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Research Article

Parenteral Corticosteroids After Fragility Fracture Increases the Odds of a Repeat Fracture

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a Conflicts of Interest Statement for Dr. David

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Conflicts of Interest Statement for Gregory Benes

c Conflicts of Interest Statement for Dr. Dasa

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Conflicts of Interest Statement for Dr. Krause

e Dr. Lauren Leslie is part of the Ochsner Sports Medicine Institute as a neuromusculoskeletal and sports medicine specialist. She completed her neuromusculoskeletal medicine residency at Michigan State University, where she served as chief resident and received the American Academy of Osteopathy award as resident of the year. Dr. Leslie completed her sports medicine fellowship at Edward Via Virginia College of Osteopathic Medicine/Virginia Tech, where she served as an associate team physician for Virginia Tech and Radford University athletics. She now serves as the team physician for Loyola University New Orleans as well as many local high schools. Dr. Leslie's primary specialty is neuromusculoskeletal medicine. She has a specific interest in osteopathic manipulative medicine including osteopathy in the cranial field, movement biomechanics, and concussion management and research. She has training in both diagnostic and interventional ultrasound techniques, including orthobiologic injections.

Visit Dr. Leslie's Website

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f Dr. Deryk Jones is head of the Ochsner Sports Medicine Institute (OSMI), a program that recently joined with Dr. James Andrews to form the Ochsner Andrews Sports Medicine Institute. He double majored in biology and philosophy at Emory University and played collegiate soccer there as well. He received his M.D. degree from Stanford University where his interest and focus on articular cartilage research began. Orthopaedic training was at the Harvard Combined Program completing a prestigious Chiefship at the Massachusetts General Hospital in 1997. He then performed a fellowship in Shoulder Surgery and Sports Medicine at the University of Pittsburgh in 1998 and on completion joined the staff at Tulane University Medical School; he currently maintains appointments in Orthopaedic Surgery as a Clinical Assistant Professor at Tulane University and a Full Professor at the University of Queensland, Australia. He is a fellow of the American Academy of Orthopaedic Surgeons and the American Orthopaedic Association. He is board certified in orthopaedic surgery and subspecialty certified in sports medicine through 2030.

In 2004, he created OSMI and runs a program with over 160 athletic trainers, numerous operative and non-operative clinicians, physical therapist, and performance trainers. The program has locations throughout New Orleans and the state of Louisiana as well as the Mississippi gulf coast. He directs an operative fellowship training three board certified orthopaedist and one research fellow in sport medicine per year. OSMI also has residency programs in sports medicine assistantship and sports medicine physical therapy as well. He directs research focused on outcomes in shoulder, elbow, knee, hip and foot and ankle pathologic conditions evaluating operative and non-operative options and has published numerous articles on these subjects. He specializes in treatment techniques utilizing biologic reconstructive surgery and has been on the leading edge of innovations in regenerative medicine. His specific focus is on the treatment and regeneration of articular cartilage injuries

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g Dr. Chapple's primary role as Director of Biostatistics is planning cancer clinical trials in mice, humans, and cell lines – while also executing statistical analyses. Dr. Chapple is an expert in adaptive clinical trial designs, particularly Bayesian methods. His 2019 paper "A hybrid Phase I-II/III clinical trial design allowing for dose re-optimization in Phase III" proposed a new framework for seamless drug development through the three stages of clinical trial design. This paper was recognized globally by the statistical community when it received the award for "Best Paper" from Biometrics, a top tier statistical journal. Dr. Chapple has received worldwide recognition for his contributions to adaptive clinical trial design methodology and he hopes this expertise can propel his institution towards innovative cancer therapies, rapid advances in treatment of chronic diseases, and the long-term goal of personalized/precision medicine.

Dr. Chapple has produced many new trial designs and methods, which are accompanied with user-friendly R packages. Dr. Chapple trained under Dr. Peter Thall at MD Anderson, who is a pioneer in Bayesian adaptive trials. He later refined these skills working with cancer researchers from other institutions. Dr. Chapple's adaptive trial designs were used to dose-find in pediatric brain tumors in a trial conducted at Harvard and the Dana Farber Cancer Center.

Louisiana State University

Keywords: corticosteroids, pharmacology, orthopedics, polypharmacy, dosage, fracture, repeat fracture

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Purpose

To determine if corticosteroid use is associated with repeat fragility fractures and the trends in corticosteroid usage in this population.

Methods

2,643 patients with repeat fractures were identified in the Research Action for Health Network (REACHnet). Each patient had a non-traumatic fracture diagnosis code with at least one year of medical history prior to the fracture and at least two years of follow-up time. Multivariable logistic regression was used to identify corticosteroid trends over time, predictors of a repeat fracture, and the effect of timing and type of corticosteroid on repeat fracture.

Results

Corticosteroid use was associated with a significantly increased risk of a second fragility fracture (Adjusted Odds Ratio, aOR = 1.39, 95% CI = 1.13-1.71). Parenteral corticosteroids were associated with significantly increased odds of re-fracture (aOR = 1.37. 95% CI = 1.08-1.74). Corticosteroid usage after initial fracture showed significantly increased odds of repeat fracture (aOR = 1.52, 95% CI = 1.20-1.91). Parenteral corticosteroid use after fracture was associated with an increased risk of re-fracture (aOR = 1.52, 95% CI 1.18-1.96). Increased total dosage of steroids was not associated with an increase in the rate of repeat fractures.

Conclusions

Parenteral corticosteroid administration, especially if used after the initial fracture, was most likely to be associated with a repeat fracture. If steroids are indicated, the dosage may not alter repeat fracture risk. The method of administration or the timing may play a larger role, especially parenteral steroids after fracture. Physicians should weigh benefits and risk with parenteral corticosteroid use in fragility fracture patients.

INTRODUCTION

Osteoporotic fragility fractures are associated with significant morbidity, mortality, and economic burden (Burge et al. 2006). As the population ages, the incidence of fragility fractures is predicted to increase, particularly among elderly individuals (Omsland and Magnus 2014) due to age-related decrease in bone mineral density, cognitive impairment, and impaired mobility (Egan et al. 2008). Having a fragility fracture substantially increases the incidence of a second hip fracture (Berry et al. 2007; Kanis et al. 2004; Colón-Emeric et al. 2003), and this effect cannot be explained by risk factors alone, as the incidence of repeat fractures are significantly higher than expected (Ryg et al. 2009). Due to the significant health and economic burden of fragility fractures, interventions to decrease the incidence of a repeat fracture should be implemented.

Many medical conditions and lifestyle factors increase osteoporotic fractures. The association between certain medications and primary fractures has been extensively studied. Medications related to an increased risk of fragility fractures include neurotropic drugs such as antidepressants

Dr. Chapple has designed hundreds of studies and has supported many research departments at LSUHSC including: Orthopedics, OBGYN, Hematology Oncology, Dermatology, Oral Surgery, Endodontics, Cancer, Virology, Cellular Biology, Inflammation, and treatment disparities research. As a joint professor in Orthopedics, Dr. Chapple works on large scale electronic records databases which requires processing longitudinal information from patients on hospital encounters, diagnoses, procedures, prescriptions, and lab values.

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and anxiolytics, sedatives and benzodiazepines, gastrointestinal drugs such as H2 antagonists and proton pump inhibitors, and endocrine drugs such as thyroid hormone replacement therapy (Mortensen et al. 2020). Another class of medications significantly associated with increased fracture risk are corticosteroids, which cause decreased bone mineral density (Vestergaard, Rejnmark, and Mosekilde 2005; Van Staa et al. 2000) by promoting apoptosis of osteoblasts and osteocytes while simultaneously stimulating osteoclast activity via upregulation of RANKL and downregulation of osteoprotegerin (Compston 2018). Inhaled and topical corticosteroids have minimal impact on increased fracture risk, but greater than 2.5 mg of systemic prednisolone equivalents per day is associated with an increased fracture risk (Vestergaard, Rejnmark, and Mosekilde 2005).

Because the association of corticosteroids and other medications with fragility fractures is well known, their use should be limited in high-risk patients unless necessary. Despite this, treatment with medications that increase fall risk is still widely used before and after osteoporotic fractures (Sjöberg et al. 2010), and there seems to be no change in their use after the initial fracture (Munson et al. 2016). While many studies have examined the association of medications and primary fragility fracture, few studies have explored the impact on repeat fractures. This study aims to explore trends in systemic corticosteroid use surrounding fragility fractures and their impact on repeat fragility fractures to improve treatment of at-risk patients.

METHODS

Patients from the Research Action for Health Network (REACHnet) database were identified by having one of the fragility fracture codes seen in Table S1 from 2011-2015. If they had an associated trauma code in Table S1 within 7 days of fragility fracture, they were excluded. Repeat fractures were also excluded if a patient had a trauma code within 7 days of fragility fracture, leaving 11,373 patients. 2,598 patients were excluded for not having at least one year of medical history available before the initial fragility fracture. Another 5,770 patients were excluded for not having at least 2 years of follow-up time after the initial fracture or a subsequent fragility fracture within 2 years. 67 patients were removed for missing BMI, 24 were removed for being self-payers, 59 were removed for not having white or black race, 9 were removed for missing Hispanic ethnicity status, and 35 were removed for having a fracture in 2016, which is outside the time window. This left 2,643 patients in our cohort. Charleston Comorbidity Index (CCI) was calculated for each patient excluding age, since age was also used in corresponding regressions.

Categorical covariates are summarized by reporting count (%) and continuous covariates are summarized by reporting mean (sd). Categorical covariates are compared between re-fracture groups (no/yes) using a Fisher exact test, with continuous covariates compared using a two-sample t-test. Multivariable logistic regression is used to predict re-fracture within 1-2 years after initial fracture as a function of patient covariates to determine which factors are related to increased re-fracture risk, after adjustment.

The primary variables studied for an association with repeat fractures were timing of corticosteroid administration (before or initial fracture) and method of corticosteroid administration (oral or parenteral). Parenteral corticosteroids include intravenous and intramuscular injections. ICD codes for prescriptions indicative of intra-articular injections, including all prescriptions for triamcinolone, were excluded. The list of steroids and dosages are provided in Table S2. Demographic factors (race, ethnicity, and insurance type), risk factors (alcohol use, tobacco use, BMI, age, osteoporosis diagnosis, and CCI), and history of other drug use (bisphosphonates and PPI) were also studied to identify an association with corticosteroid use or repeat fracture. Finally, logistic regression was performed for patients who took each steroid type to determine if increased cumulative dosage was associated with an increased risk of re-fracture. All steroid types were converted into prednisone equivalents.

RESULTS

DEMOGRAPHICS

Table 1 displays the demographic characteristics of patients included in the study. Fragility fracture patients were mostly white, of non-Hispanic ethnicity, and had a diagnosis of osteoporosis (85.5%). They were also older and had a high adjusted CCI. Among the 2,643 patients with a fragility fracture, 1,125 (42.6%) of patients received corticosteroids within 1 year prior to fragility fracture or in the following two years. 676 (25.6% overall) fragility fracture patients received a parenteral corticosteroid, while 795 (30.1%) received an oral corticosteroid. Without adjusting for other covariates, patients on corticosteroids had a slightly higher but insignificant risk of repeat fracture (22.4% vs 19.2%, p=.052) compared to non-users. 465 (17.6%) patients were given corticosteroids before initial fracture and 968 (36.6%) of patients were given corticosteroids after their initial fragility fracture. Among the patients given corticosteroids after fracture, 588 (22.2% overall) were given parenteral

Table 1. Demographics of patient population. The table reveals each studied demographic variable or medication use and its association with corticosteroid use

	All (2643)	Corticosteroid Use (1125)	No Corticosteroid Use (1518)	p-values
Repeat fracture	544 (20.6)	252 (22.4)	292 (19.2)	0.052
No Repeat fracture	2099 (79.4)	873 (77.6)	1226 (80.8)	
Demographic Factors				
White Race	2408 (91.1)	1006 (89.4)	1402 (92.4)	0.011
Black Race	235 (8.9)	119 (10.6)	116 (7.6)	
Hispanic Ethnicity	84 (3.2)	35 (3.1)	49 (3.2)	0.954
Non-Hispanic ethnicity/ unknown	2559 (96.8)	1090 (96.9)	1469 (96.8)	
Private Insurance	129 (4.9)	81 (7.2)	48 (3.2)	<.001
Public Insurance	2502 (94.7)	1039 (92.4)	1463 (96.4)	
Known Risk Factors				
Alcohol Use	54 (2)	22 (2)	32 (2.1)	0.893
Smoking	866 (32.8)	393 (34.9)	473 (31.2)	0.045
BMI>30	1104 (41.8)	559 (49.7)	545 (35.9)	<.001
Age>=70	2067 (78.2)	806 (71.6)	1261 (83.1)	<.001
Osteoporosis	2261 (85.5)	974 (86.6)	1287 (84.8)	0.214
Age (continuous)	77.3 (9.34)	75.35 (9.47)	78.76 (8.97)	<.001
CCI	3.02 (2.59)	3.43 (2.82)	2.72 (2.36)	<.001
Bisphosphonate Use	614 (23.2)	319 (28.4)	295 (19.4)	<.001
PPI	931 (35.2)	537 (47.7)	394 (26)	<.001
Calcium	188 (7.1)	116 (10.3)	72 (4.7)	<.001
Vitamin D	181 (6.8)	108 (9.6)	73 (4.8)	<.001

corticosteroids and 635 (24.0%) were given oral corticosteroids.

Patients who were given corticosteroids within this time were also significantly more likely to be African American (10.6% vs 7.6%, p-value=.011), have private insurance (7.2%

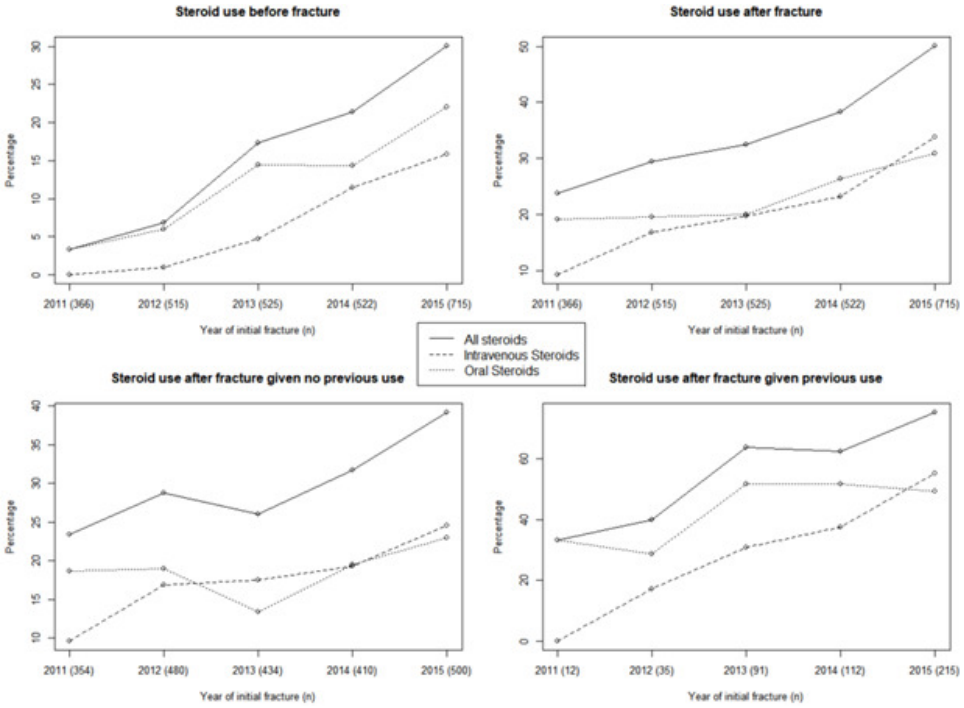

Figure 1. Corticosteroid use over time (top left) before initial fragility fracture, (top right) after initial fragility fracture, (bottom left) after initial fragility fracture, given no previous corticosteroid use, (bottom right) after initial fragility fracture given previous corticosteroid use.

vs 3.2%, p-value<.001), and be a smoker (34.9% vs 31.2%, p=.045). They were significantly more likely to have BMI >30 (49.7% vs 35.9%, p<.001), to use bisphosphonates (28.4% vs 19.4%, p<.001) or proton pump inhibitors (47.7% vs 26%, p<.001), and had a higher Charleston comorbidity index (3.43 vs 2.72, p<.001). Figure S1 displays results from a multivariable logistic regression predicting corticosteroid use. Significant predictors of corticosteroid use included BMI over 30, osteoporosis, bisphosphonate use, CCI, year, and the largest predictor, PPI use (adjusted odds ratio, aOR = 1.91, 95% CI = 1.61-2.28). Increased age was associated with a decreased odds that a patient received corticosteroids.

CORTICOSTEROID USE OVER TIME

Figure 1 displays corticosteroid use rates before initial fragility fracture (up to 1 year), after initial fragility fracture (up to 2 years), and two conditional corticosteroid use plots after initial fracture.

The percentage of patients with a fragility fracture increased over time, but this may be related more to the inclusion criteria. Patients with a fragility fracture had increased pre-fracture corticosteroid use over the years 2011-2015, from 3.3% to 30.1%. This upward trend is also seen for both oral and parenteral corticosteroids separately. Patients presenting with a fragility fracture were even more likely to receive a corticosteroid after fracture than before, with a rate increasing from 23.8% in 2011 to 50.1% in 2015. The two bottom plots examine the rates of corticosteroid use after initial fracture in two subsets of patients, those without corticosteroid use in the previous year and those with corticosteroid use. Patients who were not given corticosteroids before fracture were still given corticosteroids afterwards 23.4% of the time in 2011, which rose to 39.2% in 2015. Patients who were given corticosteroids prior to fragility fracture had even higher continued use over time, going from 33.3% in 2011 to 75.3% (in 215 qualifying patients) in 2015. The proportion of patients receiving parenteral corticosteroids in 2015 was also higher than those receiving oral corticosteroids (55.3% vs 49.3%).

There is a consistent pattern of prescribing more corticosteroids in these patients before initial fragility fracture, which may not be modifiable, and after fragility fracture, which should be modifiable behavior. Coupled with the conditional trends in the bottom of Figure 1, the odds of continued corticosteroid use after fracture are 4.51 times higher (95% CI = 3.63 - 5.62) for previous corticosteroid users. At the same time, the rate of re-fracture decreased over time overall, going from 25.5% in from 2011-2013 to 15.0% in 2014-2015.

PREDICTORS OF A SECOND FRAGILITY FRACTURE

Table 2 displays the demographics of patients by refracture group, along with unadjusted p-values testing whether those demographics differ by group. We see no unadjusted significant differences by race, ethnicity, insurance status, smoking, alcohol use, or older age for refracture risk. We did see significant increases in refracture risk for those with osteoporosis (21.5% vs 14.9%, p=.004) and increased CCI (3.29 vs 2.95, p=.01). Dosage information for steroid users is also shown in this table but discussed later. Table 3 investigates whether there are different cofactors of corticos-

Table 2. Demographics of patient population by refracture status, including % of refracture within each demographic group. For dosages of patients treated with steroids, we report the mean (standard deviation) or prednisone equivalent doses for timing and method of administration and its association with refracture risk.

	Refracture (653)	No Refracture (3583)	p-values	% of Refracture
Demographic Factors				
White	504 (92.6)	1904 (90.7)	0.183	20.9
Black	40 (7.4)	195 (9.3)		17
Hispanic Ethnicity	16 (2.9)	68 (3.2)	0.829	19
Non-Hispanic ethnicity/unknown	528 (97.1)	2031 (96.8)		20.6
Private Insurance	25 (4.6)	104 (5)	0.814	19.4
Pubic Insurance	514 (94.5)	1988 (94.7)		20.5
Known Risk Factors				
Alcohol Use	15 (2.8)	39 (1.9)	0.25	27.8
Smoking	173 (31.8)	693 (33)	0.627	20
BMI>30	216 (39.7)	888 (42.3)	0.295	19.6
Age>=70	438 (80.5)	1629 (77.6)	0.16	21.2
Osteoporosis	487 (89.5)	1774 (84.5)	0.004	21.5
Age	77.92 (9.39)	77.15 (9.32)	0.089	
CCI	3.29 (2.74)	2.95 (2.54)	0.01	
Bisphosphonate Use	123 (22.6)	491 (23.4)	0.743	20
PPI	200 (36.8)	731 (34.8)	0.428	21.5
Calcium	50 (9.2)	138 (6.6)	0.043	26.6
Vitamin D	41 (7.5)	140 (6.7)	0.536	22.7
Corticosteroid Dosages (among those with corticosteroids)				
Dose Parenteral Before	88.43 (83.81)	192.6 (458.03)	0.009	
Dose Parenteral After	162.73 (239.58)	166.83 (365.48)	0.879	
Dose Parenteral Total	262.03 (311.9)	415.69 (735.72)	0.178	
Dose Oral Before	26.81 (36.99)	22.7 (27.05)	0.382	
Dose Oral After	40.13 (76.64)	34.55 (78.78)	0.438	
Dose Oral Total	45.22 (80.48)	37.33 (75.16)	0.245	

teroid use and refracture. In the corticosteroid cohort, no factors were significantly associated with refracture risk except CCI (3.75 average in the refracture group vs 3.33 in the no-refracture group, p=.045). There was an increased risk (but non-significant) in alcohol users (40.9%, p=.065, n=21). In the cohort of patients without corticosteroid use, there was a significant association between refracture and average age (79.73 vs 78.52, p=.037) and osteoporosis status (p=.005). Other than those listed above, there were no significant differences in demographics between refracture groups within the two corticosteroid groups. We attempted to adjust for these potential confounding variables via multivariable logistic regression to predict a second fragility fracture, with results shown in Figure 2. The p-value for testing whether this model fits better than an intercept only model is 2.89 E-11 (difference in deviance of 80 on 14 degrees of freedom) indicating that the model predicts secondary fractures much better than an intercept only model.

Corticosteroid use was associated with a significantly increased risk of a second fragility fracture (adjusted odds ratio, aOR = 1.39, 95% CI = 1.13-1.71). A diagnosis of osteoporosis showed similar adjusted odds of a second fragility fracture (aOR = 1.39, 95% CI = 1.02-1.88). Raising patient CCI had an increased, but not quite significant, odds of complication (aOR = 1.04, 95% CI = 1.00-1.08, p-value = .051). A later year of initial fragility fracture was associated with a decreased risk of re-fracture (aOR = .81, 95% CI = .76-.87). Neither bisphosphonate use nor PPI use over the time period were associated with a significant change in risk of repeat fracture.

Figure 3 displays the adjusted odds ratios and associated 95% confidence intervals for the steroid effect broken down by administration method (oral vs parenteral), timing (steroids given before initial fragility fracture, after, and their interaction), and the administration method and timing combination (i.e. oral steroids before, after, interaction; parenteral steroids before, after, interaction). When con-

Table 3. Co-factor analysis displaying demographics of patients by refracture group within each corticosteroid use group. p = p-values from Fisher exact tests or t-tests, % = percentage of refracture within demographic groups.

	Corticosteroid Users				No Corticosteroid Use			
	Refracture (252)	No Refracture (873)	p	%	Refracture (292)	No Refracture (1226)	p	%
Demographic Factors								
White	229 (90.9)	777 (89)	0.485	22.8	275 (94.2)	1127 (91.9)	0.221	19.6
Black	23 (9.1)	96 (11)		19.3	17 (5.8)	99 (8.1)		14.7
Hispanic Ethnicity	8 (3.2)	27 (3.1)	1	22.9	8 (2.7)	41 (3.3)	0.714	16.3
Non-hispanic ethnicity/ unknown	244 (96.8)	846 (96.9)		22.4	284 (97.3)	1185 (96.7)		19.3
Private Insurance	20 (7.9)	61 (7)	0.582	24.7	5 (1.7)	43 (3.5)	0.137	10.4
Pubic Insurance	230 (91.3)	809 (92.7)		22.1	284 (97.3)	1179 (96.2)		19.4
Known Risk Factors								
Alcohol Use	9 (3.6)	13 (1.5)	0.065	40.9	6 (2.1)	26 (2.1)	1	18.8
Smoking	90 (35.7)	303 (34.7)	0.765	22.9	83 (28.4)	390 (31.8)	0.292	17.5
BMI>30	122 (48.4)	437 (50.1)	0.668	21.8	94 (32.2)	451 (36.8)	0.154	17.2
Age>=70	184 (73)	622 (71.2)	0.634	22.8	254 (87)	1007 (82.1)	0.046	20.1
Osteoporosis	224 (88.9)	750 (85.9)	0.249	23	263 (90.1)	1024 (83.5)	0.005	20.4
Age (continuous)	75.81 (9.57)	75.21 (9.44)	0.382		79.73 (8.86)	78.52 (8.99)	0.037	
CCI (continuous)	3.75 (2.97)	3.33 (2.77)	0.045		2.89 (2.47)	2.68 (2.33)	0.192	
Bisphosphonate Use	70 (27.8)	249 (28.5)	0.874	21.9	53 (18.2)	242 (19.7)	0.566	18
PPI	118 (46.8)	419 (48)	0.775	22	82 (28.1)	312 (25.4)	0.373	20.8
Calcium	31 (12.3)	85 (9.7)	0.241	26.7	19 (6.5)	53 (4.3)	0.125	26.4
Vitamin D	23 (9.1)	85 (9.7)	0.903	21.3	18 (6.2)	55 (4.5)	0.225	24.7

sidering administration method only (before or after initial fracture), parenteral corticosteroids were associated with significantly increased odds of re-fracture (aOR = 1.33. 95% CI = 1.05-1.69) but oral corticosteroids were not, despite showing slightly increased adjusted odds of re-fracture (aOR = 1.20, 95% CI=.96-1.49, p-value=.111). In terms of timing, only corticosteroids administered after initial fracture were associated with an increased odds of re-fracture (aOR = 1.50, 95% CI = 1.19-1.89). There was no apparent interaction effect for patients receiving corticosteroids in both time periods. When considering timing and administration method together, only parenteral corticosteroid use after fracture was associated with an increased risk of re-fracture (aOR = 1.49, 95% CI 1.16-1.92). Oral corticosteroid use after initial fragility fracture had slightly, but not significantly, increased odds of re-fracture (aOR = 1.22, p-value = .123). There was no significant interaction effect in corticosteroid timing for either type.

NECESSARY CORTICOSTEROID USE

Corticosteroids are a widely used medication, but there are only some medical conditions in which corticosteroids are the standard of treatment. A list of conditions where corticosteroid use was indicated, and therefore the benefit outweighed the potential increased fracture risk, is given in supplemental Table S3. Our results showed that only 44.4% of patients with parenteral corticosteroid use and 53.1% of patients with oral corticosteroid use had a diagnosis code within 7 days of corticosteroid prescription that required corticosteroid use.

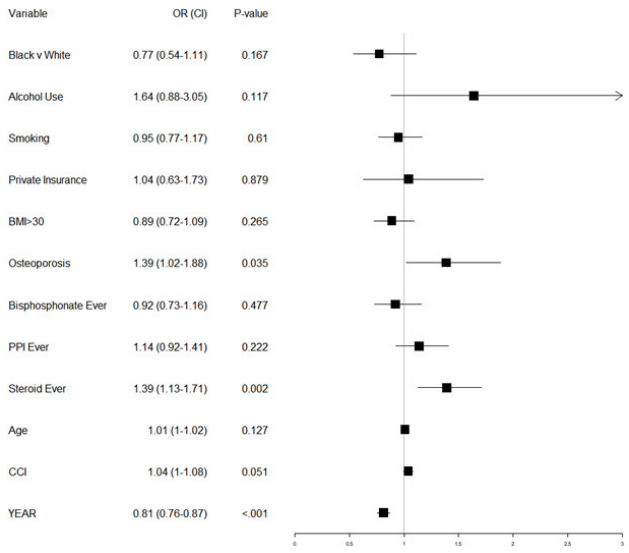

Figure 2. Multivariable logistic regression for predictors of repeat fracture.

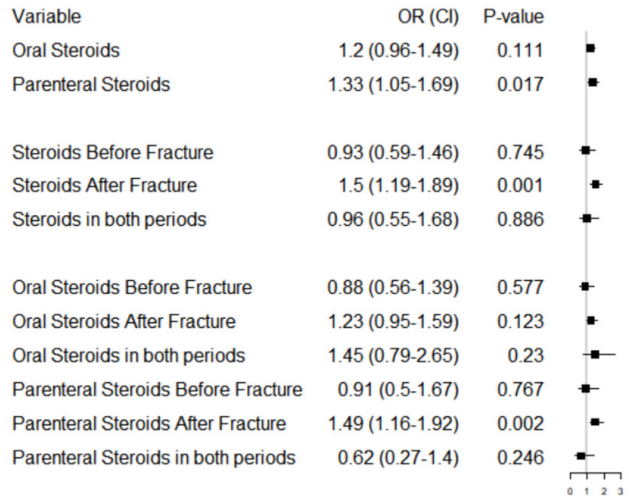

Figure 3. Multivariable logistic regression results showing corticosteroid timing, corticosteroid type, and corticosteroid type and timing's effect on re-fracture odds.

CORTICOSTEROID DOSAGE

Next, dosage of steroids was analyzed to see its effects on refracture risk among the set of patients who did receive steroids. Dosages were standardized to prednisone equivalents. Table 2 shows the mean dosage of prednisone equivalents for parenteral and oral steroids before fracture, after fracture, and in total. An increased cumulative dosage of prednisone equivalents administered parenterally before fracture was significantly associated with a decreased risk of repeat fracture (P=0.009). Dosage did not have a significant effect for any of the other categories.

Figure 4 displays the dose-effects of 6 different logistic regressions. These were (1) an adjusted model with total oral steroid dosage over the study period, (2) an adjusted model with oral steroid dosage before first fracture, (3) an adjusted model with oral steroid dosage after first fracture, (4) an adjusted model with total parenteral steroid dosage over the study period, (5) an adjusted model with parenteral steroid dosage before first fracture, (6) an adjusted model with parenteral steroid dosage after first fracture. Only patients that took each steroid type within the time frames considered were included in these analyses (i.e. decreased sample sizes for each analysis). We did this to use the most patient data when studying each dosage effect across different time periods. In this analysis, cumulative oral steroid dose equivalents trended towards an increased risk of repeat fracture but did not reach significance (p=0.089). This analysis also revealed that increased parenteral administration before fracture did not influence repeat fracture risk, contrary to the initial analysis.

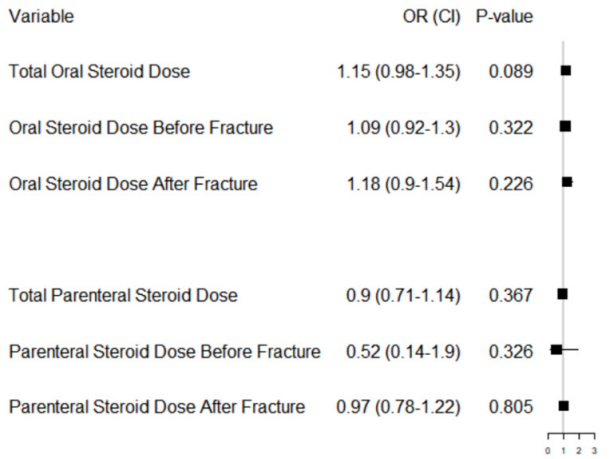

Figure 4. Logistic regression results using standardized steroid dosages to prednisone equivalents among patients who took steroids within each time period considered. There are 6 adjusted logistic regressions reported in this figure, where each dosage factor was used in addition to other patient covariates for adjustment.

DISCUSSION

Osteoporotic fractures are associated with high morbidity, mortality, and economic burden, so decreasing their incidence is crucial for patient health and well-being. Many patients with osteoporosis are older and more likely to be taking medications for other medical conditions, including medications that may increase risk for fragility fractures, including corticosteroids. In our patient population consisting of patients with a fragility fracture, 42.6% of them received a corticosteroid within one year of the fracture, indicating that it is a widely used medication, even in the osteoporosis patient population. Further, the percentage of patients in our population taking corticosteroids increased from 2011 to 2015, indicating that they are becoming even more common. Due to the widespread use of corticosteroids, it is important to know if the risk of a re-

peat fracture outweighs the benefit of the anti-inflammatory effects.

We found that oral corticosteroid use was not significantly associated with a repeat fracture, which was contrary to our hypothesis. This finding is consistent with Munson et al (2018). They did find that stopping oral corticosteroids after the initial fracture decreased the risk of a repeat fracture, but it was only significant in non-bisphosphonate users. Their hypothesis for the lack of significant increased repeat fracture risk is that corticosteroids' effects on bone mineral density take significant time, making the study window possibly too short to see the effects. Because of this, they argue that an increased repeat fracture risk may not need to alter treatment plans of oral corticosteroids in the short term.

However, Munson et al did not study parenteral corticosteroid use. Unlike oral corticosteroids, our study found that parenteral corticosteroids significantly increased repeat fracture risk, especially if given after the initial fracture. A possible explanation is that patients who receive parenteral corticosteroids are in the hospital and are therefore more likely sicker than patients who receive oral corticosteroids, which may make them prone to repeat fractures.

We hypothesized that an increased dosage of corticosteroids may increase the risk of repeat fractures because it has been shown that a higher dose of corticosteroids causes a linear increase in side effects (Huscher et al. 2008). However, after adjustment, our results did not reveal a significant effect of cumulative steroid dosage on repeat fracture risk. This finding is consistent with a previous study, which found that cumulative dose did not significantly alter primary fracture risk after adjusting for patient variables that may be confounders (van Staa et al. 2000). The lack of significant findings may indicate that a dosage effect on repeat fractures may not be present, but steroid use (including timing/method of administration) in general does.

Corticosteroids are a widely used medication, and our study showed that a significant proportion of patients received corticosteroids for another medical condition. However, only certain medical conditions indicate definite corticosteroid use [Table S3] (Hodgens and Sharman 2021). Only about half of our patient population had a diagnosis within 7 days of the corticosteroid administration that required its use. Because of the high use of corticosteroids and the known physiologic mechanism of increased fracture risk, it is critical to know if these medications should be avoided in high-risk patients. Further evaluation is needed to see if there is a definite effect of systemic corticosteroids on repeat fracture risk, and if there is a dosage threshold that may be safe for patients. Physicians should take caution with the use of unnecessary parenteral corticosteroids, especially if they had not been taking them before the initial fragility fracture, in order to prevent a repeat fracture.

There are several limitations to this study. One limitation is relying on electronic medical record coding for the data. We evaluated "necessary" corticosteroid use by having a diagnosis code within 7 days of the prescription, but it is possible that they were appropriately prescribed based on the risk/benefit analysis in the specific clinical scenario. This likely would increase the number of patients that received "necessary" corticosteroids; however, it still would not reach 100%, indicating that corticosteroids still may be overprescribed in this patient population. Additionally, because of limitations in ICD coding specificity, our study did not consider re-fractures within a 1-year window after initial fracture. ICD-9 coding does not differentiate between initial or subsequent encounters for a fracture. Therefore, the same fracture code could repeat at subsequent clinic visits and would falsely appear as repeat fractures. To be on the safe side, repeat fractures were not considered until after this one-year time period. As a result, it is possible repeat fractures that occurred were not included in the study. The goal of the study was to determine effects in medication alterations between primary and secondary fractures. Less than a one-year window between fractures would be too short of a time period to appreciate effects of drug adjustments, and thus this limitation does not impact the overall study goals. Another limitation is the time frame of the study, where we could only allow for 2 years of follow-up after the initial fracture based on the available data. With a longer time, more repeat fractures and a possible increased association with oral corticosteroids may have been seen.

In conclusion, fragility fractures are associated with significant morbidity and mortality, so decreasing their incidence is critical for patient outcomes. Our study found that parenteral corticosteroids, but not oral corticosteroids, especially when given after the initial fragility fracture, increased the risk of a subsequent fracture. Our data suggested that given steroid use, the dosage of steroids may not play a significant role in complication. This means that the decision whether to administer steroids at all may be more important than the amount, given necessity to use steroids. In the future, studies can investigate if higher

doses or longer time of administration directly increases the fracture risk. Physicians may need to take caution in overprescribing parenteral corticosteroids in osteoporotic patients at high risk for repeat fragility fractures.

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Conflicts of Interest Statement for Justin David

Gregory Benes is currently a third year medical student at Louisiana State University Health Sciences Center in New Orleans, LA. He is interested in pursuing a career in orthopedics.
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Dr. Dasa currently serves as vice chair for academic affairs for the department of orthopedics, Irvin Cahen endowed chair for research, chair of the LSU clinical practice leadership group. He is the co-founder and chief medical officer for an innovative start up, SIGHT Medical and helped co found a novel medical education platform called DOC SOCIAL.

His research interests cover all areas of adult orthopaedics focusing on joint replacement, knee arthritis, health disparities and outcomes research. He is one of the few surgeons in the world performing outpatient opioid free total knee replacements allowing patients to recover in the shortest time possible.
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Conflicts of Interest Statement for Dr. Dasa

Dr. Krause is an orthopedic trauma surgeon with LSU in New Orleans Louisiana.
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Dr. Lauren Leslie is part of the Ochsner Sports Medicine Institute as a neuromusculoskeletal and sports medicine specialist. She completed her neuromusculoskeletal medicine residency at Michigan State University, where she served as chief resident and received the American Academy of Osteopathy award as resident of the year. Dr. Leslie completed her sports medicine fellowship at Edward Via Virginia College of Osteopathic Medicine/Virginia Tech, where she served as an associate team physician for Virginia Tech and Radford University athletics. She now serves as the team physician for Loyola University New Orleans as well as many local high schools. Dr. Leslie's primary specialty is neuromusculoskeletal medicine. She has a specific interest in osteopathic manipulative medicine including osteopathy in the cranial field, movement biomechanics, and concussion management and research. She has training in both diagnostic and interventional ultrasound techniques, including orthobiologic injections.
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Dr. Deryk Jones is head of the Ochsner Sports Medicine Institute (OSMI), a program that recently joined with Dr. James Andrews to form the Ochsner Andrews Sports Medicine Institute. He double majored in biology and philosophy at Emory University and played collegiate soccer there as well. He received his M.D. degree from Stanford University where his interest and focus on articular cartilage research began. Orthopaedic training was at the Harvard Combined Program completing a prestigious Chiefship at the Massachusetts General Hospital in 1997. He then performed a fellowship in Shoulder Surgery and Sports Medicine at the University of Pittsburgh in 1998 and on completion joined the staff at Tulane University Medical School; he currently maintains appointments in Orthopaedic Surgery as a Clinical Assistant Professor at Tulane University and a Full Professor at the University of Queensland, Australia. He is a fellow of the American Academy of Orthopaedic Surgeons and the American Orthopaedic Association. He is board certified in orthopaedic surgery and subspecialty certified in sports medicine through 2030.

In 2004, he created OSMI and runs a program with over 160 athletic trainers, numerous operative and non-operative clinicians, physical therapist, and performance trainers. The program has locations throughout New Orleans and the state of Louisiana as well as the Mississippi gulf coast. He directs an operative fellowship training three board certified orthopaedist and one research fellow in sport medicine per year. OSMI also has residency programs in sports medicine assistantship and sports medicine physical therapy as well. He directs research focused on outcomes in shoulder, elbow, knee, hip and foot and ankle pathologic conditions evaluating operative and non-operative options and has published numerous articles on these subjects. He specializes in treatment techniques utilizing biologic reconstructive surgery and has been on the leading edge of innovations in regenerative medicine. His specific focus is on the treatment and regeneration of articular cartilage injuries.
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Conflicts of Interest Statement for Dr. Jones

Dr. Chapple's primary role as Director of Biostatistics is planning cancer clinical trials in mice, humans, and cell lines – while also executing statistical analyses. Dr. Chapple is an expert in adaptive clinical trial designs, particularly Bayesian methods. His 2019 paper "A hybrid Phase I-II/III clinical trial design allowing for dose re-optimization in Phase III" proposed a new framework for seamless drug development through the three stages of clinical trial design. This paper was recognized globally by the statistical community when it received the award for "Best Paper" from Biometrics, a top tier statistical journal. Dr. Chapple has received worldwide recognition for his contributions to adaptive clinical trial design methodology and he hopes this expertise can propel his institution towards innovative cancer therapies, rapid advances in treatment of chronic diseases, and the long-term goal of personalized/precision medicine.

Dr. Chapple has produced many new trial designs and methods, which are accompanied with user-friendly R packages. Dr. Chapple trained under Dr. Peter Thall at MD Anderson, who is a pioneer in Bayesian adaptive trials. He later refined these skills working with cancer researchers from other institutions. Dr. Chapple's adaptive trial designs were used to dose-find in pediatric brain tumors in a trial conducted at Harvard and the Dana Farber Cancer Center.

Dr. Chapple has designed hundreds of studies and has supported many research departments at LSUHSC including: Orthopedics, OBGYN, Hematology Oncology, Dermatology, Oral Surgery, Endodontics, Cancer, Virology, Cellular Biology, Inflammation, and treatment disparities research. As a joint professor in Orthopedics, Dr. Chapple works on large scale electronic records databases which requires processing longitudinal information from patients on hospital encounters, diagnoses, procedures, prescriptions, and lab values.
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APPENDIX

Table S1. ICD codes used for patients in this study.

	ICD Codes
Fragility Fracture Tags	M80.871A, M80.872A, M80.879, M80.071A, M80.072A, M80.079A, 733.14, 733.15, 821, 821.01, 821.2, 821.21, 821.22, 821.23, 821.29, M80.051A, M80.052, M80.052A, M80.059, M80.059A, M80.851, M80.851A, M80.852A, M80.859A, M84.453A, S72.011A, S72.012A, S72.019, S72.019A, S72.021A, S72.022A, S72.023A, S72.031A, S72.032A, S72.033, S72.033A, S72.041A, S72.042A, S72.043A, S72.091A, S72.092A, S72.099A, S72.101A, S72.102A, S72.109A, S72.141A, S72.142A, S72.143A, S72.21XA, S72.22XA, S72.23XA, S72.301A, S72.302A, S72.309A, S72.401A, S72.402A, S72.409A, S72.411A, S72.412A, S72.413A, S72.451A, S72.452A, S72.453A, S72.90XA, S72.91XA, S72.92XA, M80.031A, M80.032A, M80.039A, M80.832A, M84.439A, 733.1, M80.00X, M80.00XA, M80.80X, M80.80XA, M84.40XA, M84.48XA, M84.68XA, M80.042A, 820, 820.01, 820.02, 820.03, 820.09, 820.2, 820.21, 820.22, M84.459A, 812, 812.01, 812.02, 812.03, 812.09, 812.2, 812.21, 812.4, 812.41, 812.42, 812.43, 812.44, 812.49, M80.021A, M80.022A, M80.029A, M80.821A, M80.822A, M80.829A, S42.201A, S42.202A, S42.209A, S42.213A, S42.214A, S42.215A, S42.216A, S42.251A, S42.252A, S42.253A, S42.291A, S42.292A, S42.293A, S42.294A, S42.295A, S42.296A, S42.301A, S42.302A, S42.309A, S42.401A, S42.402A, S42.409A, S42.441A, S42.442A, S42.443A, S42.451A, S42.452A, S42.453A, S42.461A, S42.462A, S42.463A, S42.471A, S42.472A, S42.473A, M80.061A, M80.062, M80.062A, M80.069A, M80.861A, M80.862A, M80.869A, 808, 808.2, 808.8, S32.301A, S32.302A, S32.309A, S32.401A, S32.402A, S32.409A, S32.501A, S32.502A, S32.509A, S32.601A, S32.602A, S32.609A, S32.810A, S32.811A, S32.82XA, S32.89XA, S32.9XXA, M80.011A, M80.012A, M80.811A, 733.13, 805, 805.01, 805.02, 805.03, 805.04, 805.05, 805.06, 805.07, 805.08, 805.2, 805.4, 805.8, 806, 806.03, 806.04, 806.05, 806.07, 806.09, 806.2, 806.24, 806.25, 806.26, 806.27, 806.29, 806.4, 806.8, M48.50XA, M80.08X, M80.08XA, M80.88X, M80.88XA, S12.000A, S12.001A, S12.100A, S12.101A, S12.200A, S12.201A, S12.300A, S12.301A, S12.400A, S12.401A, S12.500A, S12.501A, S12.600A, S12.601A, S12.9XXA, S14.101A, S14.102A, S14.103A, S14.104A, S14.105A, S14.106A, S14.107A, S14.109A, S14.112A, S14.121A, S14.122A, S14.124A, S14.125A, S14.126A, S14.127A, S14.151A, S14.152A, S14.153A, S14.155A, S14.156A, S14.157A, S22.009A, S24.101A, S24.103A, S24.104A, S24.109A, S24.113A, S24.114A, S24.133A, S24.152A, S24.153A, S24.154A, S32.009A, S32.019A, S32.029A, S32.039A, S32.049A, S32.059A, S32.10XA, S32.2XXA, S34.101A, S34.109A, S34.113A, S34.139A, 733.12, 813.4, 813.41, 813.42, 813.43, 813.44, S52.501A, S52.502A, S52.509A, S52.531A, S52.532A, S52.539A, S52.601A, S52.602A, S52.609A, S52.90XA, S52.91XA, S52.92XA
Trauma Tags	E802.0, E806.8, E810.0, E810.1, E811.0, E812.0, E812.1, E812.2, E812.3, E812.7, E812.8, E812.9, E813.0, E813.1, E813.2, E813.3, E813.4, E813.9, E814.0, E814.1, E814.7, E814.9, E815.0, E815.1, E815.9, E816.0, E816.1, E816.2, E816.7, E817.0, E817.1, E817.2, E817.7, E817.9, E818.0, E818.1, E818.2, E818.7, E818.8, E818.9, E819.0, E819.1, E819.3, E819.4, E819.7, E819.8, E819.9, E821.0, E821.2, E821.7, E821.9, E823.0, E823.1, E823.7, E823.8, E823.9, E824.0, E824.1, E824.5, E824.8, E824.9, E825.0, E825.1, E825.2, E825.7, E825.8, E825.9, E826.1, E826.9, E828.2, E828.9, E829.0, E829.8, E829.9, E831.3, E835.2, E835.3, E835.9, E838.1, E838.3, E838.6, E838.9, E842.6, E843.3, E843.9, E848, V00.181A, V00.831A, V00.832A, V01.0, V01.09XA, V02.00XA, V03.00XA, V03.00XD, V03.00XS, V03.09XA, V03.10XA, V03.10XD, V03.19XA, V03.90XA, V03.90XD, V03.99XA, V04.99XA, V09.00XA, V09.00XS, V09.09XA, V09.20XA, V09.29XA, V09.9XXA, V09.9XXD, V10.0XXA, V10.3XXA, V10.4XXA, V10.9XXA, V11.2XXA, V12.5XXA, V14.0XXA, V16.0XXA, V17.0XXD, V18.0XXA, V18.0XXD, V18.3XXA, V18.4XXA, V19.3XXA, V19.9XXA, V23.2XXS, V27.1XXA, V27.5XXA, V28.4XXA, V29.50XA, V29.9XXA, V37.0XXA, V38.0XXA, V40.3XXA, V40.9XXA, V42.0XXA, V42.5XXA, V42.7XXA, V43.31XA, V43.51XA, V43.52X, V43.52XA, V43.52XD, V43.52XS, V43.53XA, V43.62XA, V43.62XD, V43.63XA, V43.92XA, V44.5XXA, V44.6XXA, V44.9XXA, V46.4XXA, V47.02XA, V47.0XXA, V47.4XXA, V47.52XA, V47.5XXA, V47.62XA, V47.6XXA, V47.9XXA, V48.0XXA, V48.1XXA, V48.3XXA, V48.3XXD, V48.4XXA, V48.4XXD, V48.5XXA, V48.6XXA, V49.00XA, V49.09XA, V49.10XA, V49.20XA, V49.3XXA, V49.40XA, V49.40XD, V49.40XS, V49.49XA, V49.49XD, V49.50XA, V49.50XD, V49.59XA, V49.60XA, V49.60XD, V49.60XS, V49.88XA, V49.9XXA, V49.9XXD, V49.9XXS, V53.5XXA, V53.6XXA, V57.1XXA, V58.1XXA, V58.4XXA, V59.40XA, V59.59XA, V59.88XA, V59.9XXA, V67.4, V67.6, V67.9, V68.4XXA, V70.0XXA, V73.6XXA, V78.1XXA, V78.4XXA, V78.4XXD, V78.6XXA, V79.40XA, V79.50XA, V79.59XA, V79.88XA, V80.010A, V80.010D, V82.4XXA, V83.4XXA, V86.49XA, V86.59XA, V86.65XA, V86.69XA, V87.7XXA, V87.7XXD, V87.7XXS, V87.9XXA, V88.7XXA, V88.8XXA, V89.0XXA, V89.0XXD, V89.1XXA, V89.2XXA, V89.2XXD, V89.2XXS, V89.9XXA, V89.9XXS, Z09, Z47.1
Alcohol Use Tags	291.9, 303.01, 303.02, 303.9, 303.91, 303.92, 305.01, 305.02, F10.10, F10.120, F10.121, F10.129, F10.14, F10.188, F10.19, F10.20, F10.220, F10.221, F10.229, F10.23, F10.230, F10.231, F10.232, F10.239, F10.24, F10.251, F10.259, F10.26, F10.27, F10.280, F10.282, F10.288, F10.29
Osteoporosis Tags	733.00, 733.01, 733.02, 733.03, 733.09, V82.81, V13.51, V49.81, Z13.820, Z78.0, Z87.310

Table S2. Steroids included in study with dose ranges for oral prescriptions (mg) and parenteral prescriptions (mg/mL).

Steroid	Oral Dose (mg)	Parenteral Dose (mg/mL)
Dexamethasone	(0.5-6)	(10-24)
Hydrocortisone	(5-10)	(50-500)
Methylprednisolone	(2-32)	(40-2000)
Prednisolone	(5)	-
Prednisone	(1-50)	(1)

Table S3. Diagnoses with indicated corticosteroid use

Common indications for corticosteroids, by field, include:

- **Allergy and Pulmonology**: asthma exacerbation, COPD exacerbation, anaphylaxis, urticaria and angioedema, rhinitis, pneumonitis, sarcoidosis, interstitial lung disease.
    - Asthma exacerbation: 493.9, 493.91, 493.92, J45.901, J45.909
    - COPD exacerbation: 491.21, J44.0, J44.1, J44.9
    - Anaphylaxis: 995.0, T78, T78.2
    - Urticaria: 708, L50.9
    - Angioedema: 995.1, T78.3
    - Sarcoidosis: 135, D86
    - Interstitial lung disease: 516.9, J84
- **Dermatology**: contact dermatitis, pemphigus vulgaris
    - Contact dermatitis: 692, L25
    - Pemphigus vulgaris: 694.4, L10.0
- **Endocrinology**: adrenal insufficiency, congenital adrenal hyperplasia
    - Adrenal insufficiency: 255.41, E27.1
    - Congenital adrenal hyperplasia: 255.41, 255.5, 255.8, 255.9, E27.40, E27.49, E27.8, E27.9
- **Gastroenterology**: inflammatory bowel disease, autoimmune hepatitis
    - Inflammatory bowel disease: 556, K51
    - Autoimmune hepatitis: 571.42, K75.4
- **Hematology**: hemolytic anemia, leukemia, lymphoma, idiopathic thrombocytopenic purpura
    - Hemolytic anemia: 283, D59
    - Leukemia: 208, C95
    - Lymphoma: 202, C85
    - Idiopathic thrombocytopenic purpura: 287.31, D69.3
- **Rheumatology**: rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, polymyalgia rheumatica
    - Rheumatoid arthritis: 714, M06
    - Systemic lupus erythematosus: 710.0, M32
    - Polymyositis: 710.4, M33.2
    - Dermatomyositis: 710.3, M33.0, M33.1, M33.9
    - Polymyalgia rheumatica: 725, M35.3
    - Fibromyalgia: 729.1
- **Ophthalmology**: uveitis, keratoconjunctivitis
    - Uveitis: 364.0, 364.1, 364.2, 364.3, H20
    - Keratoconjunctivitis: 370, H16.2
- **Other**: organ transplantation, antenatal lung maturation, nephrotic syndrome, cerebral edema, multiple sclerosis
    - Organ transplantation: V42, Z94
    - Nephrotic syndrome: 581, N04
    - Cerebral edema: 348.5, G93.6
    - Multiple sclerosis: 340, G35
    - Long term use of systemic steroids: Z79.52

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