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] Brahmajee K Nallamothu[1,2,4,10]

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.

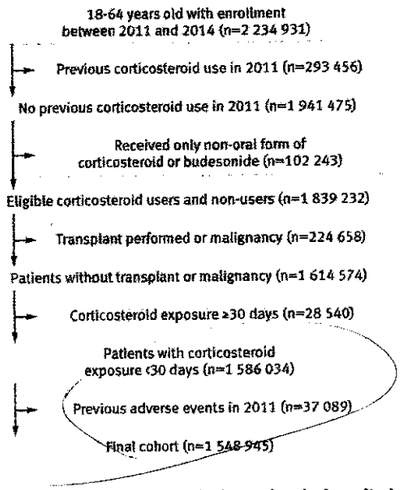

Fig 1 | Flow diagram of study inclusion and exclusion criteria

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

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

	Sepsis			Venous thromboembolism			Fractures		
Characteristics	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)	13 238	4.6 (4.4 to 4.8)	2.4 (2.4 to 2.5)	71 443	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)	14 214	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)	19 654	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)	22 681	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)	34 637	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)	36 806	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)	18 089	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)	53 354	22.4 (22.0 to 22.9)	15.3 (15.2 to 15.5)

*Per 1000 person years at risk.

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	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.

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)	P value	31-90 days* Incidence rate ratio† (95% CI)	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.