Title: Opioids and the risk of fracture: a self-controlled case series study in the Clinical Practice Research Datalink

Authors: Emily J. Peach, Fiona A. Pearce, Jack Gibson, Andrew J. Cooper, Li-Chia Chen, Roger D. Knaggs

Author affiliations: Division of Pharmacy Practice and Policy, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom (Emily J. Peach, Roger D. Knaggs); Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom (Emily J. Peach, Fiona A. Pearce, Jack Gibson); Mundipharma Research Limited, Cambridge, United Kingdom (Andrew J. Cooper); AstraZeneca, Cambridge, United Kingdom (Andrew J. Cooper); Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Manchester, United Kingdom (Li-Chia Chen); Primary Integrated Community Solutions, Nottingham, United Kingdom (Roger D. Knaggs); Pain Centre Versus Arthritis, University of Nottingham, Nottingham, United Kingdom (Roger D. Knaggs).

Main text word count: 3,496

Abstract word count: 186

Abbreviations: aIRR, adjusted incidence rate ratio; CI, confidence interval; CPRD, Clinical Practice Research Datalink; HR, hazard ratio; IQR, interquartile range; IRR, incidence rate ratio; OMEQ, oral morphine equivalent; SCCS, self-controlled case series

Correspondence: Dr Emily J. Peach; Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Clinical Sciences Building, City Hospital Campus, Nottingham, United Kingdom. NG5 1PB; emily.peach@nottingham.ac.uk

Short title: Opioids and fractures: a self-controlled analysis
ABSTRACT

Self-controlled study designs can be used to assess the association between exposures and acute outcomes while controlling for important confounders. Using routinely collected health data, a self-controlled case series design was used to investigate the association between opioid use and bone fractures in 2008–2017 among adults registered in the United Kingdom Clinical Practice Research Datalink. The relative incidence of fracture was estimated, comparing periods when exposed and unexposed to opioids, adjusted for time-varying confounders. Of 539,369 people prescribed opioids, 67,622 sustained fractures and were included. The risk of fracture was significantly increased when exposed to opioids, with an adjusted incidence rate ratio of 3.93 (95% confidence interval: 3.82, 4.04). Fracture-risk was greatest in the first week of starting opioids (adjusted incidence rate ratio: 7.81, 95% confidence interval: 7.40, 8.25) and declined with increasing duration of use. Re-starting opioids after a gap in exposure significantly increased fracture-risk (adjusted incidence rate ratio: 5.05, 95% confidence interval: 4.83, 5.29) when compared to non-use. These findings highlight the importance of raising awareness of fractures among patients at opioid initiation and demonstrate the utility of self-controlled methods for pharmacoepidemiologic research.

Keywords: opioid analgesics; bone fractures; self-controlled case series; pharmacoepidemiology
Fractures are a global public health concern; there are approximately 8.9 million osteoporotic fractures worldwide each year. (1) Opioids may increase the risk of fracture due to acute central nervous system effects, which include sedation and dizziness, and potential long-term effects on bone mineral density. (2) Prior studies have reported an increased risk of fracture in users of opioids; (3-5) however, these studies used methods to statistically match opioid users to non-users to make comparisons in fracture-risk possible, and consequently, these studies are limited by the high potential for confounding.

This study assessed the association between opioids and fractures. The study aimed to investigate the effects of the duration and dose of opioid exposure on the risk of fracture by using a self-controlled study design to minimize confounding.

METHODS
Data Source
This study used data from patients registered with United Kingdom general practices contributing data to the Clinical Practice Research Datalink (CPRD) GOLD. The CPRD GOLD is one of the largest databases of anonymized electronic health records, containing, among other routine health data, demographic information, prescription records and medical diagnoses for over 17 million individuals. Additionally, the CPRD GOLD provides linkage to Hospital Episode Statistics, an administrative database that contains hospital records for English patients. Data access was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol reference 18_282R).
Study Design

We used the self-controlled case series (SCCS) study design which has been used in previous pharmacoepidemiological studies to investigate fractures associated with thiazolidinediones,(6) and antidepressants,(7) as well as to study the association between opioids and road traffic accidents.(8)

In the SCCS design, all individuals experience the exposure and outcome of interest. Within-person comparisons are made by deriving an incidence rate ratio (IRR); comparing the rate of the outcome when exposed to the unexposed rate. Individuals, therefore, act as their own control with the major advantage that factors remaining constant within a person (e.g., genetic factors), including those that are unknown or unmeasured, are inherently controlled-for by-design.

Selection of Cases

The base cohort, from which the SCCS cohort was selected, included individuals aged 18 years and older who started opioids during the nine-year study period (June 1, 2008 to May 31, 2017).

Patients entered the study two years after the observation start date, which was the latest of: the date of practice registration, the date the practice provided research-quality data, or June 1, 2006. The study exit date was the earliest of: the date of deregistration from the practice, the date the practice ceased to provide data to the CPRD GOLD, the date the patient died, or the study end date (May 31, 2017).

Patients were excluded from the base cohort if they were prescribed an opioid in the two years between their observation start date and study entry date, if they sustained a fracture in the six months before their study entry date, or if they had a record of a fracture with a
missing date. Cases included in the SCCS cohort were those recorded as having sustained at least one fracture during follow-up.

Outcome

Fractures were identified using clinical codes for diagnoses (eTable 1), operations and procedures that were recorded in the CPRD GOLD and Hospital Episode Statistics databases. If a patient had more than one record of a fracture, the earliest record was considered the first fracture. Subsequent fracture records were assumed to be new if they occurred in a different anatomical site or were recorded more than six months after a preceding fracture to the same site. If not, these fracture records were considered to relate to the earlier fracture records and were excluded from the analysis.

Exposures

Exposure to opioids on a given day of follow-up was based on the presence of a prescription for an opioid analgesic (eTable 2). We used an approach adapted from Pye et al. (2018),(9) which systematically handles missing data and prepares prescription records for time-varying analysis (eFigure1), to generate a time-varying measure of opioid exposure. Consecutive prescriptions for identical opioid products were combined into one episode allowing for a permissible gap of 15 days. The prescription duration (in days) was calculated based on the prescribed daily dose and quantity prescribed. The stop date for each prescription record was calculated using the prescription start date and duration. Clinical equianalgesic ratios were used to covert opioid doses to oral morphine equivalent (OMEQ) doses (milligrams/day); representing the analgesic potency of an opioid, relative to oral morphine (eTable 2), and any duplicate or overlapping prescriptions were combined to generate a binary indicator for exposure or non-exposure with an OMEQ dose on each day of follow-up.
Periods of exposure to opioids were split into discrete risk periods for the first period of exposure to opioids, and any subsequent periods of opioid exposure. Risk periods reflected the proximity of opioid exposure to the date an opioid was started or re-started. Exposed risk periods consisted of: days 1-7, 8-14, 15-28, 29-365, and day 366 until the final day of opioid exposure within that period, where day 1 refers to the day after an opioid was started or re-started (Figure 1a). The date the opioid was started or re-started was not included in the exposed risk periods to reduce protopathic bias.(10)

Periods of non-exposure to opioids consisted of all follow-up time before the date the opioid was started, during any gaps between exposed periods, and after the final exposed day until the date follow-up ended. A 90-day pre-exposure period was included to eliminate bias arising from event-dependent exposure.(11) Fracture events and person-time occurring in the 90 days before, and including, the day an opioid was started or restarted, were consequently removed from the baseline (i.e., unexposed) rate of fracture (eFigure 2); the inclusion of these fracture events would have otherwise under-estimated the risk of fracture when exposed. A 28-day post-exposure period was introduced to reduce bias resulting from residual effects of opioids after cessation. Figure 1a illustrates the division of follow-up time into these discrete periods; the lengths of risk periods were curtailed if they overlapped with the start of a subsequent risk period (eFigure 3).

Confounding Variables

The SCCS design inherently controls for unmeasured time-invariant and between-individual confounding; however, within-person factors that vary over time needed to be controlled for. Following consideration of covariates included in similar studies,(3-5) and of factors found to affect fracture rates;(12-16) age, season and exposure to fracture-risk increasing drugs (eTable 3) were adjusted for in this analysis, providing they significantly improved the model
To adjust for time-varying confounders, each risk period was cut into smaller periods to account for changes in age (yearly), the season of year (3-monthly) and exposure to fracture risk increasing drugs (binary indicator in 3-month intervals), this allowed for an adjustment of fracture-risk over time as these covariates changed throughout follow-up.

Statistical Analysis

Fixed-effects Poisson regression models, conditioned on the individual, were used to estimate crude IRRs, adjusted IRRs and 95% confidence intervals (95% CI); comparing the rate of fracture when exposed with the baseline rate.

The decision of whether to fit age as a continuous or categorical variable was made by fitting age as both a continuous variable and as a categorical variable (at one-year intervals) and running separate models with each. The likelihood ratio test was run to compare model fit in both instances, with the variable with the best fit being carried forward into the final model. In building the final model, all covariates were included in a model and their effect assessed by first running the model with all covaries and then removing just the one covariate under investigation and assessing model fit using the likelihood ratio test. If the model fit was significantly (p<0.05) improved by including the covariate, then it was included in the final model. The advantage of taking a backward elimination approach is that the joint predictive ability of variables is assessed, leaving only the most important variables in the model. The results were stratified to consider effects by age group (<65, ≥65 years), sex (male, female), and OMEQ dose (<50mg/day, ≥50mg/day) to assess dose effects. Further investigative analyses explored age-sex, and dose-duration interactions.

This study was part of a program of research that used all available patients from the CPRD GOLD to form the base cohort of patients exposed to opioids. Prior to this SCCS analysis, in
a pre-hoc sample size calculation to determine study feasibility, we estimated the sample size required using the signed root likelihood ratio formula. (18) For this calculation, we used the median duration of observation for the base cohort, along with an incidence rate ratio of 1.2 based on the results of prior opioid-fracture association studies. It was estimated that 26,953 fracture cases with a median observation period of 7.1 years were needed to detect a relative incidence of 1.2 within the first 28 days of exposure, with 95% power and a 5% significance level.

A p-value <0.01 (2-tailed) was considered to indicate statistical significance. Stata/MP 15 (StataCorp, Texas, USA) was used for data management and statistical analyses.

Sensitivity Analyses

Individuals who died within 90 days of their first fracture were excluded to test the sensitivity of the results to the potential for fractures to influence the duration of observation. Fractures increase the risk of subsequent fractures; (19) the analyses were carried out for first fractures only to test the sensitivity of the results to events that are not independent of each other. Bone metastases may increase fracture-risk and the need for analgesia, patients with a record of cancer were excluded to test for sensitivity to this potential confounding factor. The analyses were repeated for alternative durations of the pre-exposure; results from analyses using a 7-day and 28-day pre-exposure period were compared to the 90-day pre-exposure period. A complete-case analysis was performed to assess for potential bias arising from the handling of missing exposure data. The analyses were repeated for only fractures identified in the Hospital Episode Statistics database because dates for events that require hospital admission may be more accurately recorded in Hospital Episode Statistics than in the CPRD GOLD database. (20) Additionally, fractures to some sites may be susceptible to delayed diagnosis; aIRRs were stratified by fracture site, and sites with aIRRs suggesting over an eight-fold
increase in fracture risk were excluded to test the sensitivity of the results to possible reverse causality. Finally, the principal analysis was repeated for falls as an outcome, as falls are likely to be a mediating factor between opioids and fractures.

RESULTS

After applying the study exclusion criteria, the base cohort comprised of 539,369 individuals (eFigure 4). Of these, 67,622 individuals who sustained a total of 87,454 fractures and contributed a total of 452,347 person-years of follow-up, were included in this SCCS study. Among these individuals, 58.7% (39,677) were female; the mean age at study entry was 56.1 years (SD: 19.6 years); 93.1% (62,983) were of white ethnicity; 23.2% (15,663) were from the least deprived areas; and the median duration of follow-up of was 7.1 years (IQR: 5.3, 8.1 years) (Table 1).

Associations with Fracture

The crude IRR for fracture during the exposed risk period, relative to the baseline (unexposed) period, was 4.18 (95% CI: 4.07, 4.30). The likelihood ratio test indicated that the addition of age and season as covariates improved the model fit (p<.001), however, exposure to fracture-risk increasing drugs did not significantly improve the model fit (p = 0.543) and consequently fracture-risk increasing drugs were omitted from the adjusted analyses. After adjusting for age and season, the aIRR for the risk of fracture when exposed to opioids was 3.93 (95% CI: 3.82, 4.04) (Table 2).

After dividing exposed time into risk periods that corresponded to the duration of opioid use, the aIRR for fracture in days 1-7 of the first exposure period, compared to the baseline risk was 7.81 (95% CI: 7.40, 8.25). The aIRRs steadily decreased as the duration of opioid use increased over the first exposure period (until a gap in exposure or cessation of opioids); the
aIRR was 1.77 (95% CI: 1.54, 2.03) for day 29-365 and 1.25 (95% CI: 0.86, 1.82) for day 366 onwards. The risk of fracture increased when opioids were restarted; the aIRR for days 1-7 of subsequent periods of exposure was 5.05 (95% CI: 4.83, 5.29), which decreased to 2.43 (95% CI: 2.30, 2.57) for day 29-365 and 1.73 (95% CI: 1.50, 1.98) for day 366 onwards (Table 2).

When exploring effects by age, no difference was found; the aIRR for the risk of fracture when exposed to opioids was 3.76 (95% CI: 3.61, 3.91) for people aged <65 years, and was 3.94 (95% CI: 3.79, 4.09) for people aged ≥65 years. After exploring the effects of opioid exposure by sex, males showed a greater risk of fracture when compared to females; the aIRR for males was 4.15 (95% CI: 3.96, 4.35) and 3.55 (95% CI: 3.42, 3.69) for females. No significant interaction was observed between age and sex.

To investigate the effects of daily OMEQ dose, risk periods were stratified into periods of low (<50mg/day) and high (≥50mg/day) doses. The risk of fracture was greater when exposed to high daily doses of opioids, showing an aIRR of 4.50 (95% CI: 4.26, 4.74) compared to 3.90 (95% CI: 3.79, 4.02) for low doses. When exploring the interaction between duration of opioid use and opioid dose similar trends over time were found amongst periods of low dose opioid use and high dose opioid use. No significant interaction was observed between dose and duration following initiation of opioids (i.e., for the first period of opioid exposure) as shown in Figure 2a. A significant interaction was observed for periods following the restart of opioids (i.e., for subsequent periods of exposure). The risk of fracture was greater in days 1-7 following the re-start of opioids for high, compared to low, OMEQ doses; the aIRR was 6.06 (95% CI: 5.60, 6.56) when the OMEQ dose was ≥50mg/day, and was 4.71 (95% CI: 4.46, 4.98) when OMEQ doses were <50mg/day (Figure 2b).
Sensitivity Analyses

The results from the sensitivity analyses did not considerably differ from the results presented in the primary analyses (eTable 4). Fractures to the spine, chest, low back, and pelvis had greater aIRRs (eFigure 5); after excluding these, aIRRs were slightly lower than the primary results (eFigure 6). Opioids were significantly associated with an increased risk of falls, which was greatest in the first week of opioid exposure, however only a weak trend was observed when restricted to falls without fracture (eFigure 7).

DISCUSSION

This study is one of the largest and longest studies, and the first study using SCCS methodology, to investigate the association between opioids and fractures. There was nearly a 4-fold increase in the risk of fracture associated with periods of opioid exposure, compared to periods of non-use. Furthermore, this study found that the risk of fracture was significantly greater when exposed to opioids compared to periods of non-use and was greatest (8-fold higher) during the initial week of use and when OMEQ doses were >50mg/day (6-fold higher) rather than 50mg/day or less (4.7-fold higher); indicating both a duration- and dose-dependent association between opioids and fractures.

The finding that opioids increase the risk of fracture immediately after starting and restarting opioids, and the magnitude of risk reported during these periods is novel. These findings support the hypothesized mechanism of action whereby opioids induce acute central nervous system effects, which results in a greater susceptibility to falls and fractures. This concept was further explored by investigating the association between opioids and falls not resulting in a fracture, which showed a lesser magnitude of association and a weak trend over time. One limitation with studying fall outcomes is the possibility that these falls may not require urgent medical attention and therefore, less likely to be recorded in electronic health records.
If they are reported, there may be a delay in doing so. The SCCS study design is reliant upon having accurate dates for outcomes, and therefore a lack of precision in ascertaining falls may explain this finding. This study also showed that while fracture-risk declined with longer durations of use, the risk of fracture remained elevated after one year of continuous opioid use which warrants further investigation of potential effects on bone mineral density.

Comparison with other studies

Our findings are consistent with other opioid-fracture association studies that have been conducted in populations outside of the United Kingdom.(21-24) including a retrospective cohort study of 2,341 people in the United States, which found that people prescribed OMEQ doses of $\geq 50$ mg/day had a higher risk of fracture (hazard ratio: 2.00; 95% CI: 1.24, 3.24) than those prescribed OMEQ doses <20mg/day (hazard ratio: 1.20; 95% CI: 0.92, 1.56), compared to people who were not using opioids.(23) Our study found a greater risk of fracture associated with higher doses, although not in the first period of opioid exposure; very few people were initiated on high doses, which may explain the absence of a significant dose-relationship in initial use.

Existing opioid-fracture association studies are susceptible to time-varying and time-invariant confounding as well as confounding by indication, making it difficult to establish whether the relationship might be one of cause and effect. This study overcame many of the limitations of prior studies by adopting a self-controlled design which circumvents issues of time-invariant unmeasured and between-individual confounding, and limits potential confounding by indication. Considering that this present study and prior studies detected a significant positive association between opioids and fractures, there is compelling evidence for the existence of an association. Furthermore, this study has controlled for confounding to a greater extent than
prior between-participant studies by-design, which suggests that the confounding present in prior studies may have attenuated the magnitude of the effect.

Strengths and limitations of this study
Factors that vary over time are not inherently controlled for when using self-controlled methods; although efforts were made to adjust for time-varying covariates, it is possible that some residual confounding remained, such as changes in lifestyle, muscle mass, BMI and pain condition, which were not well recorded. Nevertheless, the SCCS study design has the advantage of controlling for unmeasured time-invariant confounding, which cannot be controlled for by cohort and case-control designs. The target population consisted of people starting opioids; defining new-use using a two-year lookback period does not guarantee these people were new users. There is also a potential of exposure misclassification because it was assumed people had their opioid prescriptions dispensed and that they took them as indicated by the prescriber. People may have stopped their opioids, taken them differently to the prescribed directions, or obtained over-the-counter opioids via pharmacy purchases, hospitals, or illegitimate means, which would not have been recorded. Patients may have been exposed to opioids that were bought over the counter (i.e., codeine and paracetamol combinations available to purchase in the United Kingdom) which are not recorded in the CPRD GOLD database. Therefore patient-time may have been classified as unexposed when, in this example, these patients may have been exposed to opioids. In addition, patients may not have taken opioids on days classified as exposed due to the ‘when required’ nature of these medicines; this may have led to misclassification of time as exposed when patients were, in reality, not exposed to opioids. It is not known in which direction exposure misclassification may have related to the timing of a fracture, nor how this may have biased the results.
This study has several important strengths. The SCCS design relies on some assumptions, and violation of these can bias the results. The important assumptions are that: (1) events arise independently within individuals (i.e., fractures do not affect the occurrence of a subsequent fracture) and (2) events do not influence subsequent follow-up; these were tested for by our sensitivity analyses by analyzing first fractures only, and analyzing only patients who did not die within 90 days of fracture, and found not to have impacted our results. Additionally, fractures occurring on the first day of opioid exposure were incorporated into the pre-exposure risk period incidence rate, which eliminated the introduction of protopathic bias, thereby reducing the likelihood of reverse causality. However, as a result, the risk of fracture on ‘day 0’ (i.e., the first day of opioid exposure) was not estimated, and this is expected to have resulted in an under-estimation of the initial risk of fracture associated with opioids. This study defined incident fractures using the same definition as a prior CPRD GOLD study of fractures. Although the definition used could have potentially under- or over-estimated the incidence of fracture in the base cohort, the sensitivity analyses showed that studying first fractures only did not impact the study findings, further research that investigates the validity of fracture algorithms would benefit future studies.

Conclusions

This study provides evidence of the potential for opioids to increase the risk of sustaining fractures, particularly during the initial weeks of starting and restarting opioids. These findings complement the results from existing studies that have employed between-participant study designs and demonstrates the utility of self-controlled methods for pharmacoepidemiological research.
ACKNOWLEDGEMENTS

Author affiliations: Division of Pharmacy Practice and Policy, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom (Emily J. Peach, Roger D. Knaggs); Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom (Emily J. Peach, Fiona A. Pearce, Jack Gibson); Mundipharma Research Limited, Cambridge, United Kingdom (Andrew J. Cooper); AstraZeneca, Cambridge, United Kingdom (Andrew J. Cooper); Centre for Pharmacoepidemiology and Drug Safety, Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Manchester, United Kingdom (Li-Chia Chen); Primary Integrated Community Solutions, Nottingham, United Kingdom (Roger D. Knaggs); Pain Centre Versus Arthritis, University of Nottingham, Nottingham, United Kingdom (Roger D. Knaggs).

This work was supported collaboratively by the University of Nottingham and Mundipharma Research as part of an independent PhD research project.

The authors would like to acknowledge Dr Heather Whitaker (The Open University) and Professor Richard Hubbard (University of Nottingham) who provided advice regarding the design and analytic approach for this study.

RK, L-CC and AC obtained funding. EP, FP, JG, AC, L-CC, RK designed the study and analysis plan. EP obtained access to the data, and prepared and analyzed the data, and JG advised on the statistical analysis. EP, FP, JG, AC, L-CC, RK interpreted the results. EP drafted the initial and final versions of the manuscript. All authors reviewed the manuscript.

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the position of any of their current or previous affiliations. The study funders reviewed the prepared manuscript for scientific accuracy. However, they had no role
in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, nor the final decision to submit the manuscript for publication.

The authors would like to declare that RK and EP received funding for a PhD studentship from Mundipharma Research during the conduct of the study; AC received paid employment from Mundipharma Research and AstraZeneca during the conduct of the study; RK is a member of the Advisory Council on the Misuse of Drugs, National Institute for Health and Care Excellence (NICE) Chronic Pain Guideline Committee, and is the current Vice President of British Pain Society.
REFERENCES

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17(12):1726-33.

2. Coluzzi F, Pergolizzi J, Raffa RB, et al. The unsolved case of “bone-impairing analgesics”: the endocrine effects of opioids on bone metabolism. Ther Clin Risk Manag 2015;11:515-23.

3. Leach MJ, Pratt NL, Roughead EE. Risk of Hip Fracture in Older People Using Selective Serotonin Reuptake Inhibitors and Other Psychoactive Medicines Concurrently: A Matched Case-Control Study in Australia. Drugs Real World Outcomes 2017;4(2):87-96.

4. Li L, Setoguchi S, Cabral H, et al. Opioid Use for Noncancer Pain and Risk of Fracture in Adults: A Nested Case-Control Study Using the General Practice Research Database. Am J Epidemiol 2013;178(5):559-69.

5. Tolppanen A-M, Taipale H, Tanskanen A, et al. Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer’s disease - exposure-matched cohort study. BMC Geriatr 2016;16:204.

6. Douglas IJ, Evans SJ, Pocock S, et al. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med 2009;6(9):e1000154.

7. Hubbard R, Farrington P, Smith C, et al. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. Am J Epidemiol 2003;158(1):77-84.

8. Gibson JE, Hubbard RB, Smith CJP, et al. Use of Self-controlled Analytical Techniques to Assess the Association Between Use of Prescription Medications and the Risk of Motor Vehicle Crashes. Am J Epidemiol 2009;169(6):761-8.
9. Pye SR, Sheppard T, Joseph RM, et al. Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. Pharmacoepidemiol Drug Saf 2018;27(7):781-8.

10. Gerhard T. Bias: Considerations for research practice. Am J Health Syst Pharm 2008;65(22):2159-68.

11. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ 2016;354:i4515.

12. Bulajic-Kopjar M. Seasonal variations in incidence of fractures among elderly people. Inj Prev 2000;6(1):16-9.

13. Crawford JR, Parker MJ. Seasonal variation of proximal femoral fractures in the United Kingdom. Injury 2003;34(3):223-5.

14. Curtis EM, van der Velde R, Moon RJ, et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone 2016;87:19-26.

15. Hayashi S, Noda T, Kubo S, et al. Variation in fracture risk by season and weather: A comprehensive analysis across age and fracture site using a National Database of Health Insurance Claims in Japan. Bone 2018;120:512-8.

16. van Staa TP, Dennison EM, Leufkens HG, et al. Epidemiology of fractures in England and Wales. Bone 2001;29(6):517-22.

17. Greene WH. Econometric Analysis. 7th ed. Upper Saddle River, New Jersey Prentice Hall; 2012.

18. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med 2006;25(15):2618-31.

19. Johansson H, Siggeirsottir K, Harvey NC, et al. Imminent risk of fracture after fracture. Osteoporos Int 2017;28(3):775-80.
20. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013;346:f2350.

21. Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. Am J Geriatr Pharmacother 2006;4(3):219-26.

22. Miller M, Stürmer T, Azrael D, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc 2011;59(3):430-8.

23. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med 2010;25(4):310-5.

24. Shorr RI, Griffin MR, Daugherty JR, et al. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol 1992;47(4):M111-5.

25. Farrington P, Whitaker H, Ghebremichael-Weldeselassie Y. Self-controlled case series studies: a modelling guide with R. London: CRC Press; 2018.

26. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ 2016;354.
Table tiles, abbreviations, and footnotes

Table 1

Table 1. Demographic characteristics of people included in a self-controlled case series study of opioids and fractures (n = 67,622), United Kingdom, 2008–2017

| Variable                                         | No.    | %     |
|--------------------------------------------------|--------|-------|
| Duration of follow-up, median (interquartile range), years | 7.1 (5.3, 8.7) |
| Age at index, mean (standard deviation), years    | 56.1 (19.6) |
| Sex (female)                                     | 39,677 | 58.7  |
| Index of multiple deprivation, quintile           |        |       |
| 1 (least deprived)                               | 15,663 | 23.2  |
| 2                                                | 14,903 | 22.0  |
| 3                                                | 13,934 | 20.6  |
| 4                                                | 12,235 | 18.1  |
| 5 (most deprived)                                | 10,852 | 16.1  |
| Missing                                          | 35     | 0.1   |
| Ethnicity:                                       |        |       |
| White                                            | 62,983 | 93.1  |
| Asian or Asian British                           | 1,137  | 1.7   |
| Black or black British                           | 569    | 0.8   |
| Other                                            | 447    | 0.7   |
| Mixed                                            | 226    | 0.3   |
| Unknown                                          | 2,260  | 3.3   |
| Osteoporosis<sup>a</sup>                         | 8,715  | 12.9  |
| FRID during follow-up                            | 42,463 | 62.8  |

Abbreviations: FRID, fracture-risk increasing drug

<sup>a</sup> presence of an osteoporosis code at any time-point in the individual’s clinical data file.
Table 2. Incidence rate ratios for the risk of bone fracture during periods of exposure to opioids in a self-controlled case series study, United Kingdom, 2008–2017

| Risk period    | Person-years | Fractures | Unadjusted model | Fully adjusted model<sup>a,b</sup> |
|----------------|--------------|-----------|------------------|-----------------------------------|
|                |              | No.       | %                | IRR 95% CI                        | IRR 95% CI                        |
| Baseline<sup>c</sup> | 377,665      | 49,473    | 56.6             | Reference                         | Reference                         |
| Pre-exposure   | 42,779       | 26,853    | 30.7             | 5.63, 5.54, 5.72                  | 5.49, 5.40, 5.58                  |
| Post-exposure  | 9,044        | 2,626     | 3.0              | 2.37, 2.28, 2.47                  | 2.31, 2.22, 2.40                  |
| Exposed<sup>d</sup> | 22,859      | 8,502     | 9.7              | 4.18, 4.07, 4.30                  | 3.93, 3.82, 4.04                  |

First Days 1, 7 1,196 1,327 1.5 7.74, 7.32, 8.17 7.81, 7.40, 8.25
Days 8, 14 828 592 0.7 5.03, 4.64, 5.46 5.08, 4.68, 5.51
Days 15, 28 484 256 0.3 3.65, 3.22, 4.13 3.65, 3.23, 4.13
Day 29, 365 846 219 0.3 1.81, 1.58, 2.08 1.77, 1.54, 2.03
Day 366+ 201 38 <0.1 1.44, 0.99, 2.08 1.25, 0.86, 1.82

Subsequent Days 1, 7 4,248 2,080 2.4 5.45, 5.20, 5.71 5.05, 4.83, 5.29
Days 8, 14 3,175 1,114 1.3 4.02, 3.78, 4.27 3.72, 3.50, 3.96
Days 15, 28 2,788 823 0.9 3.42, 3.18, 3.67 3.12, 2.91, 3.36
Day 29, 365 7,506 1,766 2.0 2.75, 2.61, 2.91 2.43, 2.30, 2.57
Day 366+ 1,587 287 0.3 2.18, 1.91, 2.50 1.73, 1.50, 1.98

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; aIRR

<sup>a</sup> All p values <0.001.

<sup>b</sup> IRR adjusted for one-year increments in age and three-monthly intervals for season.

<sup>c</sup> Baseline refers to any time that an individual was not exposed to opioids (excluding the pre-exposure and post-exposure periods).

<sup>d</sup> Exposed refers to any time that an individual was exposed to opioids.
Figure 1. Division of exposed and unexposed follow-up time into risk periods

Notes: Fractures occurring in pre-exposure and post-exposure periods are treated as neither unexposed nor exposed time in the analysis.
Figure 2a. Incidence rate ratios for the risk of bone fracture during the first period of opioid exposure, by oral morphine equivalent dose in a self-controlled case series study, United Kingdom, 2008–2017.
Figure 2b. Incidence rate ratios for the risk of bone fracture during subsequent periods of opioid exposure, by oral morphine equivalent dose in a self-controlled case series study, United Kingdom, 2008–2017

Abbreviations: OMEQ, oral morphine equivalent

Notes: Hollow diamonds refer to aIRRs for OMEQ doses <50mg/day; black diamonds refer to aIRRs for OMEQ doses ≥50mg/day. There were insufficient data to estimate aIRRs for fracture during days 366+ of first exposures at OMEQ doses ≥50mg/day.

\(^a\) incidence rate ratios adjusted for 1-year increments in age and 3-monthly intervals for season.

\(^b\) values plotted on a logarithmic scale.
## Supplementary Online Content

| eTable 1   | Fracture codes                                   |
|------------|--------------------------------------------------|
| eTable 2   | Included opioid drugs and equianalgesic ratios   |
| eFigure 1  | Overview of opioid prescription preparation process |
| eFigure 2  | Proximity of fracture events to opioid initiation and definition of the pre-exposure risk period |
| eFigure 3  | Curtailment of overlapping risk periods           |
| eTable 3   | Fracture risk increasing drugs (excluding opioids) |
| eFigure 4  | Selection of study cohort                         |
| eTable 4   | Sensitivity analyses                              |
| eFigure 5  | Risk of fracture when exposed to opioids by anatomical site |
| eFigure 6  | Comparison of aRRs in primary analysis and after excluding fractures to spine, chest, low back and pelvis |
| eFigure 7  | Risk of falls when exposed to opioids              |
| code     | system    | description                                                                 |
|----------|-----------|-----------------------------------------------------------------------------|
| S2...11  | Read      | Arm fracture                                                                |
| S28...11 | Read      | Ill-defined fracture of arm                                                  |
| S28z.00  | Read      | Ill-defined fractures of upper limb NOS                                      |
| S28...00 | Read      | Ill-defined fractures of upper limb                                          |
| S280.00  | Read      | Closed ill-defined fractures of upper limb                                   |
| S281.00  | Read      | Open ill-defined fractures of upper limb                                     |
| S29...11 | Read      | Multiple fractures of arm                                                    |
| S294000  | Read      | Cl fractures involving multiple regions of both upper limbs                   |
| SR12000  | Read      | Closed fractures involving multiple regions of one upp limb                   |
| S120900  | Read      | Closed fracture multiple ribs                                                |
| S120100  | Read      | Closed fracture of one rib                                                   |
| S120000  | Read      | Closed fracture of rib, unspecified                                          |
| S112.00  | Read      | Closed fracture of thoracic spine with spinal cord lesion                     |
| S120.00  | Read      | Closed fracture rib                                                         |
| S122.00  | Read      | Closed fracture sternum                                                      |
| S102.00  | Read      | Closed fracture thoracic vertebra                                            |
| S102x00  | Read      | Closed fracture thoracic vertebra not otherwise specified                    |
| S102000  | Read      | Closed fracture thoracic vertebra, burst                                     |
| S102500  | Read      | Closed fracture thoracic vertebra, posterior arch                            |
| S102300  | Read      | Closed fracture thoracic vertebra, spinous process                           |
| S102200  | Read      | Closed fracture thoracic vertebra, spondylolysis                            |
| S102400  | Read      | Closed fracture thoracic vertebra, transverse process                        |
| S102100  | Read      | Closed fracture thoracic vertebra, wedge                                     |
| S150000  | Read      | Closed multiple fractures of thoracic spine                                  |
| N331011  | Read      | Collapse of thoracic vertebra                                                |
| N331F00  | Read      | Collapse of thoracic vertebra                                                |
| N331K00  | Read      | Collapse of thoracic vertebra due to osteoporosis                           |
| S127.00  | Read      | Fracture of rib                                                             |
| S128.00  | Read      | Fracture of sternum                                                          |
| S15...00 | Read      | Fracture of thoracic vertebra                                                |
| S150.00  | Read      | Multiple fractures of thoracic spine                                         |
| S29...12 | Read      | Multiple rib fractures                                                       |
| S102y00  | Read      | Other specified closed fracture thoracic vertebra                            |
| S12z.11  | Read      | Rib fracture NOS                                                            |
| N331000  | Read      | Pathological fracture of thoracic vertebra                                   |
| S103.00  | Read      | Open fracture thoracic vertebra                                              |
| S103100  | Read      | Open fracture thoracic vertebra, wedge                                       |
| S103500  | Read      | Open fracture thoracic vertebra, posterior arch                              |
| S120200  | Read      | Closed fracture of two ribs                                                 |
| S120300  | Read      | Closed fracture of three ribs                                                |
| S120400  | Read      | Closed fracture of four ribs                                                 |
| S120500  | Read      | Closed fracture of five ribs                                                 |
| S120600  | Read      | Closed fracture of six ribs                                                  |
S120700  Read  Closed fracture of seven ribs
S120800  Read  Closed fracture of eight or more ribs
S120A00  Read  Cough fracture
S120z00  Read  Closed fracture of rib(s) NOS
S121.00  Read  Open fracture rib
S121200  Read  Open fracture of two ribs
S121700  Read  Open fracture of seven ribs
S121900  Read  Open fracture multiple ribs
S121z00  Read  Open fracture of rib(s) NOS
S123.00  Read  Open fracture sternum
S127000  Read  Multiple fractures of ribs
S127100  Read  Cough fracture of ribs
S12z.12  Read  Sternum fracture NOS
S150100  Read  Open multiple fracture of thoracic spine
S29..13  Read  Multiple fractures of sternum
S4J0000  Read  Closed fracture-dislocation of sternum
S4J1000  Read  Open fracture-dislocation of sternum
S4J1200  Read  Open fracture-dislocation sterno-clavicular joint, anterior
S4J2000  Read  Closed fracture-subluxation of sternum
S4J3000  Read  Open fracture-subluxation of sternum
S12X000  Read  Closed fracture of bony thorax part unspecified
S12y000  Read  Closed fracture of other parts of bony thorax
S352300  Read  Closed fracture cuboid
S352700  Read  Closed fracture metatarsal
S350.00  Read  Closed fracture of calcaneus
S360.00  Read  Closed fracture of one or more phalanges of foot
7K1LB00  Read  Closed reduction of fracture of hallux
7K1LA00  Read  Closed reduction of fracture of toe
S356.00  Read  Fracture of metatarsal bone
S36..00  Read  Fracture of one or more phalanges of foot
S363.00  Read  Fracture of other toe
S355.00  Read  Fracture of talus
S35..11  Read  Metatarsal bone fracture
S3x4.00  Read  Multiple fractures of foot
S362100  Read  Open fracture of great toe
S350.12  Read  Os calcis fracture
S36..11  Read  Toe fracture
7K1L900  Read  Closed reduction of fracture of metatarsus
S35..12  Read  Tarsal bone fracture
S350.11  Read  Heel bone fracture
S350000  Read  Closed fracture calcaneus, extra-articular
S350100  Read  Closed fracture calcaneus, intra-articular
S351.00  Read  Open fracture of calcaneus
S351100  Read  Open fractures calcaneus, intra-articular
S352.00  Read  Closed fracture of other tarsal and metatarsal bones
S352.11  Read  March fracture
S352000  Read  Closed fracture of tarsal bone, unspecified
S352100  Read  Closed fracture of talus
S352111  Read  Closed fracture of astragalus
S352200  Read  Closed fracture navicular
S352400  Read  Closed fracture medial cuneiform
S352500  Read  Closed fracture intermediate cuneiform
S352600  Read  Closed fracture lateral cuneiform
S352800  Read  Closed fracture talus, head
S352900  Read  Closed fracture talus, neck
S352A00  Read  Closed fracture talus, body
S352B00  Read  Closed fracture metatarsal base
S352C00  Read  Closed fracture metatarsal shaft
S352D00  Read  Closed fracture metatarsal neck
S352E00  Read  Closed fracture metatarsal head
S352F00  Read  Closed fracture metatarsal, multiple
S352G00  Read  Closed tarsal fractures, multiple
S352H00  Read  Closed fracture of cuneiforms
S352J00  Read  Closed fracture of base of fifth metatarsal
S352x00  Read  Closed fracture of one or more tarsal + metatarsal bones NOS
S353.00  Read  Open fracture of other tarsal and metatarsal bones
S353000  Read  Open fracture of tarsal bone, unspecified
S353100  Read  Open fracture of talus
S353200  Read  Open fracture navicular
S353300  Read  Open fracture cuboid
S353400  Read  Open fracture medial cuneiform
S353500  Read  Open fracture intermediate cuneiform
S353600  Read  Open fracture lateral cuneiform
S353700  Read  Open fracture metatarsal
S353800  Read  Open fracture talus, head
S353900  Read  Open fracture talus, neck
S353A00  Read  Open fracture talus, body
S353B00  Read  Open fracture metatarsal base
S353C00  Read  Open fracture metatarsal shaft
S353D00  Read  Open fracture metatarsal neck
S353E00  Read  Open fracture metatarsal head
S353F00  Read  Open fracture metatarsal, multiple
S353H00  Read  Open fracture cuneiforms
S353J00  Read  Open fracture of base of fifth metatarsal
S353x00  Read  Open fracture of tarsal and metatarsal bones NOS
S360000  Read  Closed fracture proximal phalanx, toe
S360100  Read  Closed fracture middle phalanx, toe
S360200  Read  Closed fracture distal phalanx, toe
S360300  Read  Closed fracture multiple phalanges, toe
S361.00  Read  Open fracture of one or more phalanges of foot
S361000  Read  Open fracture proximal phalanx, toe
S361100  Read  Open fracture middle phalanx, toe
S361200  Read  Open fracture distal phalanx, toe
S361300  Read  Open fracture multiple phalanges, toe
S362000  Read  Closed fracture of great toe
S4H0.00  Read  Closed fracture-dislocation foot
S4H0000  Read  Closed fracture-dislocation, subtalar joint
S4H0100  Read  Closed fracture-dislocation, midtarsal joint
S4H0200  Read  Closed fracture-dislocation, tarsometatarsal joint
S4H0400  Read  Closed fracture-dislocation, IPJ, single toe
S4H0600  Read  Closed fracture-dislocation, IPJ, multiple toes
S4H1.00  Read  Open fracture-dislocation, foot
S4H1000  Read  Open fracture-dislocation, subtalar joint
S4H1100  Read  Open fracture-dislocation, midtarsal joint
S4H1200  Read  Open fracture-dislocation, tarsometatarsal joint
S4H1300  Read  Open fracture-dislocation, metatarsophalangeal joint, single
S4H1400  Read  Open fracture-dislocation, IPJ, single toe
S4H1600  Read  Open fracture-dislocation, IPJ, multiple toes
S4H2.00  Read  Closed fracture-subluxation, foot
S4H2000  Read  Closed fracture-subluxation, subtalar joint
S4H2100  Read  Closed fracture-subluxation, midtarsal joint
S4H2200  Read  Closed fracture-subluxation, tarsometatarsal joint
S4H2400  Read  Closed fracture-subluxation, IPJ, single toe
S4H2600  Read  Closed fracture-subluxation, IPJ, multiple toes
S4H3.00  Read  Open fracture-subluxation, foot
S4H3300  Read  Open fracture-subluxation, metatarsophalangeal joint, single
S4H3400  Read  Open fracture-subluxation, IPJ, single toe
Syu5400  Read  [X]Fracture of forearm, unspecified
Syu5300  Read  [X]Fracture of other parts of forearm
S234D00  Read  Closed fracture distal radius, extra-articular, other type
S234C00  Read  Closed fracture distal radius, intra-articular, die-punch
S234E00  Read  Closed fracture distal radius, intra-articular, other type
S234500  Read  Closed fracture distal ulna, unspecified
S234z00  Read  Closed fracture of forearm, lower end, NOS
S234000  Read  Closed fracture of forearm, lower end, unspecified
S23x000  Read  Closed fracture of forearm, unspecified
S23x00  Read  Closed fracture of proximal radius and ulna
S230400  Read  Closed fracture of proximal ulna, comminuted
S23x100  Read  Closed fracture of radius (alone), unspecified
S234.00  Read  Closed fracture of radius and ulna, lower end
S23x200  Read  Closed fracture of radius and ulna, NOS
S232.00  Read  Closed fracture of radius and ulna, shaft
S232x00  Read  Closed fracture of radius and ulna, shaft, NOS
S23x.00  Read  Closed fracture of radius and ulna, unspecified part
S232000  Read  Closed fracture of radius, shaft, unspecified
S234200  Read  Closed fracture of the distal radius, unspecified
S230500  Read  Closed fracture of the proximal ulna
S232100  Read  Closed fracture of the radial shaft
S23x300  Read  Closed fracture of the radius and ulna
S232200  Read  Closed fracture of the ulnar shaft
S23x200  Read  Closed fracture of ulna (alone), unspecified
S230100  Read  Closed fracture olecranon, extra-articular
S234600  Read  Closed fracture radius and ulna, distal
S232300  Read  Closed fracture radius and ulna, middle
S230A00  Read  Closed fracture radius and ulna, proximal
S230600  Read  Closed fracture radius, head
S230700  Read  Closed fracture radius, neck
S4C0000  Read  Closed fracture-dislocation distal radio-ulnar joint
S234800  Read  Closed Galeazzi fracture
7K1LE00  Read  Closed reduction of fracture of elbow
S23C.00  Read  Fracture of lower end of both ulna and radius
S23B.00  Read  Fracture of lower end of radius
S23..00  Read  Fracture of radius and ulna
S23z.00  Read  Fracture of radius and ulna, unspecified
S230800  Read  Closed fracture proximal radius, comminuted
S230900  Read  Closed fracture of the proximal radius
S231000  Read  Open fracture of proximal forearm, unspecified
S230000  Read  Closed fracture of proximal forearm, unspecified part
S230200  Read  Closed fracture of ulna, coronoid
S230300  Read  Closed Monteggia's fracture
S230800  Read  Closed fracture proximal radius, comminuted
S230900  Read  Closed fracture of the proximal radius
S230B00  Read  Closed fracture olecranon, intra-articular
S230z00  Read  Closed fracture of proximal forearm not otherwise specified
S231.00  Read  Open fracture of proximal radius and ulna
S231000  Read  Open fracture of proximal forearm, unspecified
S231100  Read  Open fracture olecranon, extra-articular
S231200  Read  Open fracture of ulna, coronoid
S231300  Read  Open Monteggia’s fracture
S231500  Read  Open fracture of the proximal ulna
S231600  Read  Open fracture radial head
S231700  Read  Open fracture radial neck
S231800  Read  Open fracture proximal radius, comminuted
S231900  Read  Open fracture of the proximal radius
S231A00  Read  Open fracture radius and ulna, proximal
S231B00  Read  Open fracture olecranon, intra-articular
S231z00  Read  Open fracture of forearm, upper end, NOS
S233.00  Read  Open fracture of radius and ulna, shaft
| Code     | Description                                      |
|----------|--------------------------------------------------|
| S02z.11 | Jaw fracture NOS                                |
| S02B.00 | Le Fort II fracture maxilla                     |
| S04..12 | Multiple skull fractures                        |
| S01..15 | Occiput bone fracture                           |
| S021.00 | Open fracture nose                              |
| 7J03100 | Reduction of fracture of nasal bones NEC other  |
| 7J03200 | Reduction of fracture of zygomatic bones        |
| S03z.00 | Skull fracture NOS                              |
| 7J06100 | Open reduction of fracture of orbit              |
| 7J06200 | Removal of fixation from fracture of orbit       |
| 7J06400 | Open reduction of fracture of orbit and internal fixation |
| 7J06700 | Packing of maxilla to correct blow-out fracture of orbit |
| 7J06800 | Internal fixation of fracture of orbit           |
| 7J03100 | Reduction of fracture of orbit                   |
| 7J03200 | Reduction of fracture of alveolus of mandible   |
| 7J03100 | Reduction of fracture of maxilla                |
| 7J03200 | Reduction of closed fracture of orbit bone      |
| 7J03y00 | Other specified reduction of fracture of facial bone |
| 7J03z00 | Reduction of fracture of facial bone NOS        |
| 7J12.00 | Reduction of fracture of mandible               |
| 7J12.11 | Reduction of fracture of jaw NEC                |
| 7J12y00 | Other specified reduction of fracture of mandible |
| 7J12z00 | Reduction of fracture of mandible NOS           |
| 7J13.00 | Reduction of fracture of maxilla                |
| 7J13000 | Reduction of fracture of alveolus of maxilla    |
| 7J13100 | Open reduction of fracture of maxilla NEC       |
| 7J13200 | Closed reduction of fracture of maxilla NEC     |
| 7J13300 | Reduction of blowout fracture of orbital floor  |
| 7J13400 | Reduction of Le Fort 1 fracture of maxilla      |
| 7J13500 | Reduction of Le Fort 2 fracture of maxilla      |
| 7J13600 | Reduction of Le Fort 3 fracture of maxilla      |
| 7J13y00 | Other specified reduction of fracture of maxilla |
| 7J13z00 | Reduction of fracture of maxilla NOS            |
| 7J17700 | Traction for fracture of jaw                    |
| S000.00 | Closed fracture vault of skull without intracranial injury |
| S001.00 | Closed fracture vault of skull with intracranial injury |
| S002.00 | Open fracture vault of skull without intracranial injury |
| S003.00 | Open fracture vault of skull with intracranial injury |
| S01..11 | Anterior fossa fracture                         |
| S01..12 | Ethmoid sinus fracture                          |
S01..13    Read    Frontal sinus fracture
S01..14    Read    Middle fossa fracture
S01..16    Read    Orbital roof fracture
S01..17    Read    Posterior fossa fracture
S01..18    Read    Sphenoid bone fracture
S01..19    Read    Temporal bone fracture
S010.00    Read    Closed fracture base of skull without intracranial injury
S011.00    Read    Closed fracture base of skull with intracranial injury
S012.00    Read    Open fracture base skull without mention intracranial injury
S013.00    Read    Open fracture base of skull with intracranial injury
S020.11    Read    Closed fracture nasal bone
S021.11    Read    Open fracture nasal bone
S022000    Read    Closed fracture mandible (site unspecified)
S022100    Read    Closed fracture of mandible, condylar process
S022200    Read    Closed fracture of mandible, subcondylar
S022300    Read    Closed fracture of mandible, coronoid process
S022400    Read    Closed fracture of mandible, ramus, unspecified
S022500    Read    Closed fracture of mandible, angle of jaw
S022600    Read    Closed fracture of mandible, symphysis of body
S022700    Read    Closed fracture of mandible, alveolar border of body
S022800    Read    Closed fracture of mandible, body, other and unspecified
S022x00    Read    Closed fracture of mandible, multiple sites
S023000    Read    Open fracture mandible (site unspecified)
S023100    Read    Open fracture of mandible, condylar process
S023200    Read    Open fracture of mandible, subcondylar
S023400    Read    Open fracture of mandible, ramus, unspecified
S023500    Read    Open fracture of mandible, angle of jaw
S023600    Read    Open fracture of mandible, symphysis of body
S023700    Read    Open fracture of mandible, alveolar border of body
S023800    Read    Open fracture of mandible, body, other and unspecified
S023x00    Read    Open fracture of mandible, multiple sites
S025000    Read    Open fracture maxilla
S025100    Read    Open fracture zygoma
S026.00    Read    Closed orbital blow-out fracture
S027.00    Read    Open orbital blow-out fracture
S02A.00    Read    Le Fort I fracture maxilla
S02C.00    Read    Le Fort III fracture maxilla
S02x.00    Read    Closed fracture other facial bone
S02y.00    Read    Open fracture other facial bone
S03..00    Read    Other and unqualified skull fractures
S030.00    Read    Closed fracture of skull NOS without intracranial injury
S031.00    Read    Closed fracture of skull NOS with intracranial injury
S033.00    Read    Open fracture of skull NOS with intracranial injury
S03z.11    Read    Depressed skull fracture NOS
S04..00    Read    Multiple fractures involving skull or face with other bones
S04..11    Read    Multiple face fractures
Read Multiple fractures involving skull and facial bones

Read Multiple fractures involving skull/face with other bones NOS

7K1J011  Read  Cl red intracaps frac neck femur fix-Garden cannulated screw

7K1J012  Read  Cl red intracaps frac neck femur fix - Smith-Petersen nail

S300400  Read  Closed fracture head of femur

S302011  Read  Closed fracture of femur, greater trochanter

S302400  Read  Closed fracture of femur, intertrochanteric

S302012  Read  Closed fracture of femur, lesser trochanter

S300y11  Read  Closed fracture of femur, subcapital

S300A00  Read  Closed fracture of femur, upper epiphysis

S30y.00  Read  Closed fracture of neck of femur NOS

S302.00  Read  Closed fracture of proximal femur, pertrochanteric

S30w.00  Read  Closed fracture of unspecified proximal femur

S300300  Read  Closed fracture proximal femur, basicervical

S302100  Read  Closed fracture proximal femur, intertrochanteric, two part

S300200  Read  Closed fracture proximal femur, midcervical section

S300y00  Read  Closed fracture proximal femur, other transcervical

S300600  Read  Closed fracture proximal femur, subcapital, Garden grade I

S300700  Read  Closed fracture proximal femur, subcapital, Garden grade II

S300800  Read  Closed fracture proximal femur, subcapital, Garden grade III

S300900  Read  Closed fracture proximal femur, subcapital, Garden grade IV

S300.00  Read  Closed fracture proximal femur, transcervical

S300z00  Read  Closed fracture proximal femur, transcervical, NOS

S300000  Read  Closed fracture proximal femur, transepiphyseal

S300311  Read  Closed fracture, base of neck of femur

7K1L400  Read  Closed reduction of fracture of hip

7K1Jd00  Read  Closed reduction of intracapsular # NOF internal fixat DHS

S302x00  Read  Cls # of proximal femur, pertrochanteric section, NOS

S300000  Read  Cls # prox femur, intracapsular section, unspecified

S300500  Read  Cls # prox femur, subcapital, Garden grade unspec.

S302300  Read  Cls # proximal femur, intertrochanteric, comminuted

S302000  Read  Cls # proximal femur, trochanteric section, unspecified

7K1J013  Read  Cls red-int fnx prox femoral #+Richard's cannulated hip screw

7K1J000  Read  Cls red-int fnx proximal femoral #+screw/nail device alone

7K1D01E  Read  DHS - Dynamic hip screw primary fixation of neck of femur

7K1D01F  Read  Dynamic hip screw primary fixation of neck of femur

S30..00  Read  Fracture of neck of femur

S30..11  Read  Hip fracture

S30y.11  Read  Hip fracture NOS

S300300  Read  Open # of proximal femur, trochanteric section, unspecified

S301311  Read  Open fracture base of neck of femur

S303400  Read  Open fracture of femur, intertrochanteric

S301y11  Read  Open fracture of femur, subcapital

S301A00  Read  Open fracture of femur, upper epiphysis

S30z.00  Read  Open fracture of neck of femur NOS

S303.00  Read  Open fracture of proximal femur, pertrochanteric
| Code    | Description                                         |
|---------|-----------------------------------------------------|
| S131.00 | Open fracture acetabulum                            |
| S131y00| Other specified open fracture acetabulum             |
| S131z00| Open fracture acetabulum NOS                        |
| S301400 | Open fracture head, femur                           |
| S303011| Open fracture of femur, greater trochanter          |
| S4E0.00 | Closed fracture-dislocation, hip joint               |
| S4E1.00 | Open fracture-dislocation, hip joint                 |
| S4E2.00 | Closed fracture-subluxation, hip joint               |
| S3...11 | Fracture of lower limb                              |
| 7K1LC00 | Closed reduction of fracture of lower limb          |
| S370.00 | Closed fracture of lower limb, level unspecified     |
| S371.00 | Open fracture of lower limb, level unspecified       |
| S3x...00| Other, multiple and ill-defined fractures of lower limb |
| S3x0.00 | Other, multiple and ill-defined closed fractures lower limb |
| S3x1.00 | Other, multiple and ill-defined open fractures of lower limb |
| SR15000 | Closed fractures involving multiple regions upper with lower limb |
| SyuL400 | [X]Sequela of other fractures of lower limb         |
| S130.00 | Closed fracture acetabulum                           |
| S104.00 | Closed fracture lumbar vertebra                      |
| S104000| Closed fracture lumbar vertebra, burst               |
| S104500| Closed fracture lumbar vertebra, posterior arch      |
| S104300| Closed fracture lumbar vertebra, spinous process     |
| S104200| Closed fracture lumbar vertebra, spondyloysis       |
| S104400| Closed fracture lumbar vertebra, transverse process  |
| S104600| Closed fracture lumbar vertebra, tricolumnar        |
| S104100| Closed fracture lumbar vertebra, wedge               |
| S114.00 | Closed fracture of lumbar spine with spinal cord lesion |
| S13y.00 | Closed fracture of pelvis NOS                        |
| S134600| Closed fracture pelvis, iliac wing                   |
| S134100| Closed fracture pelvis, ischium                      |
| S132100| Closed fracture pelvis, multiple pubic rami - stable |
| S132000| Closed fracture pelvis, single pubic ramus           |
| S132.00 | Closed fracture pubis                               |
| S132x00| Closed fracture pubis NOS                           |
| S4J0100 | Closed fracture-dislocation of pelvis                |
| S4J2100 | Closed fracture-subluxation of pelvis                |
| N331111| Collapse of lumbar vertebra                         |
| N331G00| Collapse of lumbar vertebra                         |
| N331J00| Collapse of lumbar vertebra due to osteoporosis      |
| S10B400| Fracture of acetabulum                              |
| S10B200| Fracture of coccyx                                  |
| S10B.00| Fracture of lumbar spine and pelvis                 |
| S10B000| Fracture of lumbar vertebra                         |
| S10B500| Fracture of pubis                                   |
| S13...00| Fracture or disruption of pelvis                     |
SR11.00 Read Fractures involving thorax with lower back and pelvis
S108600 Read Multiple fractures of lumbar spine and pelvis
S13z.00 Read Open fracture of pelvis NOS
S134.00 Read Other or multiple closed fracture of pelvis
S134z00 Read Other or multiple closed fracture of pelvis NOS
N331100 Read Pathological fracture of lumbar vertebra
S105.00 Read Open fracture lumbar vertebra
S105000 Read Open fracture lumbar vertebra, burst
S105100 Read Open fracture lumbar vertebra, wedge
S105400 Read Open fracture lumbar vertebra, transverse process
S106.00 Read Closed fracture sacrum
S106000 Read Closed compression fracture sacrum
S106100 Read Closed vertical fracture of sacrum
S107.00 Read Open fracture sacrum
S107000 Read Open compression fracture sacrum
S107100 Read Open vertical fracture of sacrum
S108.00 Read Closed fracture pelvis, coccyx
S109.00 Read Open fracture pelvis, coccyx
S115.00 Read Open fracture of lumbar spine with spinal cord lesion
S116.00 Read Closed fracture of sacrum with spinal cord lesion
S116z00 Read Closed fracture of sacrum with spinal cord lesion NOS
S117.00 Read Open fracture of sacrum with spinal cord lesion
S117300 Read Open fracture of sacrum with other spinal cord injury
S118.00 Read Closed fracture of coccyx with spinal cord lesion
S118z00 Read Closed fracture of coccyx with spinal cord lesion NOS
S132200 Read Closed fracture pelvis, multiple pubic rami - unstable
S132y00 Read Other specified closed fracture pubis
S133.00 Read Open fracture of pubis
S133000 Read Open fracture pelvis, single pubic ramus
S133100 Read Open fracture pelvis, multiple pubic rami - stable
S133200 Read Open fracture pelvis, multiple pubic rami - unstable
S133y00 Read Other specified open fracture of pubis
S133z00 Read Open fracture of pubis NOS
S134000 Read Closed fracture of ilium, unspecified
S134300 Read Closed fracture pelvis, ischial tuberosity
S134400 Read Closed fracture pelvis, anterior superior iliac spine
S134500 Read Closed fracture pelvis, anterior inferior iliac spine
S134700 Read Closed vertical fracture of ilium
S134800 Read Closed fracture dislocation of sacro-iliac joint
S135.00 Read Other or multiple open fracture of pelvis
S135000 Read Open fracture of ilium, unspecified
S135100 Read Open fracture pelvis, ischium
S135300 Read Open fracture pelvis, ischial tuberosity
S135400 Read Open fracture pelvis, anterior superior iliac spine
S135600 Read Open fracture pelvis, iliac wing
S135800 Read Open fracture dislocation of sacro-iliac joint
S135y00  Read  Other open fracture of pelvis
S135z00  Read  Other/multiple open fracture of pelvis NOS
S4J1100  Read  Open fracture-dislocation of pelvis
S4J3100  Read  Open fracture-subluxation of pelvis
S344.00  Read  Closed fracture ankle, bimalleolar
S342.00  Read  Closed fracture ankle, lateral malleolus
S34x.00  Read  Closed fracture ankle, unspecified
S334.00  Read  Closed fracture distal tibia
S334000  Read  Closed fracture distal tibia, extra-articular
S339000  Read  Closed fracture of distal fibula
S33x100  Read  Closed fracture of fibula, unspecified part, NOS
S330.00  Read  Closed fracture of tibia and fibula, proximal
S33x200  Read  Closed fracture of tibia and fibula, unspecified part
S33x000  Read  Closed fracture of tibia, unspecified part, NOS
S332.00  Read  Closed fracture of tibia/fibula, shaft
S320400  Read  Closed fracture patella, comminuted (stellate)
S330100  Read  Closed fracture proximal fibula
S330300  Read  Closed fracture proximal tibia, medial condyle (plateau)
S332100  Read  Closed fracture shaft of fibula
S4F0.00  Read  Closed fracture-dislocation, knee joint
S4F2.00  Read  Closed fracture-subluxation, knee joint
7K1L800  Read  Closed reduction of fracture of ankle
7K1L600  Read  Closed reduction of fracture of knee
7K1L700  Read  Closed reduction of fracture of tibia and or fibula
S34..00  Read  Fracture of ankle
S34z.00  Read  Fracture of ankle, NOS
S339.00  Read  Fracture of fibula alone
S349.00  Read  Fracture of lateral malleolus
S338.00  Read  Fracture of lower end of tibia
S35...0  Read  Fracture of one or more tarsal and metatarsal bones
S32...0  Read  Fracture of patella
S32z.00  Read  Fracture of patella, NOS
S337.00  Read  Fracture of shaft of tibia
S33...0  Read  Fracture of tibia and fibula
S336.00  Read  Fracture of upper end of tibia
S4F...0  Read  Fracture-dislocation or subluxation knee
S3x3.00  Read  Multiple fractures of lower leg
S345.00  Read  Open fracture ankle, bimalleolar
S339100  Read  Open fracture of distal fibula
S33x200  Read  Open fracture of tibia and fibula, unspecified part, NOS
S33y000  Read  Open fracture of tibia, unspecified part, NOS
S3xx0.00  Read  Other, multiple and ill-defined fractures of lower limb NOS
S344.12  Read  Pott's fracture - ankle
7K1F500  Read  Primary open reduction fracture patella fixat tension band
S320.00  Read  Closed fracture of the patella
S320000  Read  Closed fracture patella, transverse
S320100  Read  Closed fracture patella, proximal pole
S320200  Read  Closed fracture patella, distal pole
S320300  Read  Closed fracture patella, vertical
S321.00  Read  Open fracture of the patella
S321000  Read  Open fracture patella, transverse
S321100  Read  Open fracture patella, proximal pole
S321200  Read  Open fracture patella, distal pole
S321400  Read  Open fracture patella, comminuted (stellate)
S330000  Read  Closed fracture of the proximal tibia
S330011  Read  Closed fracture of tibial condyles
S330012  Read  Closed fracture of tibial tuberosity
S330200  Read  Closed fracture of tibia and fibula, proximal
S330400  Read  Closed fracture proximal tibia, lateral condyle (plateau)
S330500  Read  Closed fracture proximal tibia, bicondylar
S330600  Read  Closed fracture spine, tibia
S330700  Read  Closed fracture tubercle, tibia
S330800  Read  Closed fracture fibula, head
S330900  Read  Closed fracture fibula, neck
S330z00  Read  Closed fracture of tibia and fibula, proximal NOS
S331.00  Read  Open fracture of tibia and fibula, proximal
S331000  Read  Open fracture of the proximal tibia
S331011  Read  Open fracture of tibial condyles
S331012  Read  Open fracture of tibial tuberosity
S331100  Read  Open fracture proximal fibula
S331200  Read  Open fracture of tibia and fibula, proximal
S331300  Read  Open fracture proximal tibia, medial condyle (plateau)
S331400  Read  Open fracture proximal tibia, lateral condyle (plateau)
S331600  Read  Open fracture spine, tibia
S331700  Read  Open fracture tubercle, tibia
S331800  Read  Open fracture fibula, head
S331900  Read  Open fracture fibula, neck
S331A00  Read  Open fracture tibial plateau
S331z00  Read  Open fracture of tibia and fibula, proximal NOS
S332000  Read  Closed fracture shaft of tibia
S332200  Read  Closed fracture of tibia and fibula, shaft
S332z00  Read  Closed fracture of tibia and fibula, shaft, NOS
S333.00  Read  Open fracture of tibia/fibula, shaft
S333000  Read  Open fracture shaft of tibia
S333100  Read  Open fracture shaft of fibula
S333200  Read  Open fracture of tibia and fibula, shaft
S333z00  Read  Open fracture of tibia and fibula, shaft, NOS
S334100  Read  Closed fracture distal tibia, intra-articular
S335.00  Read  Open fracture distal tibia
S335000  Read  Open fracture distal tibia, extra-articular
S335100  Read  Open fracture distal tibia, intra-articular
S33B.00  Read  Open fracture of distal tibia and fibula
S33C.00 Read Closed fracture of distal tibia and fibula
S33x.00 Read Closed fracture of tibia and fibula, unspecified part, NOS
S33x.11 Read Lower leg fracture NOS
S33xz00 Read Closed fracture of tibia and fibula, unspecified part, NOS
S33y.00 Read Open fracture of tibia and fibula, unspecified part, NOS
S33y200 Read Open fracture of tibia and fibula, unspecified part
S340.00 Read Closed fracture ankle, medial malleolus
S341.00 Read Open fracture ankle, medial malleolus
S342000 Read Closed fracture ankle, lateral malleolus, low
S342100 Read Closed fracture ankle, lateral malleolus, high
S343.00 Read Open fracture ankle, lateral malleolus
S343000 Read Open fracture ankle, lateral malleolus, low
S343100 Read Open fracture ankle, lateral malleolus, high
S344.11 Read Dupuytren's fracture, fibula
S344000 Read Closed fracture ankle, bimalleolar, low fibular fracture
S344100 Read Closed fracture ankle, bimalleolar, high fibular fracture
S345000 Read Open fracture ankle, bimalleolar, low fibular fracture
S345100 Read Open fracture ankle, bimalleolar, high fibular fracture
S346.00 Read Closed fracture ankle, trimalleolar
S346000 Read Closed fracture ankle, trimalleolar, low fibular fracture
S346100 Read Closed fracture ankle, trimalleolar, high fibular fracture
S347.00 Read Open fracture ankle, trimalleolar
S347000 Read Open fracture ankle, trimalleolar, low fibular fracture
S347100 Read Open fracture ankle, trimalleolar, high fibular fracture
S34y.00 Read Open fracture ankle, unspecified
S4F1.00 Read Open fracture-dislocation, knee joint
S4F3.00 Read Open fracture-subluxation, knee joint
S4F4.00 Read Closed fracture-dislocation, patello-femoral joint
S4F5.00 Read Open fracture-dislocation, patello-femoral joint
S4F6.00 Read Closed fracture-subluxation, patello-femoral joint
S4F7.00 Read Open fracture-subluxation, patello-femoral joint
S4G0.00 Read Closed fracture-dislocation, ankle joint
S4G1.00 Read Open fracture-dislocation, ankle joint
S4G2.00 Read Closed fracture-subluxation, ankle joint
S4G3.00 Read Open fracture-subluxation, ankle joint
SC0X.00 Read Sequelae of other fracture of thorax and pelvis
SR10000 Read Closed fractures involving head with neck
SR16000 Read Closed fracture inv thorax with low back and pelvis and limbs
SR1z.00 Read Multiple fractures, unspecified
SR1z000 Read [X]Closed multiple fractures unspecified
SR1z100 Read [X]Open multiple fractures unspecified
S100.00 Read Closed fracture of cervical spine
S110.00 Read Closed fracture of cervical spine with cord lesion
N331E00 Read Collapse of cervical vertebra
N331H00 Read Collapse of cervical vertebra due to osteoporosis
S10A000 Read Fracture of first cervical vertebra
S10A.00 Read Fracture of neck
S10A100 Read Fracture of second cervical vertebra
S10A200 Read Multiple fractures of cervical spine
N331A00 Read Osteoporosis + pathological fracture cervical vertebrae
N331C00 Read Pathological fracture of cervical vertebra
S100000 Read Closed fracture of unspecified cervical vertebra
S100100 Read Closed fracture atlas
S100111 Read C1 vertebra closed fracture - no spinal cord lesion
S100200 Read Closed fracture axis
S100211 Read C2 vertebra closed fracture without spinal cord lesion
S100300 Read Closed fracture of third cervical vertebra
S100311 Read C3 vertebra closed fracture without spinal cord lesion
S100400 Read Closed fracture of fourth cervical vertebra
S100411 Read C4 vertebra closed fracture without spinal cord lesion
S100500 Read Closed fracture of fifth cervical vertebra
S100511 Read C5 vertebra closed fracture without spinal cord lesion
S100600 Read Closed fracture of sixth cervical vertebra
S100611 Read C6 vertebra closed fracture without spinal cord lesion
S100700 Read Closed fracture of seventh cervical vertebra
S100711 Read C7 vertebra closed fracture without spinal cord lesion
S100800 Read Closed fracture atlas, isolated arch or articular process
S100900 Read Closed fracture atlas, comminuted
S100A00 Read Closed fracture axis, odontoid process
S100B00 Read Closed fracture axis, spondylolisthesis
S100C00 Read Closed fracture axis, spinous process
S100D00 Read Closed fracture axis, transverse process
S100E00 Read Closed fracture axis, posterior arch
S100G00 Read Closed fracture cervical vertebra, burst
S100H00 Read Closed fracture cervical vertebra, wedge
S100J00 Read Closed fracture cervical vertebra, spondylolisthesis
S100K00 Read Closed fracture cervical vertebra, spinous process
S100L00 Read Closed fracture cervical vertebra, transverse process
S100M00 Read Closed fracture cervical vertebra, posterior arch
S100x00 Read Multiple closed fractures of cervical vertebrae
S100z00 Read Closed fracture of cervical spine not otherwise specified
S101.00 Read Open fracture of cervical spine
S101000 Read Open fracture of unspecified cervical vertebra
S101100 Read Open fracture atlas
S101111 Read C1 vertebra open fracture without spinal cord lesion
S101200 Read Open fracture axis
S101211 Read C2 vertebra open fracture without spinal cord lesion
S101311 Read C3 vertebra open fracture without spinal cord lesion
S101500 Read Open fracture of fifth cervical vertebra
S101511 Read C5 vertebra open fracture without spinal cord lesion
S101600 Read Open fracture of sixth cervical vertebra
C6 vertebra open fracture without spinal cord lesion
C7 vertebra open fracture without spinal cord lesion
Open fracture atlas, comminuted
Open fracture axis, odontoid process
Multiple open fractures of cervical vertebrae
Closed fracture of hyoid bone
Open fracture of hyoid bone
[X]Fracture of other parts of shoulder and upper arm
[X]Fracture of shoulder and upper arm, unspecified
Closed fracture clavicle, lateral end
Closed fracture distal humerus, supracondylar
Closed fracture of clavicle
Closed fracture of distal humerus, trochlea
Closed fracture of elbow, unspecified part
Closed fracture of humerus NOS
Closed fracture of humerus, shaft
Closed fracture of humerus, shaft or unspecified part
Closed fracture of humerus, shaft or unspecified part NOS
Closed fracture of humerus, upper epiphysis
Closed fracture of proximal humerus not otherwise specified
Closed fracture of proximal humerus, anatomical neck
Closed fracture of proximal humerus, unspecified part
Closed fracture of the distal humerus
Closed fracture of the proximal humerus
Closed fracture proximal humerus, four part
Closed fracture proximal humerus, greater tuberosity
Closed fracture proximal humerus, head
Closed fracture proximal humerus, neck
Closed fracture proximal humerus, three part
Closed fracture scapula, acromion
Closed fracture scapula, glenoid
Closed fracture-dislocation shoulder
Closed fracture-subluxation, distal radio-ulnar jt
Closed reduction of fracture of shoulder
Collar bone fracture
Elbow fracture - closed
Fracture of clavicle
Fracture of humerus
Fracture of humerus NOS
Fracture of lower end of humerus
Fracture of scapula
Fracture of shaft of humerus
Fracture of upper end of humerus
Fracture of upper limb
Fracture-dislocation or subluxation shoulder
Multiple fractures of clavicle, scapula and humerus
| Code   | Description                                      |
|--------|--------------------------------------------------|
| 7K1LF00 | Read Closed reduction of fracture of humerus      |
| 7K1LN00 | Read Closed reduction of fracture of upper limb   |
| S200000 | Read Closed fracture of clavicle, unspecified part|
| S200100 | Read Closed fracture clavicle, medial end        |
| S200200 | Read Closed fracture clavicle, shaft              |
| S200z00 | Read Closed fracture of clavicle NOS              |
| S201.00 | Read Open fracture of clavicle                   |
| S201000 | Read Open fracture of clavicle, unspecified part  |
| S201100 | Read Open fracture clavicle, medial end          |
| S201200 | Read Open fracture clavicle, shaft                |
| S201300 | Read Open fracture clavicle, lateral end         |
| S201z00 | Read Open fracture of clavicle NOS               |
| S21.11  | Read Shoulder blade fracture                     |
| S210.00 | Read Closed fracture of scapula                  |
| S210000 | Read Closed fracture of scapula, unspecified part |
| S210200 | Read Closed fracture scapula, coracoid           |
| S210400 | Read Closed fracture scapula, blade              |
| S210500 | Read Closed fracture scapula, spine               |
| S210600 | Read Closed fracture scapula, neck               |
| S210z00 | Read Closed fracture of scapula NOS              |
| S211.00 | Read Open fracture of scapula                    |
| S211000 | Read Open fracture of scapula, unspecified part   |
| S211100 | Read Open fracture scapula, acromion             |
| S211200 | Read Open fracture scapula, coracoid             |
| S211300 | Read Open fracture scapula, glenoid              |
| S211400 | Read Open fracture scapula, blade                |
| S211600 | Read Open fracture scapula, neck                 |
| S211z00 | Read Open fracture of scapula NOS                |
| S221.00 | Read Open fracture of the proximal humerus       |
| S221.11 | Read Shoulder fracture - open                    |
| S221000 | Read Open fracture of proximal humerus, unspecified part |
| S221100 | Read Open fracture proximal humerus, neck        |
| S221200 | Read Open fracture of proximal humerus, anatomical neck |
| S221300 | Read Open fracture proximal humerus, greater tuberosity |
| S221400 | Read Open fracture proximal humerus, head        |
| S221500 | Read Open fracture of humerus, upper epiphysis   |
| S221600 | Read Open fracture proximal humerus, three part   |
| S221700 | Read Open fracture proximal humerus, four part    |
| S221z00 | Read Open fracture of proximal humerus not otherwise specified |
| S223.00 | Read Open fracture of humerus, shaft or unspecified part |
| S223000 | Read Open fracture of humerus NOS                |
| S223100 | Read Open fracture of humerus, shaft              |
| S223z00 | Read Open fracture of humerus, shaft or unspecified part NOS |
| S224200 | Read Closed fracture distal humerus, lateral condyle |
| S224300 | Read Closed fracture distal humerus, medial condyle |
| S224400 | Read Closed fracture of distal humerus, condyle(s) unspecified |
S10x.00  Read  Closed fracture of spine, unspecified,
S112z00 Read  Closed fracture of thoracic spine with cord lesion NOS
S114100 Read  Closed spinal fracture with complete lumbar cord lesion
S114000 Read  Closed spinal fracture with unspecified lumbar cord lesion
S112700 Read  Cls spinal fracture with complete thorac cord lesion, T7-12
S112A00 Read  Cls spinal fracture with posterior thorac cord lesion, T7-12
S112600 Read  Cls spinal fracture with unspec thoracic cord lesion, T7-12
S112000 Read  Cls spinal fracture with unspec thoracic cord lesion, T1-6
S112100 Read  Cls spinal fracture wth complete thoracic cord lesion, T1-6
N331.11  Read  Collapse of spine NOS
N331L00 Read  Collapse of vertebra due to osteoporosis NOS
N331.12  Read  Collapse of vertebra NOS
N331D00 Read  Collapsed vertebra NOS
7J41.00  Read  Decompression of fracture of spine
N1y1.00  Read  Fatigue fracture of vertebra
7J43100 Read  Fixation of fracture of spine using Harrington rod
S11..00 Read  Fracture of spine with spinal cord lesion
S11z.00  Read  Fracture of spine with spinal cord lesion NOS
S10..00 Read  Fracture of spine without mention of spinal cord injury
S10z.00  Read  Fracture of spine without mention of spinal cord lesion NOS
S10.11  Read  Fracture of transverse process spine - no spinal cord lesion
S11..12 Read  Fracture of vertebra with spinal cord lesion
S10..12 Read  Fracture of vertebra without spinal cord lesion vert
14G8.00 Read  H/O: vertebral fracture
7J42400 Read  Halo skull traction for fracture of spine
N331800 Read  Osteoporosis + pathological fracture lumbar vertebrae
N331900 Read  Osteoporosis + pathological fracture thoracic vertebrae
N331.14  Read  Osteoporotic vertebral collapse
7J41000 Read  Complex decompression of fracture of spine
7J41100 Read  Anterior decompression of fracture of spine
7J41200 Read  Posterior decompression of fracture of spine
7J41300 Read  Vertebroplasty of fracture of spine
7J41400 Read  Posterior decompression of fracture of spine NEC
7J41y00 Read  Other specified decompression of fracture of spine
7J41z00 Read  Decompression of fracture of spine NOS
7J42.00  Read  Other reduction of fracture of spine
7J42.11  Read  Other reduction of fracture of spine and stabilisation
7J42000 Read  Open reduction of fracture of spine & excis facet of spine
7J42100 Read  Open reduction of fracture of spine NEC
7J42200 Read  Manipulative reduction of fracture of spine
7J42300 Read  Spinal extension traction for fracture of spine
7J42500 Read  Spinal traction for fracture of spine NEC
7J42600 Read  Primary bedrest stabilisation of spinal fracture
7J42700 Read  Primary collar stabilisation of spinal fracture
7J42900 Read  Primary cast stabilisation of spinal fracture
7J42B00 Read  Primary other external stabilisation of spinal fracture
| Code     | Description                                                                                         |
|----------|-----------------------------------------------------------------------------------------------------|
| 7J42C00 | Revision to bedrest stabilisation of spinal fracture                                               |
| 7J42D00 | Revision to collar stabilisation of spinal fracture                                                 |
| 7J42G00 | Revision to external fixation stabilisation spinal fracture                                        |
| 7J42J00 | Primary closed reduction spinal fracture alone                                                      |
| 7J42L00 | Primary cls reduction spinal fracture+bedrest stabilisation                                        |
| 7J42M00 | Primary cls reduc spinal fracture+skull traction stabilisation                                    |
| 7J42y00 | Other specified other reduction of fracture of spine                                              |
| 7J42z00 | Other reduction of fracture of spine NOS                                                            |
| 7J43.00 | Fixation of fracture of spine                                                                      |
| 7J43.11 | Internal fixation of fracture of spine                                                              |
| 7J43000 | Primary open reduc spinal fracture+internal fix+plate                                               |
| 7J43200 | Fixation of fracture of spine and skull traction HFO                                                |
| 7J43211 | Barr skull traction for fracture of spine                                                           |
| 7J43300 | Primary open reduc spinal fracture+internal fix+wire                                               |
| 7J43400 | Primary open reduc spinal fracture+internal fix+rod system                                          |
| 7J43700 | Primary open reduc spinal fracture+other internal fix                                               |
| 7J43900 | Rvsn open reduc spinal fracture+internal fix+plate                                                 |
| 7J43A00 | Rvsn open reduc spinal fracture+internal fix+rod system                                            |
| 7J43C00 | Rvsn open reduc spinal fracture+internal fix+internl fixator                                       |
| 7J43E00 | Removal of fracture fixation device from spine                                                      |
| 7J43y00 | Other specified fixation of fracture of spine                                                       |
| S10y.00 | Open fracture of spine, unspecified,                                                                 |
| S110000 | Cls spinal fracture with unspec cervical cord lesion, C1-4                                        |
| S110100 | Cls spinal fracture with complete cervcl cord lesion, C1-4                                        |
| S110600 | Cls spinal fracture with unspec cervical cord lesion, C5-7                                        |
| S110700 | Cls spinal fracture with complete cervcl cord lesion, C5-7                                        |
| S110800 | Cls spinal fracture with anterior cervcl cord lesion, C5-7                                        |
| S111000 | Closed fracture of cervical spine with cord lesion NOS                                              |
| S113.00 | Open fracture of cervical spine with spinal cord lesion                                              |
| S113.00 | Open fracture of thoracic spine with spinal cord lesion                                              |
| S113.00 | Opn spinal fracture with unspec thoracic cord lesion, T1-6                                         |
| S113A00 | Opn spinal fracture with posterior thorac cord lesion, T7-12                                       |
| S114500 | Closed spinal fracture with cauda equina lesion                                                     |
| S312500 | Closed fracture distal femur, lateral condyle                                                      |
| S312300 | Closed fracture distal femur, supracondylar                                                        |
| S312000 | Closed fracture of distal femur, unspecified                                                       |
| S312100 | Closed fracture of femoral condyle, unspecified                                                     |
| S312.11 | Closed fracture of femur, distal end                                                               |
| S312.12 | Closed fracture of femur, lower epiphysis                                                         |
| S310.00 | Closed fracture of femur, shaft or unspecified part                                                |
| S310000 | Closed fracture of femur, unspecified part                                                          |
| S302200 | Closed fracture proximal femur, subtrochanteric                                                    |
| 7K1L500 | Closed reduction of fracture of femur                                                               |
| S312z.00 | Fracture of femur, NOS                                                                              |
| S315.00 | Fracture of lower end of femur                                                                    |
S314.00  Read  Fracture of shaft of femur
S3x2.00  Read  Multiple fractures of femur
S311.00  Read  Open fracture of femur, shaft or unspecified part
S31..00  Read  Other fracture of femur
S305.00  Read  Subtrochanteric fracture
S310011  Read  Thigh fracture NOS
S303200  Read  Open fracture proximal femur, subtrochanteric
S310012  Read  Upper leg fracture NOS
S310100  Read  Closed fracture shaft of femur
S310z00  Read  Closed fracture of shaft or unspecified part, NOS
S311000  Read  Open fracture of femur, unspecified part
S311100  Read  Open fracture shaft of femur
S311z00  Read  Open fracture of femur, shaft or unspecified part, NOS
S312.00  Read  Closed fracture distal femur
S312400  Read  Closed fracture distal femur, medial condyle
S312600  Read  Closed fracture distal femur, bicondylar (T-Y fracture)
S312x00  Read  Closed fracture distal femur, comminuted/intra-articular
S312z00  Read  Closed fracture of distal femur not otherwise specified
S313.00  Read  Open fracture distal femur
S313.11  Read  Open fracture of femur, distal end
S313000  Read  Open fracture distal femur, unspecified
S313100  Read  Open fracture of femoral condyle, unspecified
S313200  Read  Open fracture of femur, lower epiphysis
S313300  Read  Open fracture distal femur, supracondylar
S313400  Read  Open fracture distal femur, medial condyle
S313500  Read  Open fracture distal femur, lateral condyle
S313x00  Read  Open fracture distal femur, comminuted/intra-articular
S313z00  Read  Open fracture of distal femur not otherwise specified
SC3D400  Read  Sequelae of fracture of femur
S1...00  Read  Fracture of neck and trunk
NyuB000  Read  [X]Other osteoporosis with pathological fracture
NyuB800  Read  [X]Unspecified osteoporosis with pathological fracture
S3z0.00  Read  Closed fracture of bones, unspecified
N331500  Read  Drug-induced osteoporosis with pathological fracture
S3z..11  Read  Fracture NOS
N331700  Read  Fracture of bone in neoplastic disease
S3zz..00  Read  Fracture of bones NOS
S3z..00  Read  Fracture of unspecified bones
TC7..00  Read  Fracture, cause unspecified
N331N00  Read  Fragility fracture
N331M00  Read  Fragility fracture due to unspecified osteoporosis
S3z0000  Read  Greenstick fracture
N331600  Read  Idiopathic osteoporosis with pathological fracture
7K1L100  Read  Manipulation of fracture of bone NEC
N331N11  Read  Minimal trauma fracture
N331M11  Read  Minimal trauma fracture due to unspecified osteoporosis
Other closed reduction of fracture of bone
Pathological fracture
Postmenopausal osteoporosis with pathological fracture
Primary open reduction fracture long bone & fixation rigid
Primary open reduction fragment of bone & fixation using
Primary closed reduction of fracture alone
Primary open reduction fracture bone & intramedull fixation
Primary wire fixation of fracture
Prim open reduction #+locked reamed intramedullary nail fxtn
Prim open reduction of #+internal fixation with plate NEC
Prim open reduction of #+internal fixation with screw(s)
K wiring of fracture
Prim open reduction fracture bone & intramedullary fixatn OS
Prim open reduction fracture bone & intramedull fixation NOS
Primary open reduction of intraarticular fracture of bone
Primary intraarticular fixation intraartic fracture bone NEC
Prim extraarticular reduction intraartic fracture bone NEC
Primary open reduction of intraarticular fracture bone OS
Primary open reduction of intraarticular fracture bone NOS
Prim open reduction of fracture and skeletal traction
Prim open reduction of fracture and external fixation
Primary open reduction of fracture alone
Primary open reduction of fracture and cast immobilisation
Primary open reduction of fracture and functional bracing
Primary open reduction of fracture and skin traction
Primary open reduction of bone fracture & external fixation
Other primary open reduction of fracture of bone NOS
Secondary open reduction of fracture of bone
Revision to open reduction of fracture of bone
Secondary open reduction of intraarticular fracture of bone
Secondary open reduce fracture bone & external fixation HFQ
Revision to open reduction of fracture alone
Revision to open reduction of fracture and skeletal traction
Revision to open reduction of fracture and external fixation
Other specified secondary open reduction of fracture of bone
Secondary open reduction of fracture of bone NOS
Closed (or no) reduction of fracture and internal fixation
Closed reduction fracture small bone & fixation using screw
Revision to wire fixation of fracture
Primary closed reduction of fracture and wire fixation
Revision to closed reduction of fracture and wire fixation
Closed reduction fracture and internal fixatn OS
Closed reduction of bone fracture and internal fixation NOS
Closed (or no) reduction of fracture and external fixation
| Code      | Description                                                   |
|-----------|---------------------------------------------------------------|
| 7K1K000   | Read Closed reduction fracture bone and fixation to skeleton HFO |
| 7K1K200   | Read Remanipulation of fracture bone and external fixation HFO |
| 7K1K700   | Read Primary functional bracing of fracture                   |
| 7K1K800   | Read Primary external fixation of fracture                     |
| 7K1K900   | Read Other primary external immobilisation of fracture         |
| 7K1KA00   | Read Revision to functional bracing of fracture               |
| 7K1KB00   | Read Revision to external fixation of fracture                |
| 7K1KC00   | Read Other revision to external immobilisation of fracture    |
| 7K1KE00   | Read Primary closed reduction of fracture and external fixation|
| 7K1Ky00   | Read Closed reduction of bone fracture and external fixation OS|
| 7K1Kz00   | Read Closed reduction of bone fracture and external fixation NOS|
| 7K1L011   | Read Manipulation of fracture and skeletal traction NEC        |
| 7K1L211   | Read Remanipulation of fracture and skeletal traction NEC      |
| 7K1L300   | Read Remanipulation of fracture of bone NEC                    |
| 7K1LT00   | Read Primary closed reduction of fracture and cast immobilisation|
| 7K1LW00   | Read Primary closed reduction of fracture and skin traction    |
| 7K1LX00   | Read Revision to closed reduction of fracture alone            |
| 7K1LZ00   | Read Primary skin traction of fracture                        |
| 7K1La00   | Read Revision to skin traction of fracture                     |
| 7K1Lb00   | Read Primary cast immobilisation of fracture                   |
| 7K1Lc00   | Read Revision to cast immobilisation of fracture               |
| 7K1Ld00   | Read Primary arthroscopic reduction of fracture                |
| 7K1Le00   | Read Primary arthroscopic reduction and fixation of fracture   |
| 7K1Lf00   | Read Revision to arthroscopic reduction of fracture            |
| 7K1Lg00   | Read Revision to arthroscopic reduction and fixation of fracture|
| 7K1Lh00   | Read Other specified other closed reduction of fracture of bone|
| 7K1Lz00   | Read Other closed reduction of fracture of bone NOS            |
| 7K1L900   | Read Primary skeletal traction of fracture                     |
| 7K1T100   | Read Debridement of open fracture                             |
| 7K1Y00    | Read Second closed reduction fracture bone and internal fixation|
| 7K1Y100   | Read Remanip fracture long bone and rigid internal fixation NEC|
| 7K1Yy00   | Read OS second closed reduct fracture bone and internal fixation|
| 7K6F200   | Read Primary open reduction of fracture dislocation of joint NEC|
| 7K6FE00   | Read Primary open reduction of fracture dislocation alone      |
| 7K6GN00   | Read Closed reduction fracture disloc joint & internal fixation|
| 7K6GX00   | Read Primary closed reduction of fracture dislocation alone    |
| 7K6H200   | Read Secondary open reduction fracture dislocation of joint NEC|
| 7K6H400   | Read Revision to closed reduction of fracture dislocation alone|
| 7K6H411   | Read Remanipulation of fracture dislocation alone              |
| 7K6H700   | Read Secondary open reduction fracture disloc joint & fixation |
| 7K6HX00   | Read Revision to open reduction fracture dislocation alone     |
| 7K6Hh00   | Read Sec open red fracture dislocat joint and intern fixation NEC|
| 82...11   | Read Closed reduction of fracture                              |
| N1y2.00   | Read Pars interarticularis stress fracture                     |
| N331.13   | Read Sponanteous fracture                                     |
| N331200   | Read Postoophorectomy osteoporosis with pathological fracture  |
S234912  Read  Closed volar Barton fracture-subluxation
S234900  Read  Closed volar Barton's fracture
S234911  Read  Closed volar Barton's fracture-dislocation
S26.11  Read  Finger fracture
S242.00  Read  Fracture at wrist and hand level
S2B.00  Read  Fracture of bone of hand
S24.00  Read  Fracture of carpal bone
S242100  Read  Fracture of first metacarpal bone
S25.00  Read  Fracture of metacarpal bone
S263.00  Read  Fracture of other finger
S242200  Read  Fracture of other metacarpal bone
S242000  Read  Fracture of scaphoid
S262.00  Read  Fracture of thumb
S4C.00  Read  Fracture-dislocation or subluxation of wrist
S4D.00  Read  Fracture-dislocation/subluxation finger/thumb
S25..11  Read  Hand fracture - metacarpal bone
S242300  Read  Multiple fractures of metacarpal bones
S235100  Read  Open Colles' fracture
S261000  Read  Open fracture of phalanx or phalanges, unspecified
S235B00  Read  Open fracture radial styloid
S234.11  Read  Wrist fracture - closed
7K1LJ00  Read  Closed reduction of fracture of thumb
7K1LK00  Read  Closed reduction of fracture of metacarpus
7K1LM00  Read  Closed reduction of fracture of wrist
S234111  Read  Smith's fracture - closed
S235.11  Read  Wrist fracture - open
S235111  Read  Smith's fracture - open
S235700  Read  Open Smith's fracture
S235900  Read  Open volar Barton's fracture
S235A00  Read  Open dorsal Barton's fracture
S235F00  Read  Open Barton's fracture
S24.11  Read  Hand fracture - carpal bone
S240.00  Read  Closed fracture of carpal bone
S240000  Read  Closed fracture of carpal bone, unspecified
S240200  Read  Closed fracture lunate
S240300  Read  Closed fracture triquetral
S240400  Read  Closed fracture pisiform
S240600  Read  Closed fracture trapezoid
S240800  Read  Closed fracture hamate
S240900  Read  Closed fracture hamate, hook
S240A00  Read  Closed fracture scaphoid, proximal pole
S240B00  Read  Closed fracture scaphoid, waist, transverse
S240C00  Read  Closed fracture scaphoid, waist, oblique
S240D00  Read  Closed fracture scaphoid, waist, comminuted
S240E00  Read  Closed fracture scaphoid, tuberosity
S240F00  Read  Closed fracture carpal bones, multiple
| Code     | Description                                                   |
|----------|---------------------------------------------------------------|
| S260000  | Read Closed fracture of phalanx or phalanges, unspecified     |
| S260300  | Read Closed fracture thumb proximal phalanx                   |
| S260400  | Read Closed fracture thumb proximal phalanx, base             |
| S260500  | Read Closed fracture thumb proximal phalanx, shaft            |
| S260600  | Read Closed fracture thumb proximal phalanx, neck             |
| S260700  | Read Closed fracture thumb proximal phalanx, head             |
| S260800  | Read Closed fracture thumb distal phalanx                     |
| S260900  | Read Closed fracture thumb distal phalanx, base               |
| S260A00  | Read Closed fracture thumb distal phalanx, shaft              |
| S260B00  | Read Closed fracture thumb distal phalanx, tuft               |
| S260C00  | Read Closed fracture thumb distal phalanx, mallet             |
| S260D00  | Read Closed fracture finger proximal phalanx                  |
| S260E00  | Read Closed fracture finger proximal phalanx, base            |
| S260F00  | Read Closed fracture finger proximal phalanx, shaft           |
| S260G00  | Read Closed fracture finger proximal phalanx, neck            |
| S260H00  | Read Closed fracture finger proximal phalanx, head            |
| S260J00  | Read Closed fracture finger proximal phalanx, multiple        |
| S260K00  | Read Closed fracture finger middle phalanx                    |
| S260L00  | Read Closed fracture finger middle phalanx, base              |
| S260M00  | Read Closed fracture finger middle phalanx, shaft             |
| S260N00  | Read Closed fracture finger middle phalanx, neck              |
| S260P00  | Read Closed fracture finger middle phalanx, head              |
| S260Q00  | Read Closed fracture finger middle phalanx, multiple          |
| S260R00  | Read Closed fracture finger distal phalanx                    |
| S260S00  | Read Closed fracture finger distal phalanx, base              |
| S260T00  | Read Closed fracture finger distal phalanx, shaft             |
| S260U00  | Read Closed fracture finger distal phalanx, tuft              |
| S260V00  | Read Closed fracture finger distal phalanx, mallet            |
| S260W00  | Read Closed fracture finger distal phalanx, multiple          |
| S260X00  | Read Closed fractures of phalanx or phalanges, multiple sites |
| S260Z00  | Read Closed fracture of one or more phalanges of hand NOS     |
| S26100   | Read Open fracture of one or more phalanges of hand           |
| S261300  | Read Open fracture thumb proximal phalanx                     |
| S261400  | Read Open fracture thumb proximal phalanx, base               |
| S261500  | Read Open fracture thumb proximal phalanx, shaft              |
| S261600  | Read Open fracture thumb proximal phalanx, neck               |
| S261700  | Read Open fracture thumb proximal phalanx, head               |
| S261800  | Read Open fracture thumb distal phalanx                       |
| S261900  | Read Open fracture thumb distal phalanx, base                 |
| S261A00  | Read Open fracture thumb distal phalanx, shaft                |
| S261B00  | Read Open fracture thumb distal phalanx, tuft                 |
| S261C00  | Read Open fracture thumb distal phalanx, mallet               |
| S261D00  | Read Open fracture finger proximal phalanx                    |
| S261E00  | Read Open fracture finger proximal phalanx, base              |
| S261F00  | Read Open fracture finger proximal phalanx, shaft             |
| S261G00  | Read Open fracture finger proximal phalanx, neck              |
S261H00  Read  Open fracture finger proximal phalanx, head
S261J00  Read  Open fracture finger proximal phalanx, multiple
S261K00  Read  Open fracture finger middle phalanx
S261L00  Read  Open fracture finger middle phalanx, base
S261M00  Read  Open fracture finger middle phalanx, shaft
S261N00  Read  Open fracture finger middle phalanx, neck
S261P00  Read  Open fracture finger middle phalanx, head
S261R00  Read  Open fracture finger distal phalanx
S261S00  Read  Open fracture finger distal phalanx, base
S261T00  Read  Open fracture finger distal phalanx, shaft
S261U00  Read  Open fracture finger distal phalanx, tuft
S261V00  Read  Open fracture finger distal phalanx, mallet
S261W00  Read  Open fracture finger distal phalanx, multiple
S261x00  Read  Open fracture of phalanx or phalanges, multiple sites
S261z00  Read  Open fracture of one or more phalanges of hand NOS
S264.00  Read  Multiple fractures of fingers
S27.00  Read  Multiple fractures of hand bones
S271.00  Read  Closed multiple fractures of hand bones
S272.00  Read  Multiple fractures of hand bones NOS
S4C0.00  Read  Closed fracture dislocation of wrist
S4C0100  Read  Closed fracture-dislocation radiocarpal joint
S4C0200  Read  Closed fracture-dislocation mid carpal
S4C0300  Read  Closed fracture-dislocation, carpometacarpal joint
S4C0400  Read  Closed fracture-dislocation lunate (volar)
S4C0500  Read  Closed fracture-dislocation peri-lunate (dorsal)
S4C0600  Read  Closed fracture-dislocation peri-lunate trans-scaphoid
S4C1.00  Read  Open fracture dislocation wrist
S4C1000  Read  Open fracture-dislocation, distal radio-ulnar joint
S4C1100  Read  Open fracture-dislocation radiocarpal joint
S4C1300  Read  Open fracture-dislocation carpometacarpal joint
S4C1600  Read  Open fracture-dislocation peri-lunate trans-scaphoid
S4C2200  Read  Closed fracture-subluxation mid carpal
S4C2300  Read  Closed fracture-subluxation, carpometacarpal joint
S4C2400  Read  Closed fracture-subluxation lunate (volar)
S4C2600  Read  Closed fracture-subluxation peri-lunate trans-scaphoid
S4C2y00  Read  Closed fracture-subluxation other carpal
S4C3.00  Read  Open fracture-subluxation of the wrist
S4C3000  Read  Open fracture-subluxation, distal radio-ulnar joint
S4C3100  Read  Open fracture-subluxation radiocarpal joint
S4C3300  Read  Open fracture-subluxation, carpometacarpal joint
S4C3600  Read  Open fracture-subluxation peri-lunate trans-scaphoid
S4D0.00  Read  Closed fracture-dislocation digit
S4D0000  Read  Closed fracture-dislocation digit, unspecified
S4D0100  Read  Closed fracture-dislocation, metacarpophalangeal joint
S4D0200  Read  Closed fracture-dislocation IPJ, unspecified
S4D0300 Read  Closed fracture-dislocation, distal interphalangeal joint
S4D0400 Read  Closed fracture-dislocation, proximal interphalangeal joint
S4D0500 Read  Closed fracture-dislocation, interphalangeal joint thumb
S4D0600 Read  Closed fracture-dislocation multiple digits
S4D1.00 Read  Open fracture-dislocation digit
S4D1100 Read  Open fracture-dislocation, metacarpophalangeal joint
S4D1200 Read  Open fracture-dislocation IPJ, unspecified
S4D1300 Read  Open fracture-dislocation, distal interphalangeal joint
S4D1400 Read  Open fracture-dislocation, proximal interphalangeal joint
S4D1500 Read  Open fracture-dislocation, interphalangeal joint thumb
S4D1600 Read  Open fracture-dislocation multiple digits
S4D2.00 Read  Closed fracture-subluxation digit
S4D2000 Read  Closed fracture-subluxation digit, unspecified
S4D2100 Read  Closed fracture-subluxation, metacarpophalangeal joint
S4D2200 Read  Closed fracture-subluxation IPJ, unspecified
S4D2300 Read  Closed fracture-subluxation, distal interphalangeal joint
S4D2400 Read  Closed fracture-subluxation, proximal interphalangeal joint
S4D2500 Read  Closed fracture-subluxation, interphalangeal joint thumb
S4D2600 Read  Closed fracture-subluxation multiple digits
S4D3.00 Read  Open fracture-subluxation digit
S4D3100 Read  Open fracture-subluxation, metacarpophalangeal joint
S4D3300 Read  Open fracture-subluxation, distal interphalangeal joint
S4D3400 Read  Open fracture-subluxation, proximal interphalangeal joint
S4D3500 Read  Open fracture-subluxation, interphalangeal joint thumb
S4D3600 Read  Open fracture-subluxation multiple digits
SC3C000 Read  Sequelae of fracture at wrist and hand level
T02  ICD-10 Fractures involving multiple body regions
T02.0  ICD-10 Fractures involving head with neck
T02.1  ICD-10 Fractures involving thorax with lower back and pelvis
T02.2  ICD-10 Fractures involving multiple regions of one upper limb
T02.3  ICD-10 Fractures involving multiple regions of one lower limb
T02.4  ICD-10 Fractures involving multiple regions of both upper limbs
T02.5  ICD-10 Fractures involving multiple regions of both lower limbs
T02.6  ICD-10 Fractures involving multiple regions of upper limb(s) with lower limb(s)
T02.7  ICD-10 Fractures involving thorax with lower back and pelvis with limb(s)
T02.8  ICD-10 Fractures involving other combinations of body regions
T02.9  ICD-10 Multiple fractures, unspecified
T08  ICD-10 Fracture of spine, level unspecified
T10  ICD-10 Fracture of upper limb, level unspecified
T12  ICD-10 Fracture of lower limb, level unspecified
T14.2  ICD-10 Fracture of unspecified body region
S02  ICD-10 Fracture of skull and facial bones
S02.0  ICD-10 Fracture of vault of skull
S02.1  ICD-10 Fracture of base of skull
S02.2  ICD-10 Fracture of nasal bones
S02.3 ICD-10 Fracture of orbital floor
S02.4 ICD-10 Fracture of malar and maxillary bones
S02.5 ICD-10 Fracture of tooth
S02.6 ICD-10 Fracture of mandible
S02.7 ICD-10 Multiple fractures involving skull and facial bones
S02.8 ICD-10 Fractures of other skull and facial bones
S02.9 ICD-10 Fracture of skull and facial bones, part unspecified
S12 ICD-10 Fracture of neck
S12.0 ICD-10 Fracture of first cervical vertebra
S12.1 ICD-10 Fracture of second cervical vertebra
S12.2 ICD-10 Fracture of other specified cervical vertebra
S12.7 ICD-10 Multiple fractures of cervical spine
S12.8 ICD-10 Fracture of other parts of neck
S12.9 ICD-10 Fracture of neck, part unspecified
S22 ICD-10 Fracture of rib(s), sternum and thoracic spine
S22.0 ICD-10 Fracture of thoracic vertebra
S22.1 ICD-10 Multiple fractures of thoracic spine
S22.2 ICD-10 Fracture of sternum
S22.3 ICD-10 Fracture of rib
S22.4 ICD-10 Multiple fractures of ribs
S22.5 ICD-10 Flail chest
S22.8 ICD-10 Fracture of other parts of bony thorax
S22.9 ICD-10 Fracture of bony thorax, part unspecified
S32 ICD-10 Fracture of lumbar spine and pelvis
S32.0 ICD-10 Fracture of lumbar vertebra
S32.1 ICD-10 Fracture of sacrum
S32.2 ICD-10 Fracture of coccyx
S32.3 ICD-10 Fracture of ilium
S32.4 ICD-10 Fracture of acetabulum
S32.5 ICD-10 Fracture of pubis
S32.7 ICD-10 Multiple fractures of lumbar spine and pelvis
S32.8 ICD-10 Fracture of other and unspecified parts of lumbar spine and pelvis
S42 ICD-10 Fracture of shoulder and upper arm
S42.0 ICD-10 Fracture of clavicle
S42.1 ICD-10 Fracture of scapula
S42.2 ICD-10 Fracture of upper end of humerus
S42.3 ICD-10 Fracture of shaft of humerus
S42.4 ICD-10 Fracture of lower end of humerus
S42.7 ICD-10 Multiple fractures of clavicle, scapula and humerus
S42.8 ICD-10 Fracture of other parts of shoulder and upper arm
S42.9 ICD-10 Fracture of shoulder girdle, part unspecified
S52 ICD-10 Fracture of girdle
S52.0 ICD-10 Fracture of upper end of ulna
S52.1 ICD-10 Fracture of upper end of radius
S52.2 ICD-10 Fracture of shaft of ulna
S52.3 ICD-10 Fracture of shaft of radius
V08.1 OPCS-4 Reduction of fracture of alveolus of maxilla
V08.2 OPCS-4 Open reduction of fracture of maxilla NEC
V08.3 OPCS-4 Closed reduction of fracture of maxilla NEC
V08.8 OPCS-4 Other specified
V08.9 OPCS-4 Unspecified
V09 OPCS-4 Reduction of fracture of other bone of face
V09.1 OPCS-4 Reduction of fracture of nasoethmoid complex of bones
V09.2 OPCS-4 Reduction of fracture of nasal bone NEC
V09.3 OPCS-4 Reduction of fracture of zygomatic complex of bones
V09.8 OPCS-4 Other specified
V09.9 OPCS-4 Unspecified
V11 OPCS-4 Fixation of bone of face
V11.1 OPCS-4 Intermaxillary fixation of maxilla
V11.2 OPCS-4 Internal fixation of maxilla NEC
V11.3 OPCS-4 Extraoral fixation of maxilla
V11.4 OPCS-4 Fixation of maxilla NEC
V11.5 OPCS-4 Removal of fixation from bone of face
V11.8 OPCS-4 Other specified
V11.9 OPCS-4 Unspecified
V15 OPCS-4 Reduction of fracture of mandible
V15.1 OPCS-4 Reduction of fracture of alveolus of mandible
V15.2 OPCS-4 Open reduction of fracture of mandible NEC
V15.3 OPCS-4 Closed reduction of fracture of mandible NEC
V15.8 OPCS-4 Other specified
V15.9 OPCS-4 Unspecified
V17 OPCS-4 Fixation of mandible
V17.1 OPCS-4 Intermaxillary fixation of mandible
V17.2 OPCS-4 Internal fixation of mandible NEC
V17.3 OPCS-4 Extraoral fixation of mandible
V17.4 OPCS-4 Removal of fixation from mandible
V17.8 OPCS-4 Other specified
V17.9 OPCS-4 Unspecified
V44 OPCS-4 Decompression of fracture of spine
V44.1 OPCS-4 Complex decompression of fracture of spine
V44.2 OPCS-4 Anterior decompression of fracture of spine
V44.3 OPCS-4 Posterior decompression of fracture of spine NEC
V44.4 OPCS-4 Vertebroplasty of fracture of spine
V44.5 OPCS-4 Balloon kyphoplasty of fracture of spine
V44.8 OPCS-4 Other specified
V44.9 OPCS-4 Unspecified
V45 OPCS-4 Other reduction of fracture of spine
V45.1 OPCS-4 Open reduction of fracture of spine and excision of facet of spine
V45.2 OPCS-4 Open reduction of fracture of spine NEC
V45.3 OPCS-4 Manipulative reduction of fracture of spine
V45.8 OPCS-4 Other specified
V45.9 OPCS-4 Unspecified
V46 OPCS-4 Fixation of fracture of spine
V46.1 OPCS-4 Fixation of fracture of spine using plate
V46.2 OPCS-4 Fixation of fracture of spine using Harrington rod
V46.3 OPCS-4 Fixation of fracture of spine using wire
V46.4 OPCS-4 Fixation of fracture of spine and skull traction HFQ
V46.5 OPCS-4 Removal of fixation device from spine
V46.8 OPCS-4 Other specified
V46.9 OPCS-4 Unspecified

W19 OPCS-4 Primary open reduction of fracture of bone and intramedullary fixation
W19.1 OPCS-4 Primary open reduction of fracture of neck of femur and open fixation using pin and plate
W19.2 OPCS-4 Primary open reduction of fracture of long bone and fixation using rigid nail NEC
W19.3 OPCS-4 Primary open reduction of fracture of long bone and fixation using flexible nail
W19.4 OPCS-4 Primary open reduction of fracture of small bone and fixation using screw
W19.5 OPCS-4 Primary open reduction of fragment of bone and fixation using screw
W19.6 OPCS-4 Primary open reduction of fragment of bone and fixation using wire system
W19.8 OPCS-4 Other specified
W19.9 OPCS-4 Unspecified

W20 OPCS-4 Primary open reduction of fracture of bone and extramedullary fixation
W20.1 OPCS-4 Primary open reduction of fracture of long bone and extramedullary fixation using plate NEC
W20.2 OPCS-4 Primary open reduction of fracture of long bone and extramedullary fixation using cerclage
W20.3 OPCS-4 Primary open reduction of fracture of long bone and extramedullary fixation using suture
W20.4 OPCS-4 Primary open reduction of fracture of long bone and complex extramedullary fixation NEC
W20.5 OPCS-4 Primary open reduction of fracture of ankle and extramedullary fixation NEC
W20.6 OPCS-4 Wiring of sternum
W20.8 OPCS-4 Other specified
W20.9 OPCS-4 Unspecified

W21 OPCS-4 Other primary open reduction of fracture of bone
W21.1 OPCS-4 Primary reduction of intra-articular fracture of bone using arthrotomy as approach
W21.2 OPCS-4 Primary excision of intra-articular fragment of intra-articular fracture of bone
W21.3 OPCS-4 Primary fixation of fragment of chondral cartilage of intra-articular fracture of bone
W21.4 OPCS-4 Primary intra-articular fixation of intra-articular fracture of bone NEC
W21.5 OPCS-4 Primary extra-articular reduction of intra-articular fracture of bone
W21.8 OPCS-4 Other specified
W21.9 OPCS-4 Unspecified

W22 OPCS-4 Other primary open reduction of fracture of bone
W22.1 OPCS-4 Primary open reduction of fracture of bone and skeletal traction HFQ
W22.2 OPCS-4 Primary open reduction of fracture of bone and external fixation HFQ
W22.8 OPCS-4 Other specified
W22.9 OPCS-4 Unspecified

W23 OPCS-4 Secondary open reduction of fracture of bone
W23.1 OPCS-4 Secondary open reduction of fracture of bone and intramedullary fixation HFQ
W23.2 OPCS-4 Secondary open reduction of fracture of bone and extramedullary fixation HFQ
W23.3 OPCS-4 Secondary open reduction of intra-articular fracture of bone
W23.4 OPCS-4 Secondary open reduction of fracture of bone and skeletal traction HFQ
W23.5 OPCS-4 Secondary open reduction of fracture of bone and external fixation HFQ
W23.6 OPCS-4 Secondary open reduction of fracture of bone and internal fixation HFQ
| Code | Description |
|------|-------------|
| W23.8 | Other specified |
| W23.9 | Unspecified |
| W24 | Closed reduction of fracture of bone and internal fixation |
| W24.1 | Closed reduction of intracapsular fracture of neck of femur and fixation using nail or screw |
| W24.2 | Closed reduction of fracture of long bone and rigid internal fixation NEC |
| W24.3 | Closed reduction of fracture of long bone and flexible internal fixation NEC |
| W24.4 | Closed reduction of fracture of small bone and fixation using screw |
| W24.5 | Closed reduction of fragment of bone and fixation using screw |
| W24.6 | Closed reduction of fracture of bone and fixation using nail or screw |
| W24.8 | Other specified |
| W24.9 | Unspecified |
| W25 | Closed reduction of fracture of bone and external fixation |
| W25.1 | Closed reduction of fracture of bone and fixation to skeleton HFQ |
| W25.2 | Closed reduction of fracture of bone and fixation using functional bracing system |
| W25.3 | Remanipulation of fracture of bone and external fixation HFQ |
| W25.8 | Other specified |
| W25.9 | Unspecified |
| W26 | Other closed reduction of fracture of bone |
| W26.1 | Manipulation of fracture of bone and skeletal traction NEC |
| W26.2 | Manipulation of fracture of bone NEC |
| W26.3 | Remanipulation of fracture of bone and skeletal traction NEC |
| W26.4 | Remanipulation of fracture of bone NEC |
| W26.8 | Other specified |
| W26.9 | Unspecified |
| W27 | Fixation of epiphysis |
| W27.1 | Permanent cross union epiphysodesis |
| W27.2 | Epiphysioplasty |
| W27.3 | Insertion of staple into epiphysis |
| W27.4 | Removal of staple from epiphysis |
| W27.5 | Temporary fixation of epiphysis |
| W27.8 | Other specified |
| W27.9 | Unspecified |
| W28 | Other internal fixation of bone |
| W28.1 | Application of internal fixation to bone NEC |
| W28.2 | Adjustment to internal fixation of bone NEC |
| W28.3 | Removal of internal fixation from bone NEC |
| W28.4 | Insertion of intramedullary fixation and cementing of bone |
| W28.8 | Other specified |
| W28.9 | Unspecified |
| W29 | Skeletal traction of bone |
| W29.1 | Application of skeletal traction to bone NEC |
| W29.2 | Adjustment to skeletal traction of bone |
| W29.3 | Removal of skeletal traction from bone |
| W29.8 | Other specified |
| W29.9 | Unspecified |
| W30 | Other external fixation of bone |
| Code  | Code Description                                      |
|-------|------------------------------------------------------|
| W30.1 | Application of external fixation to bone NEC         |
| W30.2 | Adjustment to external fixation of bone NEC           |
| W30.3 | Removal of external fixation from bone NEC            |
| W30.4 | Application of external ring fixation to bone NEC     |
| W30.8 | Other specified                                      |
| W30.9 | Unspecified                                          |
| W65.1 | Primary open reduction of fracture dislocation of joint and skeletal traction HFQ |
| W65.3 | Primary open reduction of fracture dislocation of joint NEC |
| W65.4 | Primary open reduction of fracture dislocation of joint and internal fixation NEC |
| W65.5 | Primary open reduction of fracture dislocation of joint and combined internal and external fixation |
| W66.1 | Primary closed reduction of fracture dislocation of joint and skeletal traction HFQ |
| W66.3 | Primary manipulative closed reduction of fracture dislocation of joint NEC |
| W66.4 | Primary closed reduction of fracture dislocation of joint and internal fixation |
| W67.1 | Secondary open reduction of fracture dislocation of joint and skeletal traction HFQ |
| W67.3 | Secondary open reduction of fracture dislocation of joint NEC |
| W67.5 | Remanipulation of fracture dislocation of joint      |
| W67.7 | Secondary open reduction of fracture dislocation of joint and internal fixation NEC |
| X48   | Immobilisation using plaster cast                     |
| X48.1 | Application of plaster cast                           |
| X48.2 | Change of plaster cast                                |
| X48.3 | Removal of plaster cast                               |
| X48.8 | Other specified                                       |
| X48.9 | Unspecified                                           |
| X49   | Other external support of limb                        |
| X49.1 | Application of splint NEC                            |
| X49.2 | Change of splint NEC                                  |
| X49.3 | Removal of splint NEC                                 |
| X49.4 | Skin traction                                        |
| X49.5 | Application of sling NEC                              |
| X49.6 | Application of elastic support bandage NEC            |
| X49.7 | Application of gauze support bandage NEC              |
| X49.8 | Other specified                                       |
| X49.9 | Unspecified                                           |
### eTable 2. Included opioid drugs and equianalgesic ratios

| Opioid Drug, Source | Form<sup>a</sup> | Equianalgesic Ratio |
|---------------------|------------------|---------------------|
| Alfentanil<sup>[4]</sup> | SPR              | 30.00               |
| Buprenorphine<sup>[2]</sup> | TD               | 110.00              |
|                     | OD               | 50.00               |
| Codeine<sup>[7]</sup>     |                  | 0.15                |
| Dextromoramide<sup>[3]</sup> |              | 2.00                |
| Dextropropoxyphene<sup>[7]</sup> |           | 0.15                |
| Diamorphine<sup>b</sup>   |                  | 1.00                |
| Dihydrocodeine<sup>[7]</sup> |              | 0.13                |
| Dipipanone<sup>[5]</sup>  |                  | 0.50                |
| Fentanyl<sup>[7,3,5,1]</sup> | TD             | 100.00              |
|                     | OD               | 50.00               |
|                     | SPR              | 160.00              |
| Hydromorphone<sup>[7]</sup> |                | 6.00                |
| Methadone<sup>[2]</sup>   |                  | 3.00                |
| Meptazinol<sup>[5]</sup>  |                  | 0.03                |
| Morphine<sup>[7]</sup>    |                  | 1.00                |
| Oxycodone<sup>[7]</sup>   |                  | 1.50                |
| Pentazocine<sup>[1]</sup> |                  | 0.37                |
| Pethidine<sup>[7]</sup>   |                  | 0.10                |
| Tapentadol<sup>[2]</sup>  |                  | 0.40                |
| Tramadol<sup>[7]</sup>    |                  | 0.20                |

<sup>a</sup> form is an oral preparation unless otherwise stated.

<sup>b</sup> rarely prescribed as an oral formulation; equianalgesic ratio based on advice from a specialist pain management pharmacist.

Abbreviations: SPR, sprays (buccal and nasal); TD, transdermal patch; OD, orodispersible.
### eFigure 1. Overview of opioid prescription preparation process

|                          | Setting values                                      | Generating variables                          | Identifying records                                      | Imputing/handling values                                      | Removing records                                      |
|--------------------------|-----------------------------------------------------|-----------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------|
| **Cleaning**             |                                                     |                                               | Missing and implausible quantities                       | Missing and implausible quantities in a series of steps       | Patients with any remaining missing or implausible values |
| Quantity and dose        | Minimum and maximum quantity and daily dose         |                                               | Missing and implausible doses                             | Missing and implausible doses in a series of steps            | Patients with any remaining missing or implausible doses |
|                         |                                                     |                                               |                                                          |                                                              |                                                       |
| **Duration**             |                                                     |                                               | Records with multiple durations                           | Replace with mean of durations if ≤30 days apart (those >30 set to missing) |                                                       |
| Duration and stop date   | Maximum value for duration                          | Duration based on quantity and dose; stop date based on start date and duration | Missing and implausible durations                        | Missing and implausible durations via a series of steps       |                                                       |
|                         |                                                     |                                               |                                                          |                                                              |                                                       |
| **Gap and Overlaps**     |                                                     |                                               | Records for identical products with the same start date  | Replace duration with the sum of durations                    | Excess records after combining                          |
| Overlapping identical products | Permissible gap                                    |                                               | Records with overlapping days                             | Start and stop dates, and durations for overlapping days moved to gaps and end of records | Overlapping days that extended beyond end of follow-up     |
|                         |                                                     |                                               | Records for identical products that have a permissible gap (<15 days) | Stop date and duration extended to close the permissible gap |                                                       |
|                         |                                                     |                                               |                                                          |                                                              |                                                       |
| OMEQ dose                |                                                     |                                               | OMEQ dose/day for each record                             | Overlapping records for different products                    | Join records for any opioid into continuous exposed periods and drop excess records |
| OMEQ dose/day            | Equianalgesic ratio                                 |                                               |                                                          |                                                              |                                                       |
|                         |                                                     |                                               |                                                          |                                                              |                                                       |
| Total OMEQ dose/day      | Opioid exposure status (yes/no)                     |                                               |                                                          |                                                              |                                                       |
|                         |                                                     |                                               |                                                          |                                                              |                                                       |

[Figure legend on following page]
Abbreviations: OMEQ, oral morphine equivalent.

\(^{a}\) adaptation and extension of the DrugPrep framework and respective Stata code published by Pye et al. (2018).\(^{6}\)

\(^{b}\) step 1: the value (quantity and/or daily dose) was replaced with the value recorded for a subsequent prescription for the same product, for the same patient. If there was no subsequent prescription for the product, or if the value for the subsequent prescription was missing or implausible, step 2 was followed. Step 2: the value was replaced with the value recorded for the previous prescription for the same product, for the same patient. If there was no previous prescription for the product, or if the value on the previous prescription was missing or implausible, step 3 was followed. Step 3: the value was replaced with the median value for the individual patient, taken from all plausible values recorded for their prescriptions for the same product. If there were no other prescriptions for the product, or if the values recorded for all other prescriptions were also missing or implausible, step 4 was followed. Step 4: the value was replaced with the population-median value, taken from all plausible values recorded for all prescriptions for the same product, across all patients in the study cohort. If there were no other prescriptions for the product, or if the values recorded on all other prescriptions were also missing or implausible, these records were removed, as detailed in the following section.

\(^{c}\) step 1: the ‘new duration’ was replaced using the median duration for the individual patient, taken from all of their prescriptions for the same product. If there were no other prescriptions for the product, or if the durations recorded on all other prescriptions were also missing, step 2 was followed. Step 2: the ‘new duration’ was replaced using the population-median duration, taken from all prescriptions for the same product, across the entire study cohort.
eFigure 2. Proximity of fracture events to opioid initiation and definition of the pre-exposure risk period

Notes: Time-point 0 indicates that the date of fracture and opioid initiation were the same. A positive value indicates that a fracture occurred after opioid initiation, and a negative value indicates that a fracture occurred before opioid initiation. The rate of fracture stabilizes >90 days before opioid initiation which indicated that 90 days was an appropriate duration for the pre-exposure risk period.
**eFigure 3. Curtailment of overlapping risk periods**

| Exposure status | Risk period | Duration (days) | First exposure | Stop | Subsequent exposure |
|-----------------|-------------|-----------------|----------------|------|---------------------|
| Exposed         | Day 1-7     | 7               | Exposed        | 7    | Exposed             |
| Unexposed       | Day 8-14    | 7               | Unexposed      | 7    | 7                   |
| Exposed         | Day 15-28   | 3               |                | 8    | 7                   |

**Notes:** In this example the risk period ‘Day 15-28’ for the first exposed period, which is ordinarily 14 days in duration was curtailed at three days due to the stop date of the period of exposure. An eight day gap followed which was too short to incorporate a 28-day post-exposure period, baseline period and 90-day pre-exposure period; therefore the pre-exposure period took priority and was curtailed to eight days due to the restart of an opioid.
| Psychoactive Drugs                                                                 | Cardiopulmonary Drugs                                                                 | Steroid and Glucocorticoid Drugs               |
|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------|
| agomelatine co-beneldopa levetiracetam pericyazine sertraline                      | acebutolol cilazapril frusene metoprolol riociguat                                    | betamethasone dexamethasone methylprednisolone prednisone |
| alprazolam co-careldopa levoopromazine perphenazine sodium oxybate                 | aliskiren clonidine furosemide minoxidil sildenafil                                     | deflazacort hydrocortisone prednisolone        |
| amantadine diazepam lithium phenelzine sodium valproate                             | ambrisentan co-amilofrise hydralazine moexipril sodium nitroprusside                    |                                                   |
| amisulpiride dosulepin lofepramine phenobarbital sulpiride                          | amilodipine co-flumactone imidapril nadolol spironolactone                               |                                                   |
| amitriptyline doxepin loprazolam phenytolin temazepam                               | azilsartan co-triamterzide indapamide nebivolol tadalfil                                 |                                                   |
| apomorphine duloxetine lorazepam pimozone thiopental                                | bendroflumethiazide cyclopenthiazide indoramin olmesartan telmisartan                   |                                                   |
| aripiprazole entacapone lorazepam pramipexole tugabine                               | bisoprolol digoxin irbesartan oxprenolol terazosin                                     |                                                   |
| asenapine escitalopram lorzetepam pregabalin tolcapon                                 | bosentan doxazosin labetalol perindopril timolol                                        |                                                   |
| benperidol eslicarbazepine melatonin primidone topiramate                           | bumetanide enalapril lasilactone phenoxybenzamine torasemide                             |                                                   |
| bromocriptine ethosuximide meprobamate prochlorperazine tranylcypromine             | candesartan eplerenone lisinopril phentolamine trandolapril                             |                                                   |
| buspirone fluoxetine mianserin procyclidine trazodone                                | captopril eprosartan losartan prazosin triamterene                                      |                                                   |
| cabergoline flupentixol mirtazapine promazine trifluoperazine                        | carbidilol esmolol macitentan propanolol valsartan                                      |                                                   |
| carbamazepine flupentixol moclubemide promethazine trihexyphenidyl                   | celiprolol flecainide methylidopa quinapril xipamide                                    |                                                   |
| chloral hydrate fluphenazine nitrazepam quetiapine trimipramine                     | chlortalidone fosinopril metolazone ramipril                                            |                                                   |
| chlordiazepoxide flurazepam nortriptyline rasagiline valproic acid                   |                                                                     |                                                   |
| chlorpromazine fluvoxamine olanzapine reboxetine venlafaxine                        |                                                                         |                                                   |
| citalopram gabapentin orphenadrine retigabine vigabatrin                             |                                                                         |                                                   |
| clobazam haloperidol oxycarbazepine risperidone zaleplon                              |                                                                         |                                                   |
| clomipramine imipramine paliperidone ropinerole zolpidem                             |                                                                         |                                                   |
| clomethiazole isoconboxazid paroxetine rotigotine zonisamide                          |                                                                         |                                                   |
| clonazepam lacosamide perampanel rufinamide zopiclone                                |                                                                         |                                                   |
| clozapine lamotrigine pergolide selegiline zuclopentin                                |                                                                         |                                                   |
|                                                                      |                                                                         |                                                   |

67
eFigure 4. Selection of study cohort

Registered in the CPRD database
n=17 033 457

- Data is not of ‘acceptable’ standard (n=2 191 613)
- Patient not registered during study period (n=5 970 718)
- Practice not submitting data to the CPRD during study period (n=285 536)

Registered in up-to-standard CPRD practice during study period
n=8 585 590

- <2 years of registration history (n=571 663)
- <1 day of follow-up (n=1 417 743)
- Age <18 years at study entry (n=1 498 206)
- Unknown sex (n=79)

Adults with ≥2 years CPRD registration
n=5 097 899

- No opioid during follow-up (n=3 307 566)
- Opioid records with missing or implausible values (n=287)
- Opioid during 2-year registration history (n=832 382)

New users of opioids
n=957 664

- No linkage to additional databases (HES and IMD) (n=413 967)

Linkage to additional databases
n=543 697

- Fracture records with missing date (n=451)
- Fracture ≤6 months before study entry (n=3 877)
- No fracture recorded during follow-up (n=471 747)

Study cohort: Opioid users with fractures
n=67 622

Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation.

Notes: Study period from June 1 2008, to May 31 2017.
### eTable 4. Sensitivity analyses

| Risk period          | 1<sup>a</sup> | 2<sup>b</sup> | 3<sup>c</sup> | 4<sup>d</sup> | 5<sup>e</sup> | 6<sup>f</sup> | 7<sup>g</sup> |
|----------------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|                      | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) | aIRR<sup>h</sup> (95% CI) |
| Baseline             | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Pre-exposure         | 5.53 (5.44-5.62) | 5.81 (5.71-5.92) | 5.68 (5.55-5.82) | 4.88 (4.75-5.01) | 6.01 (5.89-6.13) | 12.85 (12.55-13.16) | 9.65 (9.48-9.83) |
| Post-exposure        | 2.25 (2.16-2.34) | 2.27 (2.17-2.38) | 2.26 (2.13-2.40) | 2.36 (2.22-2.51) | 2.21 (2.11-2.33) | 1.85 (1.79-1.91) | 2.25 (2.17-2.33) |
| First exposure       |               |               |               |               |               |               |               |
| Days 1-7             | 7.73 (7.31-8.17) | 7.74 (7.28-8.24) | 7.95 (7.37-8.57) | 6.92 (6.31-7.59) | 8.00 (7.49-8.54) | 6.10 (5.77-6.44) | 7.18 (6.80-7.59) |
| Days 8-14            | 5.08 (4.68-5.51) | 4.90 (4.46-5.37) | 4.96 (4.43-5.56) | 4.34 (3.78-4.99) | 4.89 (4.42-5.41) | 3.96 (3.65-4.29) | 4.68 (4.31-5.07) |
| Days 15-28           | 3.60 (3.17-4.08) | 3.61 (3.13-4.16) | 3.39 (2.82-4.07) | 2.71 (2.17-3.38) | 3.48 (2.97-4.07) | 2.79 (2.47-3.16) | 3.37 (2.98-3.81) |
| Days 29-365          | 1.74 (1.51-2.01) | 1.80 (1.53-2.12) | 1.67 (1.34-2.09) | 1.74 (1.42-2.14) | 1.58 (1.32-1.90) | 1.33 (1.15-1.53) | 1.64 (1.43-1.89) |
| Day 366+             | 1.34 (0.92-1.96) | 1.07 (0.66-1.74) | 1.47 (0.83-2.61) | 1.17 (0.69-1.98) | 1.26 (0.81-1.96) | 0.92 (0.63-1.34) | 1.15 (0.79-1.68) |
| Subsequent exposures |               |               |               |               |               |               |               |
| Days 1-7             | 4.80 (4.58-5.04) | 5.13 (4.86-5.42) | 4.74 (4.32-5.20) | 4.77 (4.43-5.14) | 4.77 (4.48-5.08) | 3.58 (3.42-3.74) | 4.84 (4.62-5.06) |
| Days 8-14            | 3.56 (3.34-3.79) | 3.75 (3.49-4.04) | 3.04 (2.66-3.47) | 3.49 (3.16-3.84) | 3.58 (3.29-3.88) | 2.62 (2.47-2.79) | 3.57 (3.36-3.80) |
| Days 15-28           | 3.04 (2.82-3.27) | 3.06 (2.80-3.34) | 3.04 (2.61-3.53) | 2.84 (2.53-3.19) | 2.83 (2.56-3.13) | 2.21 (2.06-2.38) | 3.04 (2.83-3.26) |
| Days 29-365          | 2.37 (2.24-2.50) | 2.31 (2.16-2.48) | 2.12 (1.86-2.38) | 2.40 (2.20-2.62) | 2.46 (2.29-2.65) | 1.73 (1.64-1.83) | 2.40 (2.27-2.53) |
| Day 366+             | 1.73 (1.51-1.99) | 1.61 (1.35-1.93) | 1.27 (0.95-1.70) | 1.73 (1.39-2.15) | 1.75 (1.47-2.08) | 1.21 (1.05-1.38) | 1.70 (1.48-1.95) |

Abbreviations: aIRR, adjusted incidence rate ratio; CI, confidence interval.

<sup>a</sup> excluding patients that died ≤90 days after first fracture.
<sup>b</sup> outcome defined as first fractures only.
<sup>c</sup> excluding patients that had dose or duration data imputed i.e., complete-case analysis.
<sup>d</sup> excluding patients with fractures identified in the CPRD database.
<sup>e</sup> excluding patients with cancer recorded (ever) in the CPRD and HES databases.
<sup>f</sup> 7-day duration for pre-exposure risk period.
<sup>g</sup> 28-day duration for pre-exposure risk period.
<sup>h</sup> adjusted for 1-year increments in age, 3-monthly intervals for season.

Notes: aIRRs for the pre-exposure risk period are based on the fracture rate in the 90-day period prior to, and including the first day of opioid exposure, compared to the baseline rate of fracture. Pre-exposure aIRRs are likely influenced by opioid prescribing in response to fracture, resulting in greater aIRRs when compared to the baseline risk period.
eFigure 5. Risk of fracture when exposed to opioids by anatomical site

- Spine (n=1,415)
- Chest (n=4,553)
- Low Back, Pelvis (n=3,455)
- Arm, Shoulder (n=15,961)
- Not Specified (n=15,207)
- Multiple (n=4,004)
- Hip (n=7,089)
- Leg, Ankle, Foot (n=14,113)
- Wrist, Hand (n=9,916)
- Head, Neck (n=4,335)

Adjusted\(^a\) incidence rate ratio (95% CI)\(^b\)

\(^a\) adjusted for 3-year increments in age and 3-monthly intervals for season.

\(^b\) values plotted on logarithmic scale.
eFigure 6. Comparison of aIRRs in primary analysis and after excluding fractures to spine, chest, low back and pelvis

(a) Includes all fracture sites
(b) Excludes fractures to spine, chest, low back and pelvis

Notes: black diamonds refer to aIRRs for the first exposure; hollow diamonds refer to aIRRs for subsequent exposure periods.

a adjusted for 1-year increments in age and 3-monthly intervals for season.
b values plotted on logarithmic scale.
eFigure 7. Risk of falls when exposed to opioids

(a) Includes individuals who also sustained fractures (n=58,774)
(b) Excludes individuals who sustained fractures (n=38,756)

Notes: black diamonds refer to aIRRs for the first exposure; hollow diamonds refer to aIRRs for subsequent exposure periods.

a adjusted for 1-year increments in age and 3-monthly intervals for season.
b values plotted on logarithmic scale.
References

[1] Centers for Medicare & Medicaid Services. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors, 2017.

[2] Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, Sharma S, Kolahdooz F, Straube S. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;10:Cd012509.

[3] Keats AS, Telford J, Kurosu Y. Studies of analgesic drugs: III. Dextromoramide and a comparison of methods of estimating pain relief in man. J Pharmacol Exp Ther 1960;130(2):212.

[4] National Health Service (NHS) Scotland. Scottish Palliative Care Guidelines, 2019.

[5] National Health Service (NHS) Wales. Opiate Conversion Doses, 2010.

[6] Pye SR, Sheppard T, Joseph RM, Lunt M, Girard N, Haas JS, Bates DW, Buckeridge DL, van Staa TP, Tamblyn R, Dixon WG. Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. Pharmacoepidemiol Drug Saf 2018;27(7):781-788.

[7] Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliat Med 2011;25(7):725-732.