Trends in opioid use following balloon kyphoplasty or vertebroplasty for the treatment of vertebral compression fractures

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Received: 1 March 2021 / Accepted: 18 September 2021 / Published online: 2 November 2021
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Abstract

Summary This retrospective analysis of insurance claims evaluated real-world trends in prescription fills among patients treated with balloon kyphoplasty (N = 6,656) or vertebroplasty (N = 2,189) following diagnosis of vertebral compression fracture. Among those with evidence of opioid use, nearly half of patients discontinued or reduced prescription fills relative to pre-operative levels.

Introduction Vertebral compression fractures (VCF) are associated with debilitating pain, spinal misalignment, increased mortality, and increased healthcare-resource utilization in elderly patients. This study evaluated the effect of balloon kyphoplasty (BKP) or vertebroplasty (VP) on post-procedure opioid prescription fills and payer costs in patients with VCF.

Methods This was a retrospective analysis of a large, nationally representative insurance-claims database. Clinical characteristics, opioid prescription patterns, and payer costs for subjects who underwent either BKP or VP to treat VCF were evaluated beginning 6 months prior to surgery through 7-month follow-up that included a 30-day, postoperative medication washout. Patient demographics, changes in opioid utilization, and payer costs were analyzed.

Results A total of 8,845 patients met eligibility criteria (75.3% BKP and 24.7% VP) with a mean of age 77 and 74% female. Among the 75% of patients who used opioids, 48.7% of patients discontinued opioid medication and 8.4% reduced prescription fills versus preoperative baseline. Patients who reduced or discontinued prescriptions exhibited a decrease in all-cause payer costs relative to pre-intervention levels, which was a significantly greater change relative to patients with no change, increase, or new start of opioids.

Conclusions Intervenotional treatment for VCF was associated with decreased or discontinued opioid prescription fills and reduced payer costs in follow-up in a significant proportion of the study population. Reduction of opioid-based harms may represent a previously unrecognized benefit of vertebral augmentation for VCF, especially in this elderly and medically fragile population.

Keywords Balloon kyphoplasty · Vertebroplasty · Vertebral compression fractures · Opioids

Abbreviations

BKP Balloon kyphoplasty
CCI Charlson Comorbidity Index
CMM Conservative medical management
CPT ICD-9-CM and ICD-10-CM
ICD-9-CM and ICD-10-CM
ICD-9-CM and ICD-10-CM
ICD-9-CM and ICD-10-CM
National Drug Codes
MME Morphine milligram equivalents
NDC Vertebral compression fractures
VP Vertebral compression fractures

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Introduction

An estimated 1.5 million vertebral compression fractures (VCF) occur in the USA every year [1]. Whether as a result of osteoporosis or metastatic disease within the vertebral column, VCFs may cause disabling pain and can precipitate a progressive cascade of deformity, disability, and mortality that, in addition to the quality of life detriment, also place enormous burden on healthcare resources [2–6].

Treatment approaches for VCF include conservative medical management (CMM), consisting of analgesia, bracing, bed rest, and physical therapy or percutaneous image-guided vertebral augmentation procedures such as balloon kyphoplasty (BKP) and vertebroplasty (VP). Because VCF patients are typically elderly and medically fragile, the tradeoffs between CMM and interventional approaches are not necessarily straightforward. For example, while evidence has suggested that vertebral augmentation procedures are effective in improving patient-reported pain, quality of life, and resource utilization compared to CMM [7–15], interventional treatment is not without its own set of risks and incremental costs [16, 17]. Therefore, evidence from a broader set of outcome measures would be useful to better inform the risk-benefit analysis for these patients.

One important yet infrequently collected outcome measure in this population is patient utilization of opioid analgesics for VCF-associated pain. VCF patients treated with CMM are often prescribed a short-term regimen to treat pain during the acute VCF episode, followed by a low maintenance dose as needed to manage ongoing pain [18–21]. By way of comparison, patients with chronic back pain or cancer pain are sometimes prescribed many times that amount—as much as 90 daily morphine milligram equivalents (MME) or more as their duration of pain progresses [22, 23]. Because opioid regimens less than 20 MME daily are associated with much lower risk of opioid overdose [22], the contrast may explain why opioid utilization after VCF has not garnered significant attention as an outcome of interest. Nevertheless, even low-dose opioid use is associated with negative outcomes in elderly populations [24–28], and therefore it is of interest to know whether interventional treatments like BKP and VP can mitigate not just pain itself, but also opioid use in VCF patients. As a measure that can serve as a proxy not just for pain relief but also for opioid-associated morbidity, a study of patterns of opioid utilization before and after vertebral augmentation may provide insights to inform risk and benefit assessments of interventional treatment versus CMM.

To our knowledge, the effect of interventional treatments for VCF on opioid utilization patterns has not been formally investigated as a primary outcome. The present study was designed to evaluate how patterns in opioid utilization change among VCF patients after treatment with BKP or VP.

Methods

Data source

The source of data for this retrospective analysis was the IBM MarketScan® research database, 2008–2018 (IBM Watson Health, Armonk, New York). This database contains de-identified encounter information, inpatient and outpatient medical and pharmacy claims, demographic data, and health-plan enrollment information from more than 135 million patients covered by commercial or Medicare Advantage insurance.

Ethics statement

The database is a de-identified, HIPAA compliant, closed system of administrative claims. Therefore, this study did not require approval by an Institutional Review Board.

Patient selection

All codes used for patient selection and data collection are summarized in Appendix 1 Table 4. These include International Statistical Classification of Diseases (ICD-9-CM and ICD-10-CM) diagnosis and procedure codes, Current Procedural Terminology (CPT) procedure codes, and medication National Drug Codes (NDC).

All patients age 18 or older with a diagnosis code for pathologic VCF (i.e., non-traumatic) and a procedure code for either BKP or VP were identified, within a timeframe that allowed for a 6-month pre-surgical baseline and maximum 7-month follow-up for all patients. Patients were required to have continuous health-plan enrollment during the 12-month period before the index date. Continuous health-plan enrollment was not required during the follow-up period due to the elevated risk of death in this patient population [7, 29], with follow-up ending at the earlier of either health plan disenrollment or 7 months post-procedure, whichever occurred first. Date of death was not available in this dataset; therefore, we assumed that in this elderly population, disenrollment was likely due to death and, consequently, end of follow-up at time of disenrollment.

Patients were excluded from analysis if they underwent both a BKP and a VP procedure during the initial (index) procedure visit, or if they had subsequent BKP or VP procedure(s) performed during follow-up. Because total healthcare utilization for pain management in the setting of
cancer is high [30, 31], VCF patients with any diagnosis of active cancer, defined as one inpatient or two outpatient visits with a diagnosis code for cancer at any time during the study period, were also excluded.

To increase the likelihood that opioids prescribed were related to the acute VCF event, rather than for management of unrelated, chronic condition(s), patients with one or more opioid prescription fills during the 6 months prior to the baseline period (i.e., months 12 to 7 prior to intervention) were excluded from analyses. Additionally, those with formal diagnosis of opioid use disorder or opioid dependence at any point in the year prior to intervention were excluded.

Despite attempts to include a matched CMM comparator cohort by applying propensity-score matching models, opioid prescription fills at baseline remained higher in the intervention cohorts relative to CMM, potentially because patient perception of pain intensity was not available within the administrative claims data. Therefore, we included a 6-month baseline, with data collected prior to surgical intervention, which provided an internal means of comparison.

**Study period**

For each patient, the index date for analysis was defined as the admission date for the visit during which a BKP or VP procedure was performed (Supplemental Figure S1). The baseline period was defined as the 6 months through 1 day prior to the index date. A 1-month washout period was applied from the date of the index procedure through 1 month after discharge in order to exclude opioid prescriptions related to post-surgical pain from the procedure itself, but not from the VCF event. The post-washout follow-up time period was defined as months 1 to 7 after surgical discharge, with this time period used for opioid and cost-related study measures.

**Study measures**

**Patient demographics and baseline clinical characteristics**

Patient age, sex, and geographic region were summarized. Clinical characteristics included the Charlson Comorbidity Index (CCI) score [32] and history of specific comorbidities (osteopenia, osteoporosis, chronic pain) at baseline. Because specific date of fracture was not available, the date of first observed diagnosis of VCF in claims data was used as a proxy. The number of days from first diagnosis to procedure admission date was summarized.

**Characterization of daily opioids prescribed**

Because the available data could not be used to determine actual consumption of prescribed opioids, prescription fills were used as a surrogate measure for opioid utilization. Number of days treated with prescription opioids was calculated from pharmacy claims that included the prescription NDC, strength, units, and days’ supply. In the scenario of overlapping days’ supply from multiple prescriptions, the treated day was counted once. Average daily opioids prescribed were expressed in MMEs using published CDC conversion factors for converting opioid medication strengths to oral MME (Appendix 2 Table 5).

In order to facilitate a more granular analysis of opioid utilization, patients were assigned to four, mutually exclusive categories that were stratified according to level of daily MME based upon a patients’ prescriptions: none (no opioid prescriptions filled), low (< 2 mg/day), moderate (2 to < 7 mg/day), and high (≥ 7 mg/day). This stratification scheme was developed based on a combination of authors’ clinical experience with typical dosing for patients with acute VCF-related pain and the distribution of MME in prescription fills observed in the study population.

Average daily MME in patient prescription fills and the number of opioid treatment days were summarized at 2-month intervals both in the baseline and post-washout follow-up periods. These intervals were selected to reduce the effect of monthly fluctuations due to overlapping prescription fills or gaps between fills. Results were also stratified by opioid prescription category.

**Opioid utilization trends**

The effect of surgical intervention on levels of daily opioids prescribed was characterized by comparing patients’ prescription category in baseline against their opioid prescription category after the index procedure admission and washout period. Changes in prescription category were then analyzed according to the opioid utilization trends defined in Table 1.

To determine the potential impact of the 1-month washout period on the results, a sensitivity analysis was performed in which the change in opioid utilization trend was calculated based on data from the 6 months immediately following the discharge date of the index admission.

**Logistic regression analysis of baseline characteristics**

Baseline demographic and clinical characteristics were analyzed in a logistic regression model to determine if any of the factors were significantly associated with reduction or discontinuation of opioid prescription fills after a BKP or VP procedure. Covariates analyzed were age, sex, census region, CCI score, history of diagnosed osteopenia or osteoporosis, opioid overdose, and presence of baseline non-opioid medication use (muscle relaxants or anticonvulsants).
Payer costs, baseline versus follow-up

Generalized linear models were applied to evaluate the adjusted impact of opioid utilization trends (i.e., changes in opioid prescription category) after BKP and VP procedures on all-cause healthcare costs, controlling for age, gender, census region, CCI score, history of diagnosed osteopenia or osteoporosis, and prescription fills for non-opioid medications (muscle relaxants and anticonvulsants). Models were calculated with a Gaussian distribution and identity link function.

Statistical analyses

Sample selection, creation of analytic variables, significance testing, and regression analyses were performed using the Instant Health Data (IHD) platform (Panalgo, Boston, MA) and R software version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Mean, median, and standard deviation (SD) were used to summarize continuous measures and proportions to summarize categories. Statistical significance testing across patient subgroups was tested by one-way ANOVA for continuous variables and Pearson’s Chi-squared test for categorical variables. When baseline and follow-up opioid prescription categories were compared, the paired t test was used for continuous variables and McNemar’s Chi-square test was used for categorical variables.

Results

Demographic and clinical characteristics

After all inclusion and exclusion criteria were applied, 8,845 patients were available for analysis. Of those, 75.3% underwent BKP and 24.7% underwent VP (Supplemental Figure S2). All index procedures took place between 1/1/2009 and 04/30/2018.

Patient demographics and baseline characteristics, stratified by opioid prescription category, are summarized in Table 2. Overall, mean ± SD age of patients in this study was 77 ± 12, with the majority female (73.8%). Prevalence of muscle relaxant prescription fills slightly decreased from baseline (23.4%) to follow-up (22.0%), \( P = .0016 \), while prevalence of a muscle relaxant prescription fill showed a larger decline from baseline (24.9%) to follow-up (9.3%), \( P < .001 \).

During the baseline period, older patients (age ≥ 65) were more likely belong to the “none” or “low” opioid prescription-fill categories, while younger patients were more likely to be identified as filling prescriptions for opioids at higher levels (Table 2). Comorbidity burden, as measured by the CCI score, was significantly different among the four opioid prescription categories (\( p \) value < 0.0001). Patients with one or more comorbidities were more likely to be prescribed opioids during the baseline period than patients with no comorbidities. A higher proportion of patients in the moderate and high-prescription categories had a history of diagnosed osteopenia or osteoporosis, or a chronic pain disorder. “Moderate” and “high” levels of opioid prescriptions filled were associated with longer median times from first VCF diagnosis to surgical treatment compared to “none” or “low” opioid prescriptions filled (Table 2).

Opioid prescription fills before and after vertebral augmentation procedures

During the study, 25.0% of vertebral augmentation patients showed no evidence of any opioid prescription fill at any time in baseline or follow-up. These patients were by definition excluded from analyses of prescription-fill trends in Figs. 1 and 2 and the logistic regression analysis shown in Table 3.

The overall median (interquartile range; IQR) number of baseline opioid prescription treated days was 15 (IQR: 7–30). During the post-washout, follow-up period, the overall median (IQR) number of treated days that subjects were prescribed opioids was 30 (IQR: 10–64). Overall median (IQR) daily MME prescribed during baseline was 2.4 mg/day (1.0–5.3). During the post-washout, follow-up period,
The overall median daily MME prescribed was 4.1 mg/day (IQR: 1.6–9.7).

The distribution of patients among each of the four opioid prescription categories before and after vertebral augmentation and the differences in distribution between baseline and the post-washout period are shown in Fig. 1.

### Trends in opioid prescription fills after vertebral augmentation

When evaluating specific opioid utilization trends, 57.1% of patients with any baseline opioid use decreased or discontinued opioid prescription fills post-washout follow-up (Fig. 2). Some patients experienced an increase in opioid prescription fills after vertebral augmentation (13.9%) or newly started an opioid prescription (10.9%) in follow-up (Fig. 2).

The average number of treated days within each 2-month time window prior to and following intervention is depicted in Fig. 2A. Among the 48.7% who discontinued opioid prescription fills, the average number of treated days in the 2 months prior to surgery was 22.1 days versus 9.7 in the 2 months post-washout. Trends in average daily MME were similarly analyzed in 2-month intervals (Fig. 2B). Opioid daily dose increased during the baseline period, peaking in the 2-month period before the index procedure, which by definition included the initial VCF fracture event for the majority of patients (average time from diagnosis to surgery of 23 days). Among those who discontinued opioid prescription fills in follow-up, the average daily MME in the two months prior to surgery was 7.2 mg/day, decreasing to zero in follow-up (by definition of discontinuation).

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**Table 2** Demographics and baseline clinical characteristics*

| Baseline opioid consumption category | Overall | None | Low | Moderate | High | p value |
|-------------------------------------|---------|------|-----|----------|------|---------|
| Sample size, N                      | 8,845   | 2,941| 2,581| 2,263    | 1,060|         |
| Age, y                              |         |      |     |          |      |         |
| Mean                                | 77      | 78.1 | 78.1| 75.9     | 73.3 | < 0.0001|
| SD                                  | 12      | 12.4 | 11.4| 11.5     | 12.3 |         |
| Age group, %                        | 80      | 81   | 81  | 78       | 76   |         |
| 18–64 y                             | 18.5%   | 17.4%| 15.0%| 19.9%    | 26.9%| < 0.0001|
| ≥ 65 y                              | 81.5%   | 82.6%| 85.0%| 80.1%    | 73.1%|         |
| Female, %                           | 73.8%   | 73.5%| 75.0%| 74.5%    | 70.4%| 0.0231  |
| Region, %                           |         |      |     |          |      |         |
| Northeast                           | 11.8%   | 12.4%| 10.6%| 11.3%    | 14.2%| 0.0001  |
| South                               | 37.4%   | 35.1%| 40.0%| 37.2%    | 38.3%|         |
| West                                | 11.7%   | 10.9%| 11.7%| 11.6%    | 14.2%|         |
| Midwest                             | 38.0%   | 40.8%| 36.7%| 38.4%    | 32.5%|         |
| Missing                             | 1.1%    | 0.8% | 1.0% | 1.5%     | 0.9% |         |
| CCI score, %                        |         |      |     |          |      |         |
| 0                                   | 58.6%   | 62.5%| 59.9%| 54.9%    | 52.1%| < 0.0001|
| 1                                   | 20.3%   | 17.7%| 20.1%| 22.9%    | 22.5%|         |
| ≥ 2                                 | 21.1%   | 19.8%| 20.0%| 22.1%    | 25.5%|         |
| Baseline diagnoses, %               |         |      |     |          |      |         |
| Osteopenia                          | 11.9%   | 8.6% | 11.4%| 14.6%    | 16.4%| < 0.0001|
| Osteoporosis                        | 30.7%   | 22.6%| 30.1%| 36.9%    | 41.4%| < 0.0001|
| Chronic pain disorder               | 4.1%    | 2.6% | 3.5% | 4.7%     | 8.4% | < 0.0001|

Time from first observed VCF diagnosis to index surgery admission, days

| Mean pounding | 22.2 | 17.7 | 17.1 | 25.9 | 39.2 | < 0.0001 |
| SD           | 43.6 | 48.2 | 36.6 | 41.2 | 46.1 |         |
| Median       | 7.0  | 1    | 6    | 13   | 22.5 |         |
| IQR          | 1–23 | 1–12 | 1–16 | 3–29 | 7–55.3|         |

*Source: MDT Truven CCAE/MDCR 2008–2018

*Note: Stratifications to define historic opioid use: (A) (0 < X < 2 mg/day), moderate (2 ≤ X < 7 mg/day), (X ≥ 7 mg/day)

*p value calculated across baseline opioid use categories: Pearson’s Chi-square test for categorical measures and one-way ANOVA for continuous measures
A sensitivity analysis was performed to test the robustness of the opioid status change in the absence of applying the 1-month post-surgical washout period. When opioid prescription-fill data from the 30 days immediately following vertebral augmentation were included in the analysis, the proportion of patients categorized to the “increased,” “new start,” “same,” “decreased,” “discontinued,” or “same” opioid groups varied from −1.8% to +0.7% vs. the core analysis including a 1-month washout.

A second sensitivity analysis was completed to test the affect of including all years available in the data source (2008–2018) used in our main analysis versus only more recent years (2015–2018). Overall, the proportion of patients categorized into each opioid use group changed minimally, ranging from −2.3% to +1.0% different across the two time periods.

Covariates associated with trends in opioid prescription fills

A multivariate logistic regression analysis was performed to identify factors associated with changes in opioid prescription fills after vertebral augmentation procedures (Table 3). Factors associated with decreased or discontinued opioid prescription fills after vertebral augmentation were older age (65 or older), baseline diagnosis of osteoporosis, and baseline use of muscle relaxants. Conversely, presence of more comorbidities, as measured by higher CCI score, was associated with increased opioid prescription fills after vertebral augmentation.

Association between trends in opioid prescription fills and all-cause payer costs

Average all-cause payer costs, adjusted for patient demographic and clinical factors, were compared between the baseline and follow-up periods (Fig. 3). Patients who underwent vertebral augmentation and who maintained, increased, or started new opioid prescription fills after the procedure incurred greater average all-cause payer costs in the follow-up period than in baseline (+$160), whereas patients who decreased or discontinued opioid prescription fills incurred significantly reduced average all-cause payer costs compared to baseline (−$6,759; $P < .0001 across opioid utilization groups).

Discussion

This retrospective analysis of commercial-claims data evaluated the effect of vertebral augmentation (either BKP or VP) on fills of opioid prescriptions—as a surrogate measure for opioid utilization—in patients with VCF. Trends in opioid prescription fills were evaluated in the 7 months after intervention, less a 1-month, post-procedure washout period, relative to use in the 6 months prior to surgical intervention. Overall, 57.1% of patients...
discontinued or reduced prescription fills within 7 months after vertebral augmentation versus preoperative baseline levels.

Our observations are consistent with prior evidence that opioid use decreases after either a BKP or VP procedure. Two previous clinical trials comparing VP to CMM found that fewer patients treated with VP were using opioid medications at up to 12-month follow-up compared to patients treated with CMM [33, 34]. A randomized controlled trial comparing BKP to CMM found a statistically significant reduction in opioid use in BKP patients after 6 months, although this difference was no longer observed at 12 or 24 months [35]. Additionally, a multi-center trial comparing BKP to VP showed that the percentage of patients treated with opioids was significantly reduced at the 6-month follow-up relative to baseline in both cohorts, although the difference between patients in the two treatment cohorts was not significant [36].

These studies drew their conclusions from small study populations—usually less than 200 patients—and clinical trials that were not necessarily designed or powered with changes in opioid use as a primary outcome. Therefore, the present study is unique in that it evaluates the impact of these procedures on opioid prescription fills as a primary outcome, using a larger, real-world study population.

The average baseline daily MME was approximately 5 mg/day, with an average of 22 treated days. This represents a relatively low-dose opioid regimen compared to patients being treated for chronic back pain and is not a level most commonly associated with the current epidemic of persistent opioid use and opioid-use disorders [37]. However, it is notable that patients in this analysis were elderly, with an average age of 77 years.

Opioids are one of the most effective ways to manage short-term pain, but in the elderly they are associated with enhanced risk of adverse events due to changes in...
physiology, drug metabolism, and elimination associated with aging, even at low doses [25]. The side effects include constipation, nausea, urinary retention, respiratory depression, balance dysregulation, elevated fall risk, and changes in mental status [25, 27, 28]. Notably, opioid use longer than 12 weeks in geriatric patients is associated with an 80% increase in opioid-associated adverse reactions compared to shorter duration of use [26]. For these reasons, the American

**Table 3** Logistic regression: factors associated with avg daily MME dose reduction to a lower dose category or opioid discontinuation (conditional upon any opioid prescription fill in baseline or follow-up)

| Variable | Odds ratio | Lower CI | Upper CI | Pr(>|z|) |
|----------|------------|----------|----------|---------|
| (Intercept) | 0.0615 | | | |
| Age group: 65 and up | 1.15 | 1.01 | 1.31 | 0.0364 |
| Gender: Male | 1.09 | 0.97 | 1.22 | 0.1391 |
| Charlson Score Group: 1 | 0.8 | 0.71 | 0.91 | 0.0005 |
| Charlson Score Group: 2+ | 0.82 | 0.73 | 0.93 | 0.0025 |
| Region: South | 0.98 | 0.83 | 1.15 | 0.7892 |
| Region: West | 1.07 | 0.87 | 1.31 | 0.5314 |
| Region: Midwest | 1.02 | 0.86 | 1.2 | 0.8305 |
| Region: Missing | 1.37 | 0.83 | 2.27 | 0.2232 |
| Baseline Diagnosis Osteopenia | 1.11 | 0.95 | 1.29 | 0.1806 |
| Baseline Diagnosis Osteoporosis | 1.37 | 1.23 | 1.53 | < 0.0001 |
| Days from VCF to Surgery Group: 8–14 | 1.62 | 1.4 | 1.88 | < 0.0001 |
| Days from VCF to Surgery Group: 15–21 | 1.86 | 1.56 | 2.23 | < 0.0001 |
| Days from VCF to Surgery Group: 22–27 | 1.62 | 1.28 | 2.04 | < 0.0001 |
| Days from VCF to Surgery Group: 28+ | 1.59 | 1.4 | 1.81 | < 0.0001 |
| Baseline Anticonvulsants Prescription | 0.92 | 0.82 | 1.03 | 0.1302 |
| Baseline Muscle Relaxant Prescription | 1.26 | 1.13 | 1.41 | < 0.0001 |

*Source:* MDT Truven CCAE/MDCR 2008–2018

Logistic regression was performed to identify risk factors

![Fig. 3](image-url) Difference in adjusted all-cause payer costs in follow-up versus baseline, stratified by opioid prescription trend after a vertebral augmentation procedure. Opioid prescription fills during the washout period was excluded from analysis. Subjects with no evidence of opioid prescription fills during study period were also excluded.
Geriatric Society 2009 guidelines for management of persistent pain in older adults recommend initiating opiates at the lowest dose possible, approximately 25–50% of the adult recommended dose [24, 25, 38].

Even when doses are low, reducing, tapering, and discontinuing opioid regimens as much as possible helps to minimize adverse events and has a positive impact on the overall mental and physical well-being of elderly patients [27, 39]. This phenomenon may happen naturally; it has been shown previously that rates of opioid discontinuation among the elderly are as high as 25% due to poorly tolerated side effects [40]. This rate is consistent with our finding that age greater than 65 years was associated with opioid decrease or discontinuation after a vertebral augmentation procedure. Taking all of these considerations together, we believe it was clinically meaningful to track changes in prescription fills after vertebral augmentation procedures even if the magnitude of the dosage changes were minor.

Given the adverse effects of opioid use among an elderly, medically fragile population such as patients with VCF, the economic impact is likely to be multi-fold. We examined the effect of changes in opioid prescription fills after vertebral augmentation on total healthcare costs from the payer perspective, adjusted for potentially confounding factors such as age, gender, comorbidity status, and presence of historic non-opioid medication use. Our results suggest that decreased or discontinued fills of opioid prescriptions after vertebral augmentation procedures were associated with greater reduction in all-cause healthcare costs (vs pre-surgical costs) relative to patients who did not change, increased, or newly started opioids after surgery. Given the retrospective nature of our analysis, this result only implies correlation, with many unobservable factors in retrospective claims impacting all-cause payer costs beyond opioid prescription patterns.

Finally, an important observation of this study is that the trends in opioid prescription fills were similar in both the BKP and VP cohorts. This finding is not surprising given the difference in radiographic outcomes by approach may not be enough to vary pain outcomes—and therefore the need for opioid analgesics—across the two surgical approaches.

Study limitations

This study has a number of limitations due to its nature as a retrospective analysis from a predefined database of medical claims. Foremost, it was not possible to evaluate patient consumption of opioids directly, and instead we had to use prescription fills as a surrogate measure for opioid consumption. Patients who fill an opioid prescription may or may not consume all medication for a variety of reasons, and it was not possible to account for actual usage. Patient-reported pain scores and functional status were not available, precluding a direct analysis of the effects of BKP or VP procedures on pain relief. The study was also not able to control for how other chronic, non-VCF conditions influenced patients’ choice to fill opioid prescriptions.

Additionally, available data were limited to prescription medications filled and paid for by the patient’s insurance plan. Cash or self-pay options for prescription medications were not collected in this dataset. Therefore, our estimates of opioid prescription fills may have been affected if patients with insurance chose to pay out of pocket for their prescriptions. Our estimates were also sensitive to miscoding of pharmacy claims data for days’ supply, quantity, strength, and number of units.

It is possible that some of the prescription behavior observed in this analysis is that of the physicians and not necessarily the patients. Often prescriptions are written by the physician to have pro re nata, which may affect our conclusions if the patients did not actually consume them. Future research would be needed to understand prescribing behavior.

Finally, we were unable to include a control cohort of patients treated with CMM. Despite multiple attempts to apply propensity-score matching models, baseline opioid prescription fills remained higher in the intervention cohorts relative to CMM. We assumed that the most important confounding patient characteristic of pain intensity, which is not available in administrative claims, was driving these results and therefore the inability to select an appropriately match CMM comparator. In any case, the 6-month baseline, with data collected prior to surgical intervention, was designed to mitigate this limitation by providing a within-patient comparison as opposed to comparison to a CMM group.

Conclusions

This study showed that VCF patients who underwent vertebral augmentation, including balloon kyphoplasty or vertebroplasty procedures, significantly changed their patterns of opioid prescription fills following surgical intervention with corresponding decreases in all-cause post-surgical payer costs compared to baseline costs. Considering the known clinical risks of unaddressed VCF, the benefits of minimizing opioid use in the elderly, and the economic benefit of reducing all-cause payer costs, our findings add to the argument favoring vertebral augmentation—whether BKP or VP—over CMM as a treatment strategy to address VCF.
## Appendix 1

### Table 4 Codes list for patient selection

| Inclusion/exclusion | Code     | Description                                                                 |
|---------------------|----------|-----------------------------------------------------------------------------|
| BKP                 | 0PS43ZZ  | Reposition Thoracic Vertebra, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 0QS03ZZ  | Reposition Lumbar Vertebra, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 0QS13ZZ  | Reposition Sacrum, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 0PU43JZ  | Supplement Thoracic Vertebra with Synthetic Substitute, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 0QU03JZ  | Supplement Lumbar Vertebra with Synthetic Substitute, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 0QU13JZ  | Supplement Sacrum with Synthetic Substitute, Percutaneous Approach (requires reposition AND supplement ICD10s to be BKP) |
|                     | 22513    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (e.g., kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; thoracic |
|                     | 22514    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (e.g., kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; lumbar |
|                     | 22515    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (e.g., kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; each additional thoracic or lumbar vertebral body (List separately in addition to code for primary procedure) |
|                     | 22523    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device, 1 vertebral body, unilateral or bilateral cannulation (e.g., kyphoplasty); thoracic |
|                     | 22524    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device, 1 vertebral body, unilateral or bilateral cannulation (e.g., kyphoplasty); lumbar |
|                     | 22525    | Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device, 1 vertebral body, unilateral or bilateral cannulation (e.g., kyphoplasty); each additional thoracic or lumbar vertebral body (List separately in addition to code for primary procedure) |
|                     | 81.66    | Percutaneous vertebral augmentation |
| VP                  | 0PU43JZ  | Supplement Thoracic Vertebra with Synthetic Substitute, Percutaneous Approach (requires NO reposition ICD10 be VP) |
|                     | 0QU03JZ  | Supplement Thoracic Vertebra with Synthetic Substitute, Percutaneous Approach (requires NO reposition ICD10 be VP) |
|                     | 0QU13JZ  | Supplement Thoracic Vertebra with Synthetic Substitute, Percutaneous Approach (requires NO reposition ICD10 be VP) |
|                     | 22510    | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; cervicothoracic |
|                     | 22511    | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; lumbosacral |
|                     | 22512    | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; each additional cervicothoracic or lumbosacral vertebral body (List separately in addition to code for primary procedure) |
|                     | 22520    | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection; thoracic |
|                     | 22521    | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection; lumbar |
### Inclusion/exclusion

| Code | Description |
|------|-------------|
| 22522 | Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection; each additional thoracic or lumbar vertebral body (List separately in addition to code for primary procedure) |
| 81.65 | Percutaneous vertebroplasty |

**Pathologic VCF**

| Code | Description |
|------|-------------|
| M80.08XA | Age-related osteoporosis with current pathological fracture, vertebra(e), initial encounter for fracture |
| M80.88XA | Other osteoporosis with current pathological fracture, vertebra(e), initial encounter for fracture |
| 733.13 | Pathologic fracture of vertebrae |

**Neoplasm fracture**

| Code | Description |
|------|-------------|
| M84.50XA-M84.58XS | Pathological fracture in neoplastic disease |

**History opioid abuse/dependence**

| Code | Description |
|------|-------------|
| 965.00 | Poisoning by opium (alkaloids), unspecified |
| 965.01 | Poisoning by heroin |
| 965.02 | Poisoning by methadone |
| 965.09 | Poisoning by other opiates and related narcotics |
| 970.1 | Poisoning by opiate antagonists |
| E850.0 | Accidental poisoning by heroin |
| E850.1 | Accidental poisoning by methadone |
| E850.2 | Accidental poisoning by other opiates and related narcotics |
| E935.0 | Heroin causing adverse effects in therapeutic use |
| E935.1 | Methadone causing adverse effects in therapeutic use |
| E935.2 | Other opiates and related narcotics causing adverse effects in therapeutic use |
| E940.1 | Opiate antagonists causing adverse effects in therapeutic use |
| T40.0X1A | Poisoning by opium, accidental (unintentional), initial encounter |
| T40.0X2A | Poisoning by opium, intentional self-harm, initial encounter |
| T40.0X4A | Poisoning by opium, undetermined, initial encounter |
| T40.1X1A | Poisoning by heroin, accidental (unintentional), initial encounter |
| T40.1X2A | Poisoning by heroin, intentional self-harm, initial encounter |
| T40.1X4A | Poisoning by heroin, undetermined, initial encounter |
| T40.2X1A | Poisoning by other opioids, accidental (unintentional), initial encounter |
| T40.2X2A | Poisoning by other opioids, intentional self-harm, initial encounter |
| T40.2X4A | Poisoning by other opioids, undetermined, initial encounter |
| T40.3X1A | Poisoning by methadone, accidental (unintentional), initial encounter |
| T40.3X2A | Poisoning by methadone, intentional self-harm, initial encounter |
| T40.3X4A | Poisoning by methadone, undetermined, initial encounter |
| T40.4X1A | Poisoning by other synthetic narcotics, accidental (unintentional), initial encounter |
| T40.4X2A | Poisoning by other synthetic narcotics, intentional self-harm, initial encounter |
| T40.4X4A | Poisoning by other synthetic narcotics, undetermined, initial encounter |
| T40.601A | Poisoning by unspecified narcotics, accidental (unintentional), initial encounter |
| T40.602A | Poisoning by unspecified narcotics, intentional self-harm, initial encounter |
| T40.604A | Poisoning by unspecified narcotics, undetermined, initial encounter |
| T40.691A | Poisoning by other narcotics, accidental (unintentional), initial encounter |
| T40.692A | Poisoning by other narcotics, intentional self-harm, initial encounter |
| T40.694A | Poisoning by other narcotics, undetermined, initial encounter |
| T50.7X1A | Poisoning by analeptics and opioid receptor antagonists, accidental (unintentional), initial encounter |
| T50.7X2A | Poisoning by analeptics and opioid receptor antagonists, intentional self-harm, initial encounter |
| T50.7X4A | Poisoning by analeptics and opioid receptor antagonists, undetermined, initial encounter |
| 305.50 | Opioid abuse, unspecified |
| 305.51 | Opioid abuse, continuous |
| Inclusion/exclusion | Code     | Description                                                      |
|---------------------|----------|------------------------------------------------------------------|
|                     | 305.52   | Opioid abuse, episodic                                           |
|                     | 305.53   | Opioid abuse, in remission                                       |
|                     | F11.10   | Opioid abuse, uncomplicated                                      |
|                     | F11.11   | Opioid abuse, in remission                                       |
|                     | F11.120  | Opioid abuse with intoxication, uncomplicated                    |
|                     | F11.121  | Opioid abuse with intoxication delirium                          |
|                     | F11.122  | Opioid abuse with intoxication with perceptual disturbance       |
|                     | F11.129  | Opioid abuse with intoxication, unspecified                      |
|                     | F11.14   | Opioid abuse with opioid-induced mood disorder                   |
|                     | F11.150  | Opioid abuse with opioid-induced psychotic disorder with delusions|
|                     | F11.151  | Opioid abuse with opioid-induced psychotic disorder with hallucinations|
|                     | F11.159  | Opioid abuse with opioid-induced psychotic disorder, unspecified |
|                     | F11.181  | Opioid abuse with opioid-induced sexual dysfunction              |
|                     | F11.182  | Opioid abuse with opioid-induced sleep disorder                  |
|                     | F11.188  | Opioid abuse with other opioid-induced disorder                  |
|                     | F11.19   | Opioid abuse with unspecified opioid-induced disorder            |
|                     | 304.00   | Opioid type dependence, unspecified                              |
|                     | 304.01   | Opioid type dependence, continuous                               |
|                     | 304.02   | Opioid type dependence, episodic                                 |
|                     | 304.70   | Combinations of opioid type drug with any other drug dependence, unspecified|
|                     | 304.71   | Combinations of opioid type drug with any other drug dependence, continuous|
|                     | 304.72   | Combinations of opioid type drug with any other drug dependence, episodic|
|                     | F11.20   | Opioid dependence, uncomplicated                                 |
|                     | F11.21   | Opioid dependence, in remission                                  |
|                     | F11.220  | Opioid dependence with intoxication, uncomplicated               |
|                     | F11.221  | Opioid dependence with intoxication delirium                     |
|                     | F11.222  | Opioid dependence with intoxication with perceptual disturbance |
|                     | F11.229  | Opioid dependence with intoxication, unspecified                 |
|                     | F11.23   | Opioid dependence with withdrawal                                |
|                     | F11.24   | Opioid dependence with opioid-induced mood disorder              |
|                     | F11.250  | Opioid dependence with opioid-induced psychotic disorder with delusions|
|                     | F11.251  | Opioid dependence with opioid-induced psychotic disorder with hallucinations|
|                     | F11.259  | Opioid dependence with opioid-induced psychotic disorder, unspecified|
|                     | F11.281  | Opioid dependence with opioid-induced sexual dysfunction         |
|                     | F11.282  | Opioid dependence with opioid-induced sleep disorder             |
|                     | F11.288  | Opioid dependence with other opioid-induced disorder             |
|                     | F11.29   | Opioid dependence with unspecified opioid-induced disorder      |
|                     | F19.20   | Other psychoactive substance dependence, uncomplicated           |
## Appendix 2

### Table 5  Opioid conversion factors to MME

| Name                        | Strength | Conversion factor | Source                                                                 |
|-----------------------------|----------|-------------------|----------------------------------------------------------------------|
| Alfentanil sc               | mcg      | 30                | Palliative Care guidelines 2016                                      |
| Buprenorphine film          | mcg/hr   | 12.6              | CDC 2018 and CMS 2017 (footnote 4)                                   |
| Buprenorphine film, extended release | mcg/hr   | 12.6              | CDC 2018 and CMS 2017 (footnote 4)                                   |
| Buprenorphine tablet        | mg       | 30                | CMS 2017                                                             |
| Buprenorphine iv/sc         | mg/mL    | 33                | Buprenorphine label                                                   |
| Buprenorphine solution      | mg/mL    | 33                | Buprenorphine label                                                   |
| Buprenorphine powder        |          | N/A               | cannot assign conversion for powers (compounding)                    |
| Butorphanol iv/sc           | mg       | 7                 | CDC 2018                                                             |
| Butorphanol solution        | mg       | 7                 | CDC 2018                                                             |
| Butorphanol spray           | mg       | 7                 | CDC 2018                                                             |
| Codeine tablet              | mg       | 0.15              | CDC 2018                                                             |
| Codeine capsule             | mg       | 0.15              | CDC 2018                                                             |
| Codeine iv/sc               | mg       | 0.15              | CDC 2018                                                             |
| Codeine solution            | mg/day   | 0.15              | CDC 2018                                                             |
| Codeine liquid              | mg/day   | 0.15              | CDC 2018                                                             |
| Codeine suspension          | mg/day   | 0.15              | CDC 2018                                                             |
| Codeine powder              |          | N/A               | cannot assign conversion for powers (compounding)                    |
| Dezocine                    |          |                   | No longer commercially available (2011)                              |
| Fentanyl film or oral spray | mcg      | 0.18              | CDC 2018                                                             |
| Fentanyl film, extended release | mcg      | 0.18              | CDC 2018                                                             |
| Fentanyl film               | mcg      | 0.18              | CDC 2018                                                             |
| Fentanyl nasal spray        | mcg      | 0.16              | CDC 2018                                                             |
| Fentanyl spray              | mcg      | 0.16              | CDC 2018                                                             |
| Fentanyl patch              | mcg/hr   | 7.2               | CDC 2018 and CMS 2017 (footnote 8)                                   |
| Fentanyl tablet             | mcg      | 0.13              | CDC 2018                                                             |
| Fentanyl lozenge            | mcg      | 0.13              | CDC 2018                                                             |
| Fentanyl iv/sc              | mcg      | 0.13              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Fentanyl solution           | mcg      | 0.13              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Fentanyl solution, extended release | mcg     | 0.13              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Fentanyl powder             |          | N/A               | cannot assign conversion for powers (compounding)                    |
| Hydrocodone                 | mg       | 1                 | CDC 2018                                                             |
| Hydrocodone powder          | mg       | N/A               | cannot assign conversion for powers (compounding)                    |
| Hydrocodone capsule, extended release | mg | 1                 | CDC 2018                                                             |
| Hydrocodone tablet, extended release | mg | 1                 | CDC 2018                                                             |
| Hydrocodone tablet          | mg       | 1                 | CDC 2018                                                             |
| Hydrocodone capsule         | mg       | 1                 | CDC 2018                                                             |
| Hydrocodone elixir          | mg       | 1                 | CDC 2018                                                             |
| Hydrocodone liquid          | mg       | 1                 | CDC 2018                                                             |
| Hydrocodone solution        | mg       | 1                 | CDC 2018                                                             |
| Hydromorphone oral          | mg       | 4                 | CDC 2018                                                             |
| Hydromorphone capsule, extended release | mg | 4                 | CDC 2018                                                             |
| Hydromorphone tablet        | mg       | 4                 | CDC 2018                                                             |
| Hydromorphone tablet, extended release | mg | 4                 | CDC 2018                                                             |
| Hydromorphone iv/sc         | mg       | 4                 | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Hydromorphone solution      | mg       | 4                 | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Hydromorphone liquid        | mg       | 4                 | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Hydromorphone suppository   |          | N/A               | cannot assign conversion for powers (compounding)                    |
| Hydromorphone powder        |          | N/A               | cannot assign conversion for powers (compounding)                    |
| Name                                              | Strength | Conversion factor | Source                                                                 |
|---------------------------------------------------|----------|------------------|-----------------------------------------------------------------------|
| Hydromorphone powder, extended release            |          | N/A cannot assign conversion for powders (compounding)         |
| Levomethadyl acetate oral                        | mg       | 8                | CDC 2018                                                              |
| Levromethadyl acetate iv/sc                       | mg       | 8                | CDC 2018                                                              |
| Levoorphanol oral                                 | mg       | 11               | CDC 2018                                                              |
| Levoorphanol tablet                               | mg       | 11               | CDC 2018                                                              |
| Levoorphanol iv/sc                                | mg       | 11               | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Levoorphanol solution                            | mg       | 11               | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Levoorphanol powder                              |          | N/A cannot assign conversion for powders (compounding)         |
| Meperidine oral                                   | mg       | 0.1              | CDC 2018                                                              |
| Meperidine tablet                                 | mg       | 0.1              | CDC 2018                                                              |
| Meperidine capsule                                | mg       | 0.1              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Meperidine syrup                                  | mg       | 0.1              | CDC 2018                                                              |
| Meperidine iv/sc                                  | mg       | 0.1              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Meperidine solution                               | mg       | 0.1              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Meperidine powder                                |          | N/A cannot assign conversion for powders (compounding)         |
| Methadone tablet                                  | mg       | 3                | CDC 2018                                                              |
| Methadone tablet, dispersible                     | mg       | 3                | CDC 2018                                                              |
| Methadone concentrate                             | mg       | 3                | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Methadone solution                                | mg       | 3                | CDC 2018                                                              |
| Methadone powder                                  |          | 3                | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Methadone injectable solution                     | mg/mL    | 3                | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Morphine oral                                     | mg       | 1                | CDC 2018                                                              |
| Morphine capsule, extended release                | mg       | 1                | CDC 2018                                                              |
| Morphine tablet                                   | mg       | 1                | CDC 2018                                                              |
| Morphine tablet, extended release                 | mg       | 1                | CDC 2018                                                              |
| Morphine tablet, soluble                          | mg       | 1                | CDC 2018                                                              |
| Morphine rectal                                   | mg       | 1                | CDC 2018                                                              |
| Morphine suppository                              | mg       | 1                | CDC 2018                                                              |
| Morphine iv/sc                                    | mg/mL    | 1                | Assumption - consistent with other routes of administration in CDC 2018 for opioid class |
| Morphine solution                                 | mg/mL    | 1                | Assumption - consistent with other routes of administration in CDC 2018 for opioid class |
| Morphine Sulfate Immediate Release                | mg       | 1                |                                                                      |
| Morphine Sulfate Immediate Release                | mg/mL    | 1                |                                                                      |
| Morphine capsule                                  | mg       | 1                |                                                                      |
| Morphine liquid                                   | mg/mL    | 1                | Assumption - consistent with other routes of administration in CDC 2018 for opioid class |
| Morphine concentrate                              | mg/mL    | 1                | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Morphine powder                                   |          | N/A cannot assign conversion for powders (compounding)         |
| Morphine tincture                                 |          | N/A cannot assign conversion for powders (compounding)         |
| Morphine suppository                              | mg       | 1                |                                                                      |
| Morphine suspension, extended release             | mg/mL    | 1                |                                                                      |
| MS/S                                              | mg       | 1                |                                                                      |
| MSIR                                              | mg       | 1                |                                                                      |
| Nalbuphine                                        | mg/day   | 3                | Nielsen 2015                                                         |
| Nalbuphine solution                               | mg/day   | 3                | Nielsen 2015                                                         |
| Nalbuphine powder                                 |          | N/A cannot assign conversion for powders (compounding)         |
| Opium                                             | mg       | 1                | CDC 2018                                                              |
| Opium suppository                                 | mg       | 1                | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Oxycodone                                         | mg       | 1.5              | CDC 2018                                                              |
| Oxycodone capsule, extended release               | mg       | 1.5              | CDC 2018                                                              |
| Oxycodone capsule                                 | mg       | 1.5              | CDC 2018                                                              |
| Oxycodone tablet                                  | mg       | 1.5              | CDC 2018                                                              |
| Oxycodone tablet, extended release                | mg       | 1.5              | CDC 2018                                                              |
| Oxycodone concentrate                             | mg/mL    | 1.5              | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Oxycodone powder                                  |          | N/A cannot assign conversion for powders (compounding)         |
| Name                                | Strength | Conversion factor | Source                                                                 |
|-------------------------------------|----------|-------------------|------------------------------------------------------------------------|
| Oxycodon solution                   | mg/ml    | 1.5               | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Oxymorphone                         | mg       | 3                 | CDC 2018                                                              |
| Oxymorphone tablet                  | mg       | 3                 | CDC 2018                                                              |
| Oxymorphone tablet, extended release| mg       | 3                 | CDC 2018                                                              |
| Oxymorphone injectable solution     |          |                   | N/A cannot assign conversion for powers (compounding)                 |
| Oxymorphone suppository             | 3        |                   | Assumption — consistent with other routes of administration in CDC 2018 for opioid class |
| Pentazocine                         | mg       | 0.37              | CDC 2018                                                              |
| Pentazocine tablet                 | mg       | 0.37              | CDC 2018                                                              |
| Pentazocine solution               | mg       | 0.37              | CDC 2018                                                              |
| Propoxyphene capsule               | mg       | 0.23              | CDC 2018                                                              |
| Propoxyphene tablet                | mg       | 0.23              | CDC 2018                                                              |
| Remifentanil                       |          |                   |                                                                        |
| Pentazocine tablet                 | mg       | 0.37              | CDC 2018                                                              |
| Pentazocine solution               | mcg/day  | 2                 | ANZCA Opioid Dose Equivalence                                           |
| Tapentadol tablet                  | mg       | 0.4               | CDC 2018                                                              |
| Tapentadol tablet, extended release| mg       | 0.4               | CDC 2018                                                              |
| Tramadol capsule, extended release  | mg       | 0.1               | CDC 2018                                                              |
| Tramadol tablet                    | mg       | 0.1               | CDC 2018                                                              |
| Tramadol tablet, disintegrating     | mg       | 0.1               | CDC 2018                                                              |
| Tramadol tablet, extended release   | mg       | 0.1               | CDC 2018                                                              |

Conversion factor references:
CDC 2018: National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version. Atlanta
CDC 2018: National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version. Atlanta
Palliative Care Guidelines 2016: [http://book.pallcare.info/index.php?tid=125](http://book.pallcare.info/index.php?tid=125)
Buprenorphine label: [https://www.naabt.org/documents/buprenex_PI.pdf](https://www.naabt.org/documents/buprenex_PI.pdf)
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ANZCA Opioid Dose Equivalence: [http://fpm.anzca.edu.au/documents/opioid-dose-equivalence.pdf](http://fpm.anzca.edu.au/documents/opioid-dose-equivalence.pdf)
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-01613-3.

Acknowledgements The authors thank Jeanne McAdara PhD for professional medical writing assistance with manuscript preparation, which was funded by Medtronic. The authors maintained full freedom of investigation and control over manuscript development. Mohamed M. Alshammari and Min G.蚝声明他们已经收到了Osteoporosis International的许可，但他们没有将此论文的版权转让给Osteoporosis International。所有的作者都确认了他们在准备和修改此论文时的独立性。

Conflict of interest WN, CR, MQ, and NG are current or former employees of Medtronic. DJ has nothing to disclose; CIG declares that he has served on scientific advisory boards for Eli Lilly, Medtronic, Abbott, Saluda, Spine Biopharma, and Persica and has had research support paid directly to his department from Mainstay Medical and Solis Therapeutics; JAH declares that he is a consultant for Medtronic, on the DMC of Relievant and a grant recipient from the Neiman Health Policy Institute.

Author contribution WN, CR, MQ, CIG, and JAH designed the study; WN and CR performed the analysis; WN, CR, MQ, NG DJ, CIG, and JAH drafted the manuscript; WN, CR, MQ, NG DJ, CIG, and JAH provided critical review and feedback to the manuscript; all authors approved the final manuscript for submission.

Funding No funding was received related to the research presented in this manuscript. Professional assistance with manuscript preparation was funded by Medtronic Pain Therapies.

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