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

Akbar K Waljee,1,2,3,4 Mary A M Rogers,2,4,5 Paul Lin,2 Amit G Singal,6 Joshua D Stein,2,7,8 Rory M Marks,9 John Z Ayanian,2,5,8 Brahmajeek Nallamothu1,2,4,10

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.

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 Cushings 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

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.
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.22–31 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=2234 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=226 658) (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.

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 327 652 (65.9%) prescribing physicians and 278 425 of 327 652 (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.39–40

We assessed three acute adverse events associated with short term corticosteroid use: sepsis, venous
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.\textsuperscript{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 $\geq 3$). Student $t$ tests and $\chi^2$ 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.\textsuperscript{32,33} 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 thromboembolism, 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 $\alpha=0.05$. 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 1548965 adults in the study cohort, 327452 (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 327452 corticosteroid users, the median number of days of use was 6 (interquartile range 6-12 days) with 47.8% ($n=155171$ of 327452) receiving...
RESEARCH

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         | 327452 (100)    | 1221493 (100)       | 21.1   |
| Age (years):    |                 |                     |        |
| 18-24           | 22845 (7.0)     | 114935 (9.4)        | 16.6   |
| 25-34           | 60510 (12.6)    | 185325 (15.2)       | 17.9   |
| 35-44           | 79702 (24.3)    | 285155 (23.3)       | 21.8   |
| 45-54           | 98365 (30.0)    | 340527 (27.9)       | 22.4   |
| 55-64           | 86030 (26.3)    | 295551 (24.2)       | 22.5   |
| Men             | 159420 (48.7)   | 684510 (56.0)       | 18.9   |
| Race:           |                 |                     |        |
| White non-Hispanic | 239193 (73.1) | 844262 (69.1)       | 22.1   |
| Hispanic        | 33644 (10.3)    | 140617 (11.5)       | 19.3   |
| Black non-Hispanic | 29738 (9.1)   | 115343 (9.4)        | 20.5   |
| Asian           | 10384 (3.2)     | 61862 (5.1)         | 14.4   |
| Unknown         | 14493 (4.4)     | 59429 (4.9)         | 19.6   |
| Education:      |                 |                     |        |
| ≤12th grade     | 1316 (0.4)      | 6406 (0.5)          | 17.0   |
| High school graduate | 85743 (26.2) | 295460 (24.2)       | 22.5   |
| Some college    | 176441 (53.9)   | 655348 (53.7)       | 21.2   |
| College graduate or higher | 61690 (18.8) | 252951 (20.7)       | 19.6   |
| Unknown         | 2262 (0.7)      | 11328 (0.9)         | 16.6   |
| Elixhauser comorbidity: |         |                     |        |
| 0               | 103119 (31.5)   | 610824 (50.0)       | 16.4   |
| 1-2             | 137292 (41.8)   | 617908 (51.2)       | 24.7   |
| ≥3              | 87041 (26.6)    | 192761 (15.8)       | 31.1   |

treatment for seven or more days. Overall, the median prednisone equivalent daily dose was 20 mg/day (inter-quartile range 175-36.8 mg/day) with 23.4% (n=76701 of 327452) receiving ≥40 mg/day. The most common prescription written for oral corticosteroids was a six day methylprednisolone “dosepak,” which accounted for 46.9% (n=216437 of 461208) of prescriptions during the study period. Among corticosteroid users, 70.5% (n=230980 of 327452) received one course of treatment, 20.7% (n=67732 of 327452) received two courses, and 8.8% (n=28740 of 327452) 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=15762 of 127112), whereas people in the east south central region (29.4%, n=14892 of 50669) and west south central region (27.6%, n=66353 of 240678) 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 strata. 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 327452) in steroid users compared with 0.02% (n=293 of 1221493) in non-users during this period. The risk of venous thromboembolism was 0.14% (n=472 of 327452) in users compared with 0.09% (n=1054 of 1221493) in non-users, and the risk of fracture was 0.51% (n=1657 of 327452) in users compared with 0.39% (n=4735 of 1221493) 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
Incidence rates of adverse events by short term use of oral corticosteroids

| Characteristics | Sepsis (95% CI)* | Venous thromboembolism (95% CI)* | Fractures (95% CI)* |
|-----------------|-----------------|---------------------------------|--------------------|
| Overall         | 1.8 (1.7 to 1.9) | 4.6 (4.4 to 4.8)                | 2.4 (2.4 to 2.5)    |
| Age (years)     |                 |                                 |                    |
| 18-24           | 0.8 (0.6 to 1.2) | 0.5 (0.4 to 0.6)                | 0.7 (0.6 to 0.8)    |
| 25-34           | 0.9 (0.7 to 1.2) | 0.5 (0.4 to 0.6)                | 1.2 (1.1 to 1.3)    |
| 35-44           | 1.0 (0.8 to 1.2) | 0.6 (0.5 to 0.6)                | 1.9 (1.8 to 2.0)    |
| 45-54           | 1.8 (1.6 to 2.0) | 1.0 (1.0 to 1.1)                | 2.7 (2.6 to 2.8)    |
| 55-64           | 3.3 (3.0 to 3.6) | 1.8 (1.7 to 1.9)                | 4.1 (3.9 to 4.2)    |
| Women           | 1.7 (1.6 to 1.9) | 0.9 (0.9 to 1.0)                | 2.6 (2.5 to 2.6)    |
| Men             | 1.9 (1.7 to 2.1) | 1.0 (1.0 to 1.1)                | 2.3 (2.3 to 2.4)    |
| Race            |                 |                                 |                    |
| Non-white       | 2.0 (1.8 to 2.2) | 1.1 (1.0 to 1.2)                | 2.3 (2.2 to 2.4)    |
| White           | 1.7 (1.6 to 1.9) | 0.9 (0.9 to 1.0)                | 1.8 (1.7 to 1.9)    |

*Per 1000 person years at risk.

Comparison with other studies

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 from the analyses. In the 5-day window following the date of prescription to a seven day period also did not appreciably change the results (see web appendix table 6). In the 5-30 day window the incidence rate ratio for sepsis was 1.8 (95% confidence interval 1.5 to 2.1), and for fracture was 1.9 (95% confidence interval 1.6 to 2.2). The incidence rate ratio for sepsis was 4.33 (95% confidence interval 3.04 to 6.17), for venous thromboembolism was 3.29, and for fracture was 1.92 (95% confidence interval 1.69 to 2.16).

In the long term complications of chronic corticosteroid use, there is a paucity of randomized controlled trials and in the immune system, there is an increase in markers of bone metabolism being increased. There has been a marked increase in the use of corticosteroids in the general population, with the existence of pathophysiological changes leading to a new understanding of mechanisms underlying the increase in venous thromboembolism. The mechanisms underlying the increase in venous thromboembolism are not fully known. However, the increase in markers of bone metabolism has also been documented in animals, and in human studies there are effects on peripheral cell lines (eg, peripheral white blood cells) and bone turnover. The effects of corticosteroids on the immune system have been observed on acute phases of inflammatory responses, and in the immune system, there is an increase in markers of bone metabolism. There has been a marked increase in the use of corticosteroids in the general population, with the existence of pathophysiological changes leading to a new understanding of mechanisms underlying the increase in venous thromboembolism.
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) | P value | 31-90 days* Incidence rate ratio† (95% CI) | 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               | 175                  | 6                               | 3.33 (2.78 to 3.99)                       | <0.001  | 1.44 (1.19 to 1.76)                       | <0.001  |
| Fracture              | 20090              | 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                | 175                  | 6                               | 4.02 (2.41 to 6.69)                       | <0.001  | 2.62 (1.58 to 4.34)                       | <0.001  |
| Venous thromboembolism| 2199               | 175                  | 6                               | 3.61 (2.84 to 4.66)                       | <0.001  | 1.27 (0.96 to 1.67)                       | 0.10    |
| Fracture              | 9941               | 175                  | 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.

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. Surprisingly, 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 alternative 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)
or tricyclic antidepressants for neuropathic pain) 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 independance 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.

AUTHOR AFFILIATIONS

1VA Center for Clinical Management Research, Ann Arbor, MI, USA
2University of Michigan Medical School, Institute for Healthcare Policy and Innovation, Ann Arbor, MI, USA
3University of Michigan Medical School, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Ann Arbor, MI, USA
4Michigan Integrated Center for Health Analytics and Medical Prediction (MiCHAMP), Ann Arbor, MI, USA
5University of Michigan Medical School, Department of Internal Medicine, Division of General Medicine, Ann Arbor, MI, USA
6Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
7University of Michigan Medical School, Department of Ophthalmology and Visual Science, Ann Arbor, MI, USA
8University of Michigan School of Public Health, Department of Health Management and Policy, University of Michigan, Ann Arbor, MI, USA
9University of Michigan Medical School, Department of Internal Medicine, Division of Rheumatology, Ann Arbor, MI, USA
10University of Michigan Medical School, Department of Internal Medicine, Division of Cardiovascular Medicine, Ann Arbor, MI, USA

Contributors: AKW and BKN had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They are the guarantors. AKW and MAMR conceived and designed the study. All authors acquired, analysed, and interpreted the data; critically revised the manuscript; and gave final approval of the manuscript. AKW and BKN drafted the manuscript. AKW, MAMR, and PL were responsible for the figures. The authors are solely responsible for the design, conduct, data analyses, and drafting and editing of the manuscript and its final content. The contents do not represent the views of the US Department of Veterans Affairs or the United States government.

Funding: AKW is supported by a career development grant award (CDA 11-217) from the United States Department of Veterans Affairs Health Services Research and Development Service. AKW and BKN are supported by funding from the Michigan Institute for Data Science (MIDAS). JDS is supported by grants from Research to Prevent Blindness and WK Kellogg Foundation. Data acquisition and statistical and administrative support was supported by the Institute for Healthcare Policy and Innovation at the University of Michigan. These funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coiDisclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the University of Michigan institutional research board.

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.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.
Glucocorticoid dose thresholds associated with all-cause and the risk of pulmonary embolism: a population-based case-control study. Am J Med 2006;119:518-23. doi:10.1016/j.amjmed.2005.12.001.

Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. National Institute for Health and Care Excellence (NICE). 2009. Available at: https://www.nice.org.uk/guidance/cg80.

Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res (Hoboken) 2013;65:294-8. doi:10.1002/acr.22196.

Sarnes E, Crawford L, Watson M, Dennis G, Kuo A, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. Clin Ther 2011;33:1413-2. doi:10.1016/j.clinthera.2011.09.009.

van Staa TP, Leffers HG, Abenhaim L, Beggad B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93:105-11. doi:10.1093/qjmed/93.2.105.

Walsh L, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross-sectional study. BMJ 1996;313:344-6. doi:10.1136/bmj.313.7053.344.

Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;146:174-70. doi:10.1209/2011-0160.e400074-8.

Zieske JM, Blumenthal S, Giynki RJ, Morone N, Mogun H, Avorn J. Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 1994;154:97-101. doi:10.1001/archinte.1994.00040101031001.

Stuijer DJF, Majoor GJ, van Zaanen B, et al. Use of oral glucocorticoids and the risk of pulmonary embolism: a population-based case-control study. Chest 2013;143:1337-42. doi:10.1378/chest.12-1446.

Curris JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticosteroid use. J Rheumatol 2006;33:420-6. doi:10.1002/art.21984.

del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol 2014;66:264-72. doi:10.1002/art.38210.

Dessein PH, Joffe BI, Stanwick AE, Christian BF, Veller M. Glucocorticoids and insulin sensitivity in rheumatoid arthritis. J Rheumatol 2004;31:867-9.

Johannesdottir S, Horváth-Puhó E, Dekkers OM, et al. Use of oral glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med 2013;173:743-52. doi:10.1001/jama.2013.6396.

Davis MJ 3rd, Maradit Kremers H, Crowson S, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2007;56:820-30. doi:10.1002/art.22248.

Wess A, Elixhauser A, Bae J, Encinosa W. Origin of adverse drug events in US hospitals, 2011. 2013. ncbi.nlm.nih.gov/books/NBK169247/.

Gnosman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 2010;62:1515-26. doi:10.1002/acr.20295.

Melmed GY, Siegel CA. Quality improvement in inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2004;89:4923-8. doi:10.1210/jc.2004-0164.

Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. N Engl J Med 1986;314:150-2. doi:10.1056/NEJM198601311400104.