance claims.

PARTICIPANTS

Adults aged 18 to 64 years who were continuously enrolled from 2012 to 2014.

MAIN OUTCOME MEASURES

Rates of short term use of oral corticosteroids defined as less than 30 days duration. Incidence rates of adverse events in corticosteroid users and non-users. Incidence rate ratios for adverse events within 30 day and 31-90 day risk periods after drug initiation.

RESULTS

Of 1548 945 adults, 327 452 (21.1%) received at least one outpatient prescription for short term use of oral corticosteroids over the three year period. Use was more frequent among older patients, women, and white adults, with significant regional variation (all P<0.001). The most common indications for use were upper respiratory tract infections, spinal conditions, and allergies. Prescriptions were provided by a diverse range of specialties. Within 30 days of drug initiation, there was an increase in rates of sepsis (incidence rate ratio 5.30, 95% confidence interval 3.80 to 7.41), venous thromboembolism (3.33, 2.78 to 3.99), and fracture (1.87, 1.69 to 2.07), which diminished over the subsequent 31-90 days. The increased risk persisted at prednisone equivalent doses of less than 20 mg/day (incidence rate ratio 4.02 for sepsis, 3.61 for venous thromboembolism, and 1.83 for fracture; all P<0.001).

CONCLUSION

One in five American adults in a commercially insured plan were given prescriptions for short term use of oral corticosteroids during a three year period, with an associated increased risk of adverse events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Complications with chronic use of corticosteroids include a wide spectrum of effects on the cardiovascular, musculoskeletal, digestive, endocrine, ophthalmic, skin, and nervous systems

However, the potential risks associated with the use of short term oral corticosteroids and their overall use in a general population has not been fully characterized

WHAT THIS STUDY ADDS

This study of 1.5 million privately insured adults (18-64 years) in the US found that one in five patients in an outpatient setting used short term oral corticosteroid over a three year period (2012-14)

Within 30 days of corticosteroid initiation, the incidence of acute adverse events that result in major morbidity and mortality (sepsis, venous thromboembolism, fracture) increased by twofold, to fivefold above background rates

Greater attention to initiating prescriptions of these drugs and monitoring for adverse events may potentially improve patient safety

Introduction

Corticosteroids are powerful anti-inflammatory drugs that have been used to treat a variety of diseases for over seven decades, dating back to their introduction for rheumatoid arthritis in 1949.[1-5] A strong driver of corticosteroid use is the potent symptomatic relief they give many patients. Yet long term use of corticosteroids is generally avoided, given the risks of serious acute complications such as infection, venous thromboembolism, avascular necrosis, and fracture, as well as chronic diseases such as diabetes mellitus, hypertension, osteoporosis, and other features of iatrogenic Cushing's syndrome.[6-18] Indeed, corticosteroids are one of the most common reasons for admission to hospital for drug related adverse events,[19] and optimizing their long term use has been a major focus for clinical guidelines across diverse specialties for many years.[20-26]

In contrast with long term use, however, the risk of complications from short term use is much less understood, and evidence is generally insufficient to guide clinicians. In the outpatient setting, brief courses of oral corticosteroids are often used to treat conditions with clearly defined inflammatory pathophysiology for which there is clinical consensus for efficacy, such as asthma, chronic obstructive lung disease, rheumatoid arthritis, and inflammatory bowel disease.[27-31] Yet anecdotally corticosteroids are also used often in the short term to treat many other prevalent conditions where evidence is lacking, such as non-specific musculoskeletal pain and rashes. Despite such pervasive indications for use of oral corticosteroids, little is known about the prescribing patterns of short term use of these drugs in the general adult population, or their potential harm.

In this study we characterized short term use of oral corticosteroids in a contemporary outpatient population, and the risk of acute adverse events. We describe those who use oral corticosteroids in the short term in an outpatient setting and then report (absolute) incidence rates of adverse events in users and non-users. We chose three acute events listed as adverse

events on the Food and Drug Administration mandated drug label for oral corticosteroids (sepsis, venous thromboembolism, fracture). Given the inherent challenges related to confounding, we employed a self controlled case series (SCCS) design. This design has been used to examine drug and vaccine safety.[32 33] Using this method, each individual serves as his or her own control allowing for comparisons of adverse event rates during periods after exposure to corticosteroids versus rates during periods when not exposed.

Methods

Study design and population

The Clinformatics DataMart database (OptumInsight, Eden Prairie, MN) contains comprehensive, deidentified records of enrollees covered through a large nationwide healthcare insurer and its pharmacy services for outpatient drugs. All enrollees are included in a denominator file, regardless of whether they received services (eg, clinic visits, drug prescriptions, hospital admissions).

We identified all adults aged 18 to 64 years who were continuously enrolled between 1 January 2012 and 31 December 2014 (n=2 234 931). Those who were 65 years or older at any point during the study were excluded, owing to their eligibility for the federal Medicare program.

Patients were also required to have at least one year of continuous enrollment before the study period (1 January 2011 to 31 December 2011) to capture past use of corticosteroids and baseline comorbid conditions. To focus on new users, we excluded those who received any oral corticosteroids during 2011 (n=293 456). In addition, we excluded from the study cohort enrollees exclusively receiving non-oral forms of corticosteroids (eg, inhaler, intravenous route, or intra-articular injections only) or prescriptions for oral budesonide (n=102 243), and those with solid organ or bone marrow transplants, or malignancy (n=224 658) (see web appendix table 1). We also excluded patients who were prescribed oral corticosteroids for 30 days or more cumulatively over the study period (n=28 540). Finally, we excluded those with a history of adverse events in 2011 (n=37 089) (fig 1). Non-users in the study cohort were defined as those without any corticosteroid prescriptions who remained in the cohort after the exclusions. No additional patients were excluded from the study.

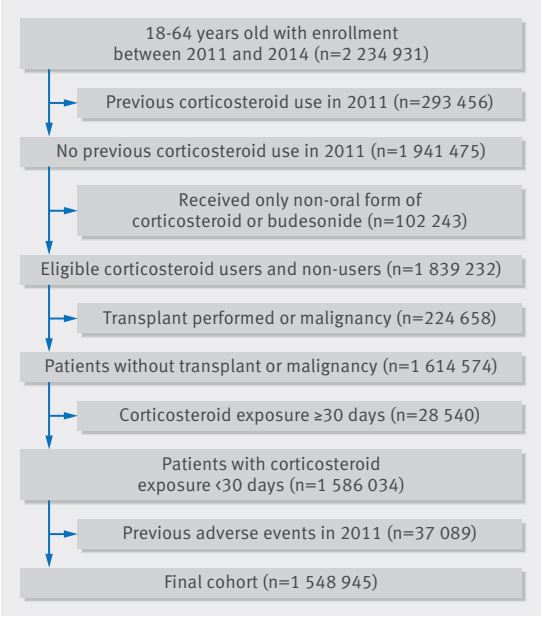

Fig 1 | Flow diagram of study inclusion and exclusion criteria

Procedures

For each enrollee, we obtained demographic information on age, sex, race or ethnicity, highest level of education, and region of the country based on a residential zip code. Race and ethnicity were identified using information obtained by OptumInsight from public records (eg, driver's license data), the surname and first names of the beneficiary, and the census block of residence (E-Tech, Ethnic Technologies, South Hackensack, NJ). Studies comparing a similar approach with information collected from self report showed a positive predictive value of 71%.[34] Missing demographic variables were uncommon (<1%) and are listed as "unknown" for the descriptive analyses only. Comorbid conditions were ascertained from outpatient and inpatient claims available for each enrollee during the study period using ICD-9-CM (international classification of diseases, ninth revision) diagnosis codes that were subsequently grouped into Elixhauser categories.[35]

Our primary exposure of interest was an outpatient prescription for an oral formulation of corticosteroids for less than 30 days, as obtained from detailed information in each pharmacy claim. Oral corticosteroid was defined by the dosage form, as categorized by the National Drug Data File from First Data Bank. The duration of corticosteroid use was based on the "days supply" variable provided within the pharmacy claim, which was defined as the "estimated day count the medication supply should last." Importantly, this information captures actual prescriptions filled (not just prescriptions written). To calculate standardized doses for each patient, all corticosteroid formulations were converted into a daily dose based on prednisone equivalent doses (see web appendix table 2).[36-38] We also identified multiple outpatient prescriptions for patients and tabulated the number of repeated doses.

Among all patients in the study cohort, we identified the specialty type of the prescribing physician and clinical conditions for which corticosteroids were administered by linking a patient's first prescription with the principal ICD-9-CM diagnosis code in the outpatient claim closest to the date of the prescription. If the closest claim was beyond three days from the prescription, we labeled this information for that patient as unknown. Overall, we were able to link 215 639 of 327 452 (65.9%) prescribing physicians and 278 425 of 327 452 (85.0%) patients who received a prescription to an ICD-9-CM diagnosis code. Diagnosis codes were grouped using clinical classification software obtained from the Agency for Healthcare Research and Quality.[35 39]

We assessed three acute adverse events associated with short term corticosteroid use: sepsis, venous

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thromboembolism, and fractures. These events were identified using ICD-9-CM diagnosis codes that reflected acute presentations, with chronic or personal history codes not included (see web appendix table 3). We specifically selected these events as they represent a broad range of corticosteroid related acute complications. Each also has been listed on the FDA mandated drug label as possible adverse reactions, can be reliably identified in claims data, and has supporting evidence of pathogenesis early after drug initiation was available.[17 40-46] For sepsis, the outcome was admission to hospital for reason of sepsis (inpatient claims with a primary diagnosis of sepsis). For venous thromboembolism and fractures, we used both outpatient and inpatient claims to identify events.

Statistical analyses

Description of corticosteroid users

We tabulated short term use of oral corticosteroids by age group (in 2014), sex, race, education, region, and number of Elixhauser comorbidities (grouped as 0, 1 to 2, and ≥3). Student *t* tests and χ^2 tests were used to assess differences by group. Regional variation in corticosteroid use was graphed by census division. We ranked the most common reasons for visits associated with the prescription, as well as specialty types of the prescribing providers.

Incidence rates of adverse events

For the entire cohort we calculated incidence rates of adverse events per 1000 person years at risk for corticosteroid users and non-users. Rates were also stratified by age, sex, and race. In addition, we calculated the cumulative risk of adverse events during the five to 90 day period after a clinic visit for corticosteroid users and non-users.

Self controlled case series

To control for patient specific characteristics while investigating the risk of adverse events, we used a self controlled case series (SCCS) design.[32 33 47] This method uses a within person approach to compare the rates of events after corticosteroid use (5-30 days and 31-90 days after the prescription was filled) with the rates before use (see web appendix figure 1). To be conservative, we modified the SCCS design so that adverse events within a four day window of when the prescription was filled were excluded to remove those who might have potentially received the oral corticosteroid concomitantly with the adverse event.

To preclude capturing multiple follow-up visits after the initial diagnosis of an adverse event, we only recorded the first event. Those who experienced an adverse event in the prestudy period of 2011 were excluded to avoid detecting legacy effects from past episodes. Patients were excluded if they were admitted to hospital within a 14 day period before the corticosteroid prescription date so that potential effects related to a recent hospital admission would be removed. Adjustment was made for time varying covariates related to concomitant drug use. In these analyses, the most commonly used classes of drugs (42 classes) were coded for each period and included in the full model; only those drug classes associated with each outcome (sepsis, venous theomboembolism, fracture) were retained in the final models.

Fixed (conditional) Poisson regression was used to calculate incidence rate ratios, offset by the natural logarithm of the days at risk to correct for differences in the lengths of observation. Effect modification by demographic factors (age, sex, race) were assessed by an interaction term.

Sensitivity analyses

We performed an analysis to deal with concerns that we were simply detecting more adverse events as a result of exposure to medical care rather than exposure to corticosteroids. For this analysis, we compared 30 day rates of hospital admissions for sepsis, venous thromboembolism, and fractures after a clinic visit in patients with matched diagnoses who did not receive corticosteroids and those who did receive corticosteroids after adjusting for age, sex, and race. Secondly, we used the cohort from the SCCS design and recalculated the incidence rate ratios after stratification by respiratory conditions or musculoskeletal conditions. These analyses assessed whether adverse events were being driven potentially by misdiagnosis (eg, sepsis may be more common because pneumonia is misdiagnosed as asthma, or fracture may be more common because vertebral fracture is misdiagnosed as back strain). Thirdly, in another sensitivity analysis we excluded patients who were using concomitant non-oral forms of corticosteroids. Lastly, we extended the four day period around the date of the prescription being filled to a seven day period.

Analyses were conducted with SAS software, v9.4 (SAS Institute), and Stata/MP14.1 (StataCorp, College Station, TX). Two tailed P values are reported for all analyses, with α=0.05. The institutional review board of the University of Michigan determined the study to be exempt from further review and waived the requirement for informed consent.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Description of corticosteroid users

Among 1 548 945 adults in the study cohort, 327 452 (21.1%) received at least one outpatient prescription for short term oral corticosteroids during the three year study period. The mean age for users was 45.5 (SD 11.6) years compared with 44.1 (SD 12.2) years for non-users (P<0.001). Among the 327 452 corticosteroid users, the median number of days of use was 6 (interquartile range 6-12 days) with 47.4% (n=155 171 of 327 452) receiving

Table 1 | Demographic characteristics of participants according to short term use or non-use of oral corticosteroids

Characteristics	No (%) of users	No (%) of non-users	User %
Overall	327 452 (100)	1 221 493 (100)	21.1
Age (years):			
18-24	22 845 (7.0)	114 935 (9.4)	16.6
25-34	40 510 (12.4)	185 325 (15.2)	17.9
35-44	79 702 (24.3)	285 155 (23.3)	21.8
45-54	98 365 (30.0)	340 527 (27.9)	22.4
55-64	86 030 (26.3)	295 551 (24.2)	22.5
Women	168 032 (51.3)	536 983 (44.0)	23.8
Men	159 420 (48.7)	684 510 (56.0)	18.9
Race:			
White non-Hispanic	239 193 (73.1)	844 262 (69.1)	22.1
Hispanic	33 644 (10.3)	140 617 (11.5)	19.3
Black non-Hispanic	29 738 (9.1)	115 343 (9.4)	20.5
Asian	10 384 (3.2)	61 842 (5.1)	14.4
Unknown	14 493 (4.4)	59 429 (4.9)	19.6
Education:			
<12th grade	1316 (0.4)	6406 (0.5)	17.0
High school graduate	85 743 (26.2)	295 460 (24.2)	22.5
Some college	176 441 (53.9)	655 348 (53.7)	21.2
College graduate or higher	61 690 (18.8)	252 951 (20.7)	19.6
Unknown	2262 (0.7)	11 328 (0.9)	16.6
Elixhauser comorbidity:			
0	103 119 (31.5)	610 824 (50.0)	14.4
1-2	137 292 (41.9)	417 908 (34.2)	24.7
≥3	87 041 (26.6)	192 761 (15.8)	31.1

treatment for seven or more days. Overall, the median prednisone equivalent daily dose was 20 mg/day (interquartile range 17.5-36.8 mg/day) with 23.4% (n=76 701 of 327 452) receiving ≥40 mg/day. The most common prescription written for oral corticosteroids was a six day methylprednisolone "dosepak," which accounted for 46.9% (n=216 437 of 461 208) of prescriptions during the study period. Among corticosteroid users, 70.5% (n=230 980 of 327 452) received one course of treatment, 20.7% (n=67 732 of 327 452) received two courses, and 8.8% (n=28 740 of 327 452) received three or more courses. For those patients with two or more prescriptions, the average prescription count was 2.4 (SD 0.7).

Compared with non-users, short term oral corticosteroid users were more often older, women, white, and had a greater number of comorbid conditions (table 1, all P<0.001). People residing in the Pacific region had the lowest use of short term oral corticosteroids (12.4%, n=15 762 of 127 112), whereas people in the east south central region (29.4%, n=14 892 of 50 669) and west south central region (27.6%, n=66 353 of 240 678) had the highest usage (see web appendix figure 2).

The most common indications for short term oral corticosteroid use were upper respiratory tract infections, spinal conditions, and intervertebral disc disorders, allergies, bronchitis, and (non-bronchitic) lower respiratory tract disorders (see web appendix table 4). These five conditions were associated with about half of all prescriptions. The two most common specialty types of physicians prescribing short term oral corticosteroids were family medicine and general internal medicine, accounting for most prescriptions (see web appendix table 4). These drugs were also frequently prescribed by specialists in emergency medicine, otolaryngology, and orthopedics.

Incidence rates of adverse events

Incidence rates of sepsis, venous thromboembolism, and fracture were statistically significantly higher in short term users of oral corticosteroid than in non-users (table 2). The differences were evident across age, sex, and race stratums. Fractures were the most common complication in users (21 events for every 1000 users annually), followed by venous thromboembolism (5 events for every 1000 users annually) and hospital admissions for sepsis (2 events for every 1000 users annually).

The absolute risk of an adverse event during the five to 90 day period after a clinic visit was calculated. For those patients with a visit, the risk of hospital admission for sepsis was 0.05% (n=170 of 327 452) in steroid users compared with 0.02% (n=293 of 1 221 493) in non-users during this period. The risk of venous thromboembolism was 0.14% (n=472 of 327 452) in users compared with 0.09% (n=1054 of 1 221 493) in non-users, and the risk of fracture was 0.51% (n=1657 of 327 452) in users compared with 0.39% (n=4735 of 1 221 493) in non-users in the 90 days after a clinic visit.

Self controlled case series

Table 3 displays the results of the SCCS. Overall, risks for sepsis, venous thromboembolism, and fracture increased within the first 30 days after initiation of corticosteroids. For example, the risk of hospital admission for sepsis increased fivefold (above baseline risk) after oral corticosteroids were used. This relation was consistent across doses. The long term risk for adverse events (31-90 days) diminished as the time from initial exposure increased.

To examine risks for particular types of patients, we explored effect modification by age, sex, and race. No significant effect modification was found after adjustment for time varying covariates, except for race; white patients had a higher short term risk of fractures than non-white patients (incidence rate ratio 2.02, 95% confidence interval 1.81 to 2.26 for white patients; 1.42, 1.14 to 1.77 for non-white patients; P=0.006 interaction term).

Sensitivity analyses

Web appendix table 5 displays the results of our analysis of 30 day rates of hospital admission for sepsis, venous thromboembolism, and fractures after a clinic visit in patients with matched diagnoses who did not receive corticosteroids and those who did receive corticosteroids after adjusting for age, sex, and race. It shows consistently higher incidence rates of adverse events in the patients who received corticosteroids. In the SCCS stratified by respiratory conditions or musculoskeletal conditions, the incidence rate ratios were recalculated (table 4). The 30 day risk of venous thromboembolism, fracture, and hospital admission for sepsis was statistically significantly increased for patients presenting with both respiratory conditions and musculoskeletal conditions. When we excluded patients using concomitant non-oral forms of

Table 2 | Incidence rates of adverse events by short term use of oral corticosteroids

Characteristics	Sepsis			Venous thromboembolism			Fractures		
	No of participants	Users (95% CI)*	Non-users (95% CI)*	No of participants	Users (95% CI)*	Non-users (95% CI)*	No of participants	Users (95% CI)*	Non-users (95% CI)*
Overall	5138	1.8 (1.7 to 1.9)	1.0 (0.9 to 1.0)	13238	4.6 (4.4 to 4.8)	2.4 (2.4 to 2.5)	71443	21.4 (21.0 to 21.8)	14.3 (14.2 to 14.4)
Age (years):									
18-24	228	0.8 (0.6 to 1.2)	0.5 (0.4 to 0.6)	302	1.3 (1.0 to 1.8)	0.7 (0.6 to 0.8)	6506	21.3 (19.8 to 22.9)	15.0 (14.6 to 15.4)
25-34	374	0.9 (0.7 to 1.2)	0.5 (0.4 to 0.6)	915	2.1 (1.8 to 2.5)	1.2 (1.1 to 1.3)	8388	16.5 (15.5 to 17.5)	11.8 (11.5 to 12.1)
35-44	695	1.0 (0.8 to 1.2)	0.6 (0.5 to 0.6)	2425	3.4 (3.1 to 3.7)	1.9 (1.8 to 2.0)	14214	17.8 (17.1 to 18.6)	11.9 (11.7 to 12.2)
45-54	1476	1.8 (1.6 to 2.0)	1.0 (1.0 to 1.1)	4200	5.0 (4.7 to 5.4)	2.7 (2.6 to 2.8)	19654	20.9 (20.2 to 21.6)	13.8 (13.6 to 14.0)
55-64	2365	3.3 (3.0 to 3.6)	1.8 (1.7 to 1.9)	5396	7.2 (6.8 to 7.7)	4.1 (3.9 to 4.2)	22681	27.7 (26.8 to 28.6)	18.5 (18.2 to 18.8)
Women	2218	1.7 (1.6 to 1.9)	0.9 (0.9 to 1.0)	6384	4.7 (4.5 to 5.0)	2.6 (2.5 to 2.6)	34637	23.0 (22.5 to 23.6)	15.0 (14.8 to 15.2)
Men	2920	1.9 (1.7 to 2.1)	1.0 (1.0 to 1.1)	6854	4.4 (4.2 to 4.7)	2.3 (2.3 to 2.4)	36806	19.6 (19.1 to 20.2)	13.8 (13.6 to 13.9)
Race:									
Non-white	1706	2.0 (1.8 to 2.2)	1.1 (1.0 to 1.2)	3826	4.6 (4.3 to 5.0)	2.3 (2.2 to 2.4)	18089	18.5 (17.8 to 19.3)	12.0 (11.8 to 12.2)
White	3432	1.7 (1.6 to 1.9)	0.9 (0.9 to 1.0)	9412	4.6 (4.4 to 4.8)	2.5 (2.4 to 2.5)	53354	22.4 (22.0 to 22.9)	15.3 (15.2 to 15.5)

*Per 1000 person years at risk.

corticosteroids from the analyses, the results were similar (see web appendix table 6). In the 5-30 day window the incidence rate ratio for sepsis was 4.84, for venous thromboembolism was 3.29, and for fracture was 1.92 (all P<0.001). Extending the four day period around the date of prescription to a seven day period also did not appreciably change the results (see web appendix table 7). The incidence rate ratio for sepsis was 4.33 (95% confidence interval 3.04 to 6.17), for venous thromboembolism was 2.94 (2.42 to 3.56), and for fracture was 1.65 (1.49 to 1.84).

Discussion

In this large, population based study of privately insured non-elderly (<64 years) adults in the US, one in five received a new outpatient prescription for short term use of oral corticosteroids over a three year period. These drugs were used for a wide range of conditions, such as upper respiratory tract infections, spinal conditions, and allergies and were commonly prescribed by both generalist and specialist physicians. Importantly, these prescriptions were associated with statistically significantly higher rates of sepsis, venous thromboembolism, and fracture despite being used for a relatively brief duration.

Comparison with other studies

Estimates of corticosteroid use from cross sectional studies range from 0.5% to 1.2% over various study periods.[7 9 10] An analysis of the National Health and Nutrition Examination Survey described self reported use of drugs taken within the previous 30 days.[7] Its findings indicated a mean duration of corticosteroid use exceeding four years among users—thus capturing a larger proportion of chronic treatment but potentially underreporting short term use. Furthermore, although the analyses were weighted, the actual sample of corticosteroid users included only 356 people. In our longitudinal analysis of 1.5 million insured Americans, the incidence was approximately 7% for short term oral corticosteroid use on a yearly basis.

Though the long term complications of chronic corticosteroid use are well known, there is a paucity of clinical data on the potential short term adverse effects of corticosteroid use, despite the existence of pathophysiological evidence suggesting possible early changes after drug initiation. For example, the impact of corticosteroids on the immune system has been widely studied, and in randomized controlled trials of prednisone (versus placebo) in healthy adults there were effects on peripheral cell lines (eg, peripheral white blood cells) within the first day after drug ingestion that were noticeable with 10 mg, 25 mg, and 60 mg doses.[48 49] Rapid alteration in markers of bone metabolism has also been documented with the initiation of corticosteroid use; mean serum concentrations of osteocalcin and both serum propeptide of type I N-terminal and C-terminal procollagen were statistically significantly decreased in the early weeks after starting prednisone.[43] The mechanisms underlying the increase in venous thromboembolism are not fully known. However,

Table 3 | Incidence rate ratios for adverse events associated with short term use of oral corticosteroids

Adverse event	No of participants	Median dose (mg/day)	Median No of days using steroids	5-30 days* Incidence rate ratio† (95% CI)	5-30 days* P value	31-90 days* Incidence rate ratio† (95% CI)	31-90 days* P value
All doses *v* no corticosteroids:							
Sepsis	1556	20	6	5.30 (3.80 to 7.41)	<0.001	2.91 (2.05 to 4.14)	<0.001
Venous thromboembolism	4343	17.5	6	3.33 (2.78 to 3.99)	<0.001	1.44 (1.19 to 1.74)	<0.001
Fracture	20 090	19	6	1.87 (1.69 to 2.07)	<0.001	1.40 (1.29 to 1.53)	<0.001
Dose: <20 mg/day *v* 0 mg/day:							
Sepsis	708	17.5	6	4.02 (2.41 to 6.69)	<0.001	2.62 (1.58 to 4.34)	<0.001
Venous thromboembolism	2139	17.5	6	3.61 (2.81 to 4.64)	<0.001	1.27 (0.96 to 1.67)	0.10
Fracture	9941	17.5	6	1.83 (1.60 to 2.10)	<0.001	1.41 (1.24 to 1.59)	<0.001
Dose: 20-39 mg/day *v* 0 mg/day:							
Sepsis	652	32	7	7.10 (4.20 to 12.01)	<0.001	2.91 (1.64 to 5.18)	<0.001
Venous thromboembolism	1713	35	7	2.83 (2.09 to 3.84)	<0.001	1.40 (1.03 to 1.90)	0.03
Fracture	8009	35	7	1.95 (1.66 to 2.30)	<0.001	1.33 (1.15 to 1.54)	<0.001
Dose: ≥40 mg/day *v* 0 mg/day:							
Sepsis	196	60	5	4.98 (1.69 to 14.72)	0.004	5.20 (1.77 to 15.25)	0.003
Venous thromboembolism	491	60	5	4.15 (2.45 to 7.03)	<0.001	2.27 (1.38 to 3.74)	0.001
Fracture	2140	60	5	1.77 (1.31 to 2.39)	<0.001	1.61 (1.26 to 2.05)	<0.001

*Number of days from date when corticosteroid prescription was filled. Reference period was 5-180 days before prescription date.
†Sepsis was adjusted for antibiotics, 5-HT3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, COX-2 inhibitors, and opiate agonists.

infection is a common trigger of thrombosis,[50] suggesting that both venous thromboembolism and sepsis may be potentially mediated through changes in the immune system. Further work is needed to clarify whether and how our observations in this large population may be linked to potential causal pathways.

Strengths and limitations of this study

Our findings are particularly of concern given the large number of patients exposed to short term oral corticosteroids in the general adult population. Clinical guidelines typically recommend using the lowest dose of steroids for the shortest period to prevent adverse events.[24 25] However, we found that even short durations of use, regardless of dose, were associated with increased risks of adverse events and that few patients were using very low doses. Only 6.3% of the prescriptions were for a prednisone equivalent dose of less than 17.5 mg/day, and 1.0% of prescriptions were for less than 7.5 mg/day; therefore, we were unable to examine events in patients given very low doses for short periods. A major reason for the higher than expected doses was the widespread use of "fixed dose" methylprednisolone dosepaks that are tapered over a short period. These dosepaks offer ease of use but do not permit the individualization of drug dosing to minimize exposure.

A substantial challenge to improving use of oral corticosteroids will be the diverse set of conditions and types of providers who administer these drugs in brief courses. This raises the need for early general medical education of clinicians about the potential risks of oral corticosteroids and the evidence basis for their use, given that use may not be specific to a particular disease or specialty. Suprisingly, the most common prescribers were not subspecialists, such as rheumatologists, who are most experienced with treating inflammatory conditions and the long term use of these drugs. We also found that the most common indications for corticosteroid use included conditions such as upper respiratory tract infections, spinal conditions, and allergies, which often have marginal benefit and for which alternate treatments may be similarly effective and safer. For example, a multimodal pain treatment regimen can be used to treat spinal pain, and non-sedating antihistamines can be used for allergies. An examination of potential determinants of corticosteroid use will be needed to inform future intervention strategies. If corticosteroid use is driven by patient preferences, education on the potential harms should be expanded. If prescriptions are primarily driven by provider decisions, decision support tools to identify alternatives to corticosteroids (eg, non-steroidal anti-inflammatory drugs for acute gout[30]

Table 4 | Incidence rate ratios for adverse events associated with short term use of oral corticosteroids, by reason for medical visit

Adverse event	5-30 days* Incidence rate ratio† (95% CI)	5-30 days* P value	31-90 days* Incidence rate ratio† (95% CI)	31-90 days* P value
Sepsis:				
Respiratory conditions‡	3.77 (1.94 to 7.35)	<0.001	2.53 (1.25 to 5.10)	0.01
Musculoskeletal conditions§	12.91 (5.49 to 30.34)	<0.001	4.32 (1.87 to 9.97)	0.001
Venous thromboembolism:				
Respiratory conditions‡	3.11 (2.20 to 4.40)	<0.001	1.27 (0.88 to 1.82)	0.20
Musculoskeletal conditions§	4.70 (3.08 to 7.17)	<0.001	2.02 (1.31 to 3.11)	0.001
Fracture:				
Respiratory conditions‡	1.96 (1.63 to 2.37)	<0.001	1.33 (1.13 to 1.56)	<0.001
Musculoskeletal conditions§	2.46 (2.02 to 3.00)	<0.001	1.65 (1.37 to 1.99)	<0.001

*Number of days from date when corticosteroid prescription was filled. Reference period was 5-180 days before prescription date.
†Sepsis was adjusted for antibiotics, 5-HT3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, COX-2 inhibitors, and opiate agonists.
‡Upper respiratory tract infection, allergy, bronchitis, lower respiratory tract disorder, upper respiratory tract disorder, or asthma.
§Spinal conditions, connective tissue disorders, or joint disorders.

or tricyclic antidepressants for neuropathic pain[51]) may be a more effective approach, but additional studies will be required to substantiate these possible alternatives as some of these drugs are available over the counter.

Our study has several limitations. Firstly, our cohort only includes commercially insured adults and excludes patients aged more than 64 years, which potentially limits the generalisability of our findings. We focused on younger adults as these individuals tend to have fewer comorbid conditions, and therefore our findings may be less likely to be biased by the high prevalence of age related comorbid conditions. Although our reference population is commercially insured adults, we have no reason to suspect this characteristic should bias a possible association between corticosteroid use and adverse events. Secondly, we determined the indication for corticosteroid use and the specific provider prescribing the drug by linking outpatient claims recorded most closely to the prescription date; thus we might have misclassified some treatment indications and specialties. Thirdly, we were unable to adequately assess the risks of adverse events at very low doses of corticosteroids, given the infrequency of use at these doses.

Fourthly, we did not evaluate all of the possible adverse events linked to oral corticosteroids but focused on three acute adverse reactions. This makes our findings even more striking as they are likely a conservative estimate of the associated risks of adverse events. For example, we only focused on hospital admissions for sepsis, ignoring less serious but likely important infections, and we did not assess some adverse events such as behavioral or psychiatric conditions. In addition, a dose- response trend was not seen and may reflect our selection criteria of using prescriptions of less than 30 days. Fifthly, although we used a within person approach to control for genetic predisposition, health related behaviors, and comorbid conditions and adjusted for time varying use of different drugs, other time varying factors could be differentially distributed between the risk and baseline periods. However, the incidence rate ratios were strong (many >3.0) so that any residual confounding would have to be appreciable to fully explain our findings. Assumptions of the SCCS design were mitigated by using only the first event for each of the three outcomes, and therefore independence of recurrent events and the potential influence of past events on subsequent drug use (if this occurred) yielded incidence rate ratios that might be somewhat conservative. Survival bias was not an issue since by design all patients were alive during the periods when the outcomes were measured (ie, the comparator period was before the first use of corticosteroids).

Conclusion

Oral corticosteroids are frequently prescribed for short term use in the US for a variety of common conditions and by numerous provider specialties. Over a three year period, approximately one in five American adults in a commercially insured plan used oral corticosteroids for less than 30 days. The short term use of these drugs was associated with increased rates of sepsis, venous thromboembolism, and fracture; even at relatively low doses. Additional studies are needed to identify optimal use of corticosteroids and to explore whether treatment alternatives may improve patient safety.

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Data sharing: No additional data are available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix: supplementary material