# Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization

## *A Population-based Study*

Stavros G. Memtsoudis, M.D., Ph.D., F.C.C.P., Jashvant Poeran, M.D., Ph.D., Nicole Zubizarreta, M.P.H., Crispiana Cozowicz, M.D., Eva E. Mörwald, M.D., Edward R. Mariano, M.D., M.A.S., Madhu Mazumdar, Ph.D.

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## ABSTRACT

**Background:** Multimodal analgesia is increasingly considered routine practice in joint arthroplasties, but supportive large-scale data are scarce. The authors aimed to determine how the number and type of analgesic modes is associated with reduced opioid prescription, complications, and resource utilization.

**Methods:** Total hip/knee arthroplasties (N = 512,393 and N = 1,028,069, respectively) from the Premier Perspective database (2006 to 2016) were included. Analgesic modes considered were opioids, peripheral nerve blocks, acetaminophen, steroids, gabapentin/pregabalin, nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, or ketamine. Groups were categorized into "opioids only" and 1, 2, or more than 2 additional modes. Multilevel models measured associations between multimodal analgesia and opioid prescription, cost/length of hospitalization, and opioid-related adverse effects. Odds ratios or percent change and 95% CIs are reported.

**Results:** Overall, 85.6% (N = 1,318,165) of patients received multimodal analgesia. In multivariable models, additions of analgesic modes were associated with stepwise positive effects: total hip arthroplasty patients receiving more than 2 modes (compared to "opioids only") experienced 19% fewer respiratory (odds ratio, 0.81; 95% CI, 0.70 to 0.94; unadjusted 1.0% [N = 1,513] *vs.* 2.0% [N = 1,546]), 26% fewer gastrointestinal (odds ratio, 0.74; 95% CI, 0.65 to 0.84; unadjusted 1.5% [N = 2,234] *vs.* 2.5% [N = 1,984]) complications, up to a –18.5% decrease in opioid prescription (95% CI, –19.7% to –17.2%; 205 *vs.* 300 overall median oral morphine equivalents), and a –12.1% decrease (95% CI, –12.8% to –11.5%; 2 *vs.* 3 median days) in length of stay (all $P < 0.05$). Total knee arthroplasty analyses showed similar patterns. Nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors seemed to be the most effective modalities used.

**Conclusions:** While the optimal multimodal regimen is still not known, the authors' findings encourage the combined use of multiple modalities in perioperative analgesic protocols. **(Anesthesiology 2018; 128:891-902)**

MULTIMODAL analgesic techniques—the simultaneous administration of two or more analgesic agents targeting pain pathways at various levels—have gained widespread favor among perioperative physicians caring for joint arthroplasty patients. This approach is used to improve pain control, while also aiming to reduce opioid utilization and related adverse effects.[1,2] Practitioners thus combined neuraxial and peripheral nerve blocks with analgesics, including nonsteroidal antiinflammatory agents, steroids, acetaminophen, and opioids.[1]

Despite ample evidence regarding the effectiveness of this approach, many questions on the utilization and influence on perioperative outcomes remain unanswered. This includes the question if there should be an upper limit in the number of different analgesic agents utilized.[1,3,4] Population-based data on this topic, specifically regarding the impact of multimodal

### What We Already Know about This Topic

- Multimodal analgesia is commonly used in joint replacement surgery with evidence of clinical effectiveness
- Population-based data indicating the influence of the number of modalities on opioid prescribing, side effects, and cost, are more limited

### What This Article Tells Us That Is New

- Using a Premier Perspective database of total hip and knee arthroplasties, patients were grouped into "opioids only" and 1, 2, or more than 2 additional modalities
- There was a stepwise modality number-associated decrease in opioid patient-controlled analgesia use, opioid prescriptions, and some opioid-related side effects, but not cost of hospitalization
- The strongest association was for cyclooxygenase-2 inhibitors and nonsteroidal antiinflammatory drugs

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pain management strategies on resource utilization measures and complications, are rare. Further, little research has been published on whether an increasing number of pain management modalities is associated with benefit.

Therefore, we studied the utilization patterns of multimodal pain management in joint arthroplasty recipients in the United States utilizing a national population-based data source. We sought to determine how an increasing number of modes included in a pain management approach would be associated with stronger reductions in perioperative opioid prescription, clinical outcomes (including opioid-related adverse effects), as well as resource utilization. The specific focus was to quantify a potential incremental effect of additional modes used. We hypothesized that among total hip and knee arthroplasty recipients: (1) a pattern toward increasing use in multimodal analgesia could be identified, and (2) an increasing number of modalities used would be associated with lower opioid prescription and better perioperative complication and economic profiles. Further, we evaluated the separate impact of the most common individual modalities on outcomes.

## Materials and Methods

### Data Source, Study Design, and Study Sample

After institutional review board approval (No. 14–0067, Mount Sinai Hospital, New York, New York; No. 2012-050-CR2, Hospital for Special Surgery, New York, New York), we extracted data from the Premier Perspective[5,6] database (Premier Healthcare Solutions, Inc., USA). This database contains detailed all-payer, patient-specific inpatient billing information. Patient records with International Classification of Diseases, Ninth Revision (ICD-9) procedure codes for primary hip (81.51) or knee (81.54) arthroplasty from 2006 to 2016 were included in this retrospective cross-sectional cohort study. From a total of 1,814,048 records we excluded nonelective procedures (N = 110,464; 6.1%), records with unknown sex (N = 294; 0.02%), unknown discharge status (N = 814; 0.05%), categorization as outpatient procedure (N = 7,341; 0.4%), surgery at a hospital that performed fewer than 30 primary lower joint replacements (to ensure sufficient sample size per cluster[7]; N = 340; 0.02%), absent billing for perioperative opioids (N = 73,282; 4.0%), and opioid prescription greater than 95th percentile (to exclude outliers; N = 81,051; 4.5%).

Submitted for publication July 31, 2017. Accepted for publication January 16, 2018. From Weill Cornell Medical College, New York, New York (S.G.M., C.C., E.E.M.); Department of Anesthesiology, Hospital for Special Surgery, New York, New York (S.G.M., C.C., E.E.M.); Department of Anesthesiology and Departments of Perioperative Medicine and Intensive Care Medicine (S.G.M., C.C., E.E.M.), Paracelsus Medical University, Salzburg, Austria; Institute for Healthcare Delivery Science, Department of Population Health Science and Policy (J.P., N.Z., M.M.), Department of Orthopaedics (J.P., N.Z.), and Department of Medicine (J.P.), Icahn School of Medicine at Mount Sinai, New York, New York; Veterans Affairs Palo Alto Health Care System, Palo Alto, California (E.R.M.); and Stanford University School of Medicine, Stanford, California (E.R.M.).

### Study Variables

An analysis plan was created *a priori* where study variables were identified, including the main effects of interest and outcomes. The main effect of interest was the use of multimodal analgesia; this was categorized into four groups: opioids only, and 1, 2, or more than 2 additional modes. Multimodal analgesia was defined as billing for opioids with at least one additional mode of pain management. This included: the use of a peripheral nerve block, acetaminophen, steroids, gabapentin/pregabalin, ketamine, nonsteroidal antiinflammatory drugs (NSAIDs), or cyclooxygenase-2 (COX-2) inhibitors given on the day of surgery or the day after. Outcomes of interest were: perioperative opioid prescription (both overall and separated by day 0 [includes intraoperative opioids], 1, and after postoperative day 1 of hospitalization) and cost and length of hospitalization, as well as opioid-related adverse effects (as previously defined in a study assessing opioid-related adverse effects[8]) including respiratory, gastrointestinal, genitourinary, and central nervous system complications. A category "other" was also considered and defined as a composite outcome including ICD-9 codes for postoperative bradycardia, rash or itching, drugs causing adverse effects with therapeutic use, and fall from bed.[8] Opioid prescription was defined using charges for opioids and was expressed in oral morphine equivalents, calculated by using the Lexicomp (Hudson, USA) "opioid agonist conversion"[9] and the GlobalRPH (Charleston, USA) "opioid analgesic converter"[10] calculator. It must be noted that these charges do not necessarily relate to actual administration of the drugs. Further, we did not have information on preoperative use of opioids. Cost of hospitalization was adjusted for inflation and expressed in 2016 U.S. dollars. Hospitals participating in Premier submit their actual cost data. A smaller number of hospitals submits charges which are then converted into costs using Medicare cost-to-charge ratios.[6]

Patient-related variables were age, sex, and race/ethnicity (White, Black, Hispanic, other). Healthcare-related factors were insurance type (commercial, Medicaid, Medicare, uninsured, other), hospital location (rural, urban), hospital bed size (less than 300, 300 to 499, greater than or equal to 500 beds), hospital teaching status, and hospital-specific number of annual hip/knee arthroplasties. Procedure-related variables included the year in which a surgery was performed, use of general and neuraxial anesthesia, and use of patient-controlled analgesia (PCA). Comorbidity burden was assessed using individual Elixhauser comorbidities.[11] In addition, variables describing history of substance use/abuse, chronic pain conditions, and psychiatric conditions (see definitions in Supplemental Digital Content 1, http://links.lww.com/ALN/B654[4]), as well as a variable indicating preoperative opioid use disorder, were included.[12] This was done because these conditions may influence perioperative outcomes, particularly through their correlation with preoperative and perioperative opioid utilization.

### Statistical Analysis

Analyses were performed separately for hip and knee replacements. Univariable associations between the number of modes used and study variables, as well as outcomes, were analyzed using the chi-square test for categorical and the Kruskal-Wallis test for continuous variables. Multilevel, multivariable regression models measured the association between the number of modes in a multimodal analgesic approach (compared to opioids only) and the predefined outcomes. Multilevel (or mixed-effects) models account for the correlation of patients within hospitals and fit separate regression lines for each hospital.[13] This step is necessary as patients within the same hospital may be correlated, because they may receive similar treatment and care. Multivariable models were adjusted for variables based on clinical and/or univariable importance at the $P < 0.15$ level; adjusted odds ratios and Bonferroni-adjusted $P$ values and 95% CI are reported, taking into account the number of hypotheses tested for in the main analyses (66 hypotheses; 11 outcomes, 2 procedures, and 3 multimodal comparisons). It must be noted that while this step may reduce the risk of type I errors, the likelihood of type II errors may be increased.[14] For all models PROC GLIMMIX in SAS v9.4 statistical software (SAS Institute, USA) was used. For opioid prescription and length and cost of hospitalization, the gamma distribution with a log link function was applied as these variables are skewed.[15,16] Additionally, we used the CONTRAST statement in PROC GLIMMIX to test whether a linear trend existed between effect estimates with increasing numbers of modes used in the multimodal analgesic approaches.

### Sensitivity Analysis

We performed a sensitivity analysis to assess the robustness of our results. This was done to address the possible issue of confounding by indication, because additional modes of analgesia and increased opioid prescription could be used in patients with greater pain. For this analysis, we restricted our cohort to hospitals with greater than or equal to 95% multimodal use. This step reflected the assumption that selected hospitals use multimodal analgesia as part of a postoperative pain protocol, thus reducing the potential effect of confounding by indication.

### A priori versus Post hoc *Analyses*

During the peer-review process the following adjustments were made to our initial *a priori* specified analyses. First, oral acetaminophen was added to our definition of multimodal analgesia. Further, we modeled analyses to examine the effects of the separate components of our multimodal definition (*i.e.*, peripheral nerve block, acetaminophen, steroids, gabapentin/pregabalin, ketamine, NSAIDs, and COX-2 inhibitors) on opioid prescription. Additionally, to assess the separate role of peripheral nerve blocks in multimodal analgesia, we added a set of models where multimodal analgesia was categorized into six mutually exclusive groups:

1. Opioids + peripheral nerve block
2. Opioids + peripheral nerve block + 1 additional mode
3. Opioids + peripheral nerve block + more than 1 additional modes
4. Opioids + 1 additional mode
5. Opioids + 2 additional modes
6. Opioids + more than 2 additional modes

Finally, results from our multilevel models were compared to results from fixed-effects models.

## Results

Of 1,540,462 procedures included, 512,393 were primary total hip and 1,028,069 were primary total knee arthroplasties. Multimodal analgesia was used in 85.6% (N = 1,318,165) of all procedures.

### Univariable Analyses

Table 1 shows all study variables and outcomes by multimodal categorization for hip arthroplasties. Supplemental Digital Content 2 (http://links.lww.com/ALN/B655) provides the breakdown by separate Elixhauser comorbidities. While all comparisons are significant at the $P < 0.001$ level, patients receiving multimodal analgesia were younger, more likely to be white, on commercial insurance, and undergoing their procedure in hospitals with higher arthroplasty volume. The most commonly used nonopioids were NSAIDs, COX-2 inhibitors, and acetaminophen. One of the most pronounced differences between multimodal groups was the less frequent use of PCAs in patients receiving multimodal analgesia: 27.1% (N = 21,384) in the "opioids only" group, as compared to 19.1% (N = 27,797), 12.6% (N = 17,516), and 6.1% (N = 9,105) in patients receiving 1, 2, and more than 2 additional analgesic modes. The highest unadjusted opioid prescription, as well as length and cost of hospitalization, were observed in the "opioids only" group; this decreased gradually with an increasing number of modes of analgesic options used. Generally, the same patterns were observed for knee arthroplasties (table 2 and Supplemental Digital Content 3 [http://links.lww.com/ALN/B656] for separate Elixhauser comorbidities).

### Utilization Patterns

Figure 1 shows patterns in multimodal analgesia utilization (*left panel*), as well as patterns in opioid prescription levels in relation to the number of analgesic modes used (*right panel*). In both hip and knee arthroplasties, the group of patients that received "opioids only" or one additional analgesic mode decreased over time with sharp increases in the use of two or more analgesic modes. The latter increase was particularly visible after 2011. Moreover, a pattern toward decreasing opioid prescription in general was seen; there were no apparent differences in patterns when stratifying by multimodal analgesia categories.

**Table 1.** Study Variables by Multimodal Categorization: Total Hip Athroplasty

| | | | Multimodal Use | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Opioids Only (N = 78,943) | | 1 Mode (N = 145,264) | | 2 Modes (N = 139,231) | | 2+ Modes (N = 148,955) | |
| Variable | N | % | N | % | N | % | N | % |
| Patient demographics | | | | | | | | |
| Age* | 67 | 59–76 | 66 | 57–74 | 65 | 57–73 | 64 | 56–72 |
| Sex | | | | | | | | |
| Female | 44,367 | 56.2 | 81,566 | 56.2 | 78,174 | 56.1 | 81,545 | 54.7 |
| Male | 34,576 | 43.8 | 63,698 | 43.9 | 61,057 | 43.9 | 67,410 | 45.3 |
| Race/ethnicity | | | | | | | | |
| White | 58,893 | 74.6 | 115,275 | 79.4 | 111,672 | 80.2 | 122,448 | 82.2 |
| Black | 5,239 | 6.6 | 10,172 | 7.0 | 9,439 | 6.8 | 10,960 | 7.4 |
| Hispanic | 732 | 0.9 | 1,140 | 0.8 | 594 | 0.4 | 325 | 0.2 |
| Other | 14,079 | 17.8 | 18,677 | 12.9 | 17,526 | 12.6 | 15,222 | 10.2 |
| Healthcare related | | | | | | | | |
| Insurance type | | | | | | | | |
| Commercial | 27,639 | 35.0 | 56,205 | 38.7 | 57,051 | 41.0 | 65,175 | 43.8 |
| Medicaid | 2,382 | 3.0 | 4,838 | 3.3 | 4,795 | 3.4 | 5,450 | 3.7 |
| Medicare | 46,321 | 58.7 | 79,197 | 54.5 | 72,582 | 52.1 | 73,124 | 49.1 |
| Uninsured | 628 | 0.8 | 1,124 | 0.8 | 936 | 0.7 | 927 | 0.6 |
| Unknown | 1,973 | 2.5 | 3,900 | 2.7 | 3,867 | 2.8 | 4,279 | 2.9 |
| Hospital location | | | | | | | | |
| Rural | 7,821 | 9.9 | 13,997 | 9.6 | 12,338 | 8.9 | 11,334 | 7.6 |
| Urban | 71,122 | 90.1 | 131,267 | 90.4 | 126,893 | 91.1 | 137,621 | 92.4 |
| Hospital size | | | | | | | | |
| < 300 beds | 26,639 | 33.7 | 53,923 | 37.1 | 57,186 | 41.1 | 60,266 | 40.5 |
| 300–499 beds | 28,000 | 35.5 | 50,143 | 34.5 | 41,690 | 29.9 | 45,691 | 30.7 |
| ≥ 500 beds | 24,304 | 30.8 | 41,198 | 28.4 | 40,355 | 29.0 | 42,998 | 28.9 |
| Hospital teaching status | | | | | | | | |
| Nonteaching | 49,298 | 62.4 | 82,622 | 56.9 | 72,829 | 52.3 | 74,552 | 50.1 |
| Teaching | 29,645 | 37.6 | 62,642 | 43.1 | 66,402 | 47.7 | 74,403 | 50.0 |
| No. of annual hip arthroplasties per hospital* | 163 | 90–297 | 172 | 98–346 | 211 | 116–424 | 276 | 135–453 |
| Procedure related | | | | | | | | |
| Year of procedure | | | | | | | | |
| 2006 | 9,670 | 12.2 | 12,352 | 8.5 | 5,662 | 4.1 | 1,237 | 0.8 |
| 2007 | 8,622 | 10.9 | 12,597 | 8.7 | 7,054 | 5.1 | 2,572 | 1.7 |
| 2008 | 8,358 | 10.6 | 12,065 | 8.3 | 7,746 | 5.6 | 3,999 | 2.7 |
| 2009 | 9,047 | 11.5 | 13,396 | 9.2 | 9,766 | 7.0 | 6,193 | 4.2 |
| 2010 | 9,248 | 11.7 | 14,265 | 9.8 | 11,002 | 7.9 | 7,863 | 5.3 |
| 2011 | 8,457 | 10.7 | 14,902 | 10.3 | 12,601 | 9.1 | 10,528 | 7.1 |
| 2012 | 7,480 | 9.5 | 14,673 | 10.1 | 14,875 | 10.7 | 14,588 | 9.8 |
| 2013 | 5,867 | 7.4 | 13,863 | 9.5 | 16,955 | 12.2 | 17,560 | 11.8 |
| 2014 | 5,330 | 6.8 | 13,450 | 9.3 | 17,755 | 12.8 | 23,139 | 15.5 |
| 2015 | 4,079 | 5.2 | 13,258 | 9.1 | 18,566 | 13.3 | 30,010 | 20.1 |
| 2016 | 2,785 | 3.5 | 10,443 | 7.2 | 17,249 | 12.4 | 31,266 | 21.0 |
| General anesthesia† | 57,024 | 72.2 | 104,065 | 71.6 | 95,611 | 68.7 | 98,605 | 66.2 |
| Neuraxial anesthesia† | 15,087 | 19.1 | 28,360 | 19.5 | 25,886 | 18.6 | 28,626 | 19.2 |
| Patient-controlled analgesia | 21,384 | 27.1 | 27,797 | 19.1 | 17,516 | 12.6 | 9,105 | 6.1 |
| NSAIDs | — | — | 57,012 | 39.2 | 78,192 | 56.2 | 106,848 | 71.7 |
| COX-2 inhibitors | — | — | 23,740 | 16.3 | 63,007 | 45.3 | 122,548 | 82.3 |
| Ketamine | — | — | 2,384 | 1.6 | 5,341 | 3.8 | 16,396 | 11.0 |
| Pregabalin/gabapentin | — | — | 7,554 | 5.2 | 26,411 | 19.0 | 94,053 | 63.1 |
| Acetaminophen | — | — | 46,776 | 32.2 | 90,852 | 65.3 | 133,077 | 89.3 |
| Steroids | — | — | 1,991 | 1.4 | 3,666 | 2.6 | 6,017 | 4.0 |
| Peripheral nerve block | — | — | 5,807 | 4.0 | 10,993 | 7.9 | 26,057 | 17.5 |

(*Continued*)

**Table 1.** (Continued)

| | | | Multimodal Use | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Opioids Only (N = 78,943) | | 1 Mode (N = 145,264) | | 2 Modes (N = 139,231) | | 2+ Modes (N = 148,955) | |
| Variable | N | % | N | % | N | % | N | % |
| Comorbidity related | | | | | | | | |
| Elixhauser comorbidities (categorized) | | | | | | | | |
| 0 | 12,888 | 16.3 | 25,637 | 17.6 | 25,604 | 18.4 | 29,099 | 19.5 |
| 1 | 22,671 | 28.7 | 42,583 | 29.3 | 40,930 | 29.4 | 44,717 | 30.0 |
| 2 | 20,329 | 25.8 | 36,856 | 25.4 | 34,917 | 25.1 | 36,286 | 24.4 |
| 3 | 12,535 | 15.9 | 22,278 | 15.3 | 20,896 | 15.0 | 21,678 | 14.6 |
| 3+ | 10,520 | 13.3 | 17,910 | 12.3 | 16,884 | 12.1 | 17,175 | 11.5 |
| History of substance use/ abuse | 9,275 | 11.7 | 17,267 | 11.9 | 15,868 | 11.4 | 17,799 | 11.9 |
| Pain conditions | 11,226 | 14.2 | 22,848 | 15.7 | 24,715 | 17.8 | 29,070 | 19.5 |
| Psychiatric comorbidities | 12,185 | 15.4 | 24,491 | 16.9 | 25,393 | 18.2 | 29,226 | 19.6 |
| Opioid use disorder | 134 | 0.2 | 278 | 0.2 | 353 | 0.3 | 496 | 0.3 |
| Opioid-related adverse effects | | | | | | | | |
| Respiratory | 1,546 | 2.0 | 2,280 | 1.6 | 1,937 | 1.4 | 1,513 | 1.0 |
| Gastrointestinal | 1,984 | 2.5 | 2,914 | 2.0 | 2,413 | 1.7 | 2,234 | 1.5 |
| Genitourinary | 2,115 | 2.7 | 3,271 | 2.3 | 3,059 | 2.2 | 2,885 | 1.9 |
| Central nervous system | 668 | 0.8 | 1,105 | 0.8 | 978 | 0.7 | 774 | 0.5 |
| Other | 1,437 | 1.8 | 2,238 | 1.5 | 1,629 | 1.2 | 1,212 | 0.8 |
| Resource utilization | | | | | | | | |
| Total opioid prescription* | 300 | 180–465 | 270 | 165–422 | 238 | 140–383 | 205 | 120–335 |
| Day 0 opioid prescription* | 145 | 59–255 | 145 | 75–240 | 135 | 72–220 | 120 | 65–200 |
| Day 1 opioid prescription* | 45 | 10–90 | 45 | 15–87 | 40 | 15–75 | 38 | 15–75 |
| Day 1+ opioid prescription* | 68 | 30–130 | 48 | 15–102 | 35 | 0–83 | 23 | 0–60 |
| Cost of hospitalization* | $16,941 | $13,899–$21,196 | $16,588 | $13,610–$20,542 | $16,267 | $13,404–$19,882 | $15,678 | $13,043–$19,016 |
| Length of stay* | 3 | 3–4 | 3 | 2–3 | 3 | 2–3 | 2 | 2–3 |

All comparisons $P < 0.001$.

*Continuous variable median and interquartile range reported, instead of N and %, respectively. †Two separate variables for anesthesia type that do not add up to 100%, as there is a group of patients with missing information on anesthesia type. 1+ indicates opioid prescription after postoperative day 1. 2+ indicates more than two additional analgesic modes.

COX-2 = cyclooxygenase-2; NSAIDs = nonsteroidal antiinflammatory drugs.

### Multivariable Analyses

Table 3 shows adjusted effect estimates for separate multimodal components for the opioid prescription outcomes. Overall, COX-2 inhibitors and NSAIDs appeared to have the strongest individual associations with outcomes, while effect estimates for other components appeared relatively modest.

Results from the main multivariable, multilevel regression analyses are reported in table 4 (full model coefficients are depicted in Supplemental Digital Content 4 [http://links.lww.com/ALN/B657] and 5 [http://links.lww.com/ALN/B658]). The decreasing gradient in complications, with an increasing number of analgesic modes used, persisted in the multivariable analyses: additions of analgesic modes were associated with stepwise positive effects. Significant linear trends in effect estimates with increasing number of analgesic modes used were seen for 14 of 22 outcomes. Significantly reduced odds for complications when using 1, 2, or more than 2 additional analgesic modes, compared to "opioids only," were more pronounced in hip arthroplasties compared to knee arthroplasties. In hip arthroplasties, associations with reduced opioid prescription after postoperative day 1 were –6.8%, –12.4%, and –18.4% for patients receiving 1, 2, or more than 2 analgesic modes in addition to opioids, respectively; this was –6.4%, –10.4%, and –15.0% in knee arthroplasties (Bonferroni adjusted $P < 0.05$). Associations with reduced opioid prescription were most apparent on the days after surgery (days 1 and after postoperative day 1). While associations with decreases in length of hospitalization of up to –12.1% and –9.3% were observed in hip and knee arthroplasty for those who received more than 2 modes of analgesics in addition to opioids, this did not translate into equivalent reductions in cost of hospitalization. Model c-statistics varied between 0.71 and 0.80, indicating adequate model discrimination.

### Sensitivity Analyses

In the sensitivity analyses, in which only hospitals with 95% or greater multimodal utilization were included (Supplemental Digital Content 6, http://links.lww.com/ALN/B659; N = 140,962 hip arthroplasties and N = 290,776 knee arthroplasties), we found similar but more pronounced

**Table 2.** Study Variables by Multimodal Categorization: Total Knee Arthroplasty

| | | | Multimodal Use | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Opioids Only (N = 143,354) | | 1 Mode (N = 288,866) | | 2 Modes (N = 286,659) | | 2+ Modes (N = 309,190) | |
| Variable | N | % | N | % | N | % | N | % |
| Patient demographics | | | | | | | | |
| Age* | 68 | 61–72 | 67 | 60–74 | 67 | 60–73 | 66 | 59–72 |
| Sex | | | | | | | | |
| Female | 90,164 | 62.9 | 182,017 | 63.0 | 181,561 | 63.3 | 191,512 | 61.9 |
| Male | 53,190 | 37.1 | 106,849 | 37.0 | 105,098 | 36.7 | 117,678 | 38.1 |
| Race/ethnicity | | | | | | | | |
| White | 101,749 | 71.0 | 220,433 | 76.3 | 223,216 | 77.9 | 249,249 | 80.6 |
| Black | 9,890 | 6.9 | 21,838 | 7.6 | 20,468 | 7.1 | 24,466 | 7.9 |
| Hispanic | 2,240 | 1.6 | 4,146 | 1.4 | 2,630 | 0.9 | 1,297 | 0.4 |
| Other | 29,475 | 20.6 | 42,449 | 14.7 | 40,345 | 14.1 | 34,178 | 11.1 |
| Healthcare related | | | | | | | | |
| Insurance type | | | | | | | | |
| Commercial | 45,292 | 31.6 | 99,964 | 34.6 | 102,762 | 35.8 | 117,797 | 38.1 |
| Medicaid | 3,470 | 2.4 | 7,931 | 2.7 | 8,566 | 3.0 | 8,995 | 2.9 |
| Medicare | 89,322 | 62.3 | 169,128 | 58.5 | 164,069 | 57.2 | 171,558 | 55.5 |
| Uninsured | 517 | 0.4 | 1,084 | 0.4 | 988 | 0.3 | 973 | 0.3 |
| Unknown | 4,753 | 3.3 | 10,759 | 3.7 | 10,274 | 3.6 | 9,867 | 3.2 |
| Hospital location | | | | | | | | |
| Rural | 15,970 | 11.1 | 32,287 | 11.2 | 32,766 | 11.4 | 28,670 | 9.3 |
| Urban | 127,384 | 88.9 | 256,579 | 88.8 | 253,893 | 88.6 | 280,520 | 90.7 |
| Hospital size | | | | | | | | |
| < 300 beds | 53,683 | 37.4 | 112,134 | 38.8 | 117,885 | 41.1 | 122,945 | 39.8 |
| 300–499 beds | 49,555 | 34.6 | 103,283 | 35.8 | 90,455 | 31.6 | 105,551 | 34.1 |
| ≥ 500 beds | 40,116 | 28.0 | 73,449 | 25.4 | 78,319 | 27.3 | 80,694 | 26.1 |
| Hospital teaching status | | | | | | | | |
| Nonteaching | 93,526 | 65.2 | 173,717 | 60.1 | 167,017 | 58.3 | 170,149 | 55.0 |
| Teaching | 49,828 | 34.8 | 115,149 | 39.9 | 119,642 | 41.7 | 139,041 | 45.0 |
| No. of annual knee arthroplasties per hospital* | 315 | 189–531 | 323 | 194–587 | 378 | 221–637 | 451 | 249–691 |
| Procedure related | | | | | | | | |
| Year of procedure | | | | | | | | |
| 2006 | 18,856 | 13.2 | 27,184 | 9.4 | 12,567 | 4.4 | 2,879 | 0.9 |
| 2007 | 16,719 | 11.7 | 28,002 | 9.7 | 16,617 | 5.8 | 5,949 | 1.9 |
| 2008 | 16,326 | 11.4 | 27,946 | 9.7 | 18,542 | 6.5 | 8,694 | 2.8 |
| 2009 | 16,730 | 11.7 | 27,850 | 9.6 | 22,167 | 7.7 | 13,744 | 4.4 |
| 2010 | 16,642 | 11.6 | 30,104 | 10.4 | 24,706 | 8.6 | 18,801 | 6.1 |
| 2011 | 15,248 | 10.6 | 29,695 | 10.3 | 28,040 | 9.8 | 24,026 | 7.8 |
| 2012 | 12,953 | 9.0 | 28,359 | 9.8 | 30,791 | 10.7 | 31,117 | 10.1 |
| 2013 | 10,344 | 7.2 | 26,169 | 9.1 | 33,360 | 11.6 | 38,333 | 12.4 |
| 2014 | 8,271 | 5.8 | 22,861 | 7.9 | 33,794 | 11.8 | 46,405 | 15.0 |
| 2015 | 6,567 | 4.6 | 22,419 | 7.8 | 34,152 | 11.9 | 58,126 | 18.8 |
| 2016 | 4,698 | 3.3 | 18,277 | 6.3 | 31,923 | 11.1 | 61,116 | 19.8 |
| General anesthesia† | 100,974 | 70.4 | 198,287 | 68.6 | 189,586 | 66.1 | 198,269 | 64.1 |
| Neuraxial anesthesia† | 31,335 | 21.9 | 60,775 | 21.0 | 60,898 | 21.2 | 67,392 | 21.8 |
| Patient-controlled analgesia | 42,014 | 29.3 | 63,755 | 22.1 | 44,912 | 15.7 | 25,220 | 8.2 |
| NSAIDs | — | — | 124,284 | 43.0 | 176,484 | 61.6 | 230,663 | 74.6 |
| COX-2 inhibitors | — | — | 47,769 | 16.5 | 114,343 | 39.9 | 238,171 | 77.0 |
| Ketamine | — | — | 3,604 | 1.2 | 9,920 | 3.5 | 32,685 | 10.6 |
| Pregabalin/gabapentin | — | — | 15,084 | 5.2 | 54,160 | 18.9 | 185,073 | 59.9 |
| Acetaminophen | — | — | 68,980 | 23.9 | 161,807 | 56.4 | 268,173 | 86.7 |
| Steroids | — | — | 3,902 | 1.4 | 7,616 | 2.7 | 13,231 | 4.3 |
| Peripheral nerve block | — | — | 25,243 | 8.7 | 48,988 | 17.1 | 93,589 | 30.3 |

(*Continued*)

**Table 2.** (Continued)

| | | | Multimodal Use | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Opioids Only (N = 143,354) | | 1 Mode (N = 288,866) | | 2 Modes (N = 286,659) | | 2+ Modes (N = 309,190) | |
| Variable | N | % | N | % | N | % | N | % |
| Comorbidity related | | | | | | | | |
| Elixhauser comorbidities (categorized) | | | | | | | | |
| 0 | 16,685 | 11.6 | 34,781 | 12.0 | 34,847 | 12.2 | 38,985 | 12.6 |
| 1 | 37,699 | 26.3 | 76,301 | 26.4 | 75,250 | 26.3 | 81,303 | 26.3 |
| 2 | 39,415 | 27.5 | 79,445 | 27.5 | 78,162 | 27.3 | 82,609 | 26.7 |
| 3 | 26,612 | 18.6 | 52,982 | 18.3 | 52,702 | 18.4 | 56,290 | 18.2 |
| 3+ | 22,943 | 16.0 | 45,357 | 15.7 | 45,698 | 15.9 | 50,003 | 16.2 |
| History of substance use/ abuse | 11,052 | 7.7 | 22,860 | 7.9 | 22,419 | 7.8 | 24,839 | 8.0 |
| Pain conditions | 17,420 | 12.2 | 39,037 | 13.5 | 46,039 | 16.1 | 58,985 | 19.1 |
| Psychiatric comorbidities | 23,793 | 16.6 | 52,086 | 18.0 | 56,948 | 19.9 | 66,988 | 21.7 |
| Opioid use disorder | 136 | 0.1 | 355 | 0.1 | 486 | 0.2 | 780 | 0.3 |
| Opioid-related adverse effects | | | | | | | | |
| Respiratory | 3,370 | 2.4 | 5,887 | 2.0 | 5,430 | 1.9 | 4,913 | 1.6 |
| Gastrointestinal | 3,266 | 2.3 | 5,816 | 2.0 | 5,582 | 1.9 | 5,492 | 1.8 |
| Genitourinary | 3,050 | 2.1 | 5,269 | 1.8 | 5,231 | 1.8 | 5,610 | 1.8 |
| Central nervous system | 1,291 | 0.9 | 2,328 | 0.8 | 2,200 | 0.8 | 2,143 | 0.7 |
| Other | 2,875 | 2.0 | 4,948 | 1.7 | 4,313 | 1.5 | 3,527 | 1.1 |
| Resource utilization | | | | | | | | |
| Total opioid prescription* | 330 | 201–500 | 305 | 190–460 | 280 | 173–423 | 252 | 153–393 |
| Day 0 opioid prescription* | 141 | 55–250 | 141 | 75–235 | 133 | 72–215 | 120 | 70–200 |
| Day 1 opioid prescription* | 53 | 15–110 | 60 | 23–105 | 55 | 23–98 | 53 | 24–91 |
| Day 1+ opioid prescription* | 83 | 38–150 | 68 | 30–124 | 60 | 23–115 | 46 | 15–105 |
| Cost of hospitalization* | $16,026 | $13,052–$20,187 | $15,941 | $12,961–$19,931 | $15,719 | $12,964–$19,402 | $15,551 | $12,997–$18,969 |
| Length of stay* | 3 | 3–4 | 3 | 3-3 | 3 | 2–3 | 3 | 2–3 |

All comparisons $P < 0.001$.

*Continuous variable median and interquartile range reported, instead of N and %, respectively. †Two separate variables for anesthesia type that do not add up to 100%, as there is a group of patients with missing information on anesthesia type. 1+ indicates opioid prescription after postoperative day 1. 2+ indicates more than two additional analgesic modes. 3+ indicates more than 3 Elixhauser comorbidities.

COX-2 = cyclooxygenase-2; NSAIDs = nonsteroidal antiinflammatory drugs.

patterns compared to the main analyses. Table 5 shows results using alternative multimodal categorizations based on separating out peripheral nerve blocks in the multimodal analgesia definition. For opioid prescription over the entire hospitalization, and on days 1 and after postoperative day 1, results did not differ to a major extent between groups with and without peripheral nerve blocks. Peripheral nerve blocks appear particularly effective in reducing opioid prescription on day 0; this reduction does not appear to be replicated when using additional analgesic modes outside of blocks.

Furthermore, groupings with and without peripheral nerve blocks showed consistent patterns of stronger associations with reduced opioid prescription with more analgesic modes used. Results from our main analyses using multilevel models did not change when using fixed-effects models.

## Discussion

In this study utilizing national population data from more than 1.5 million total hip and knee arthroplasties, we found that multimodal pain therapy was used in 85.6% of cases. We observed an increase in the use of 2 or more than 2 additional analgesic modes over time, while the proportion of patients receiving "opioids only" or only 1 additional analgesic mode decreased. A steady decrease in opioid prescription was observed with an increasing number of analgesic modes used; this was mainly driven by associations with decreased opioid prescription on postoperative days (up to –18.5% decrease in hip and knee arthroplasty, respectively). Although multimodal analgesia was associated with reductions in length of stay of up to –12.1% in hip arthroplasty and –9.3% in knee arthroplasty, the impact on cost of the overall hospitalization was limited. Sensitivity analyses confirmed robustness of our results. Moreover, additional analyses demonstrated COX-2 inhibitors and NSAIDs to have the strongest individual effect estimates for opioid prescription with modest estimates of other components; these individual effects may be altered when analgesic modes are used simultaneously. While the optimal multimodal regimen is still not known, these findings encourage the promotion of perioperative analgesic protocols that combine multiple analgesic modalities.

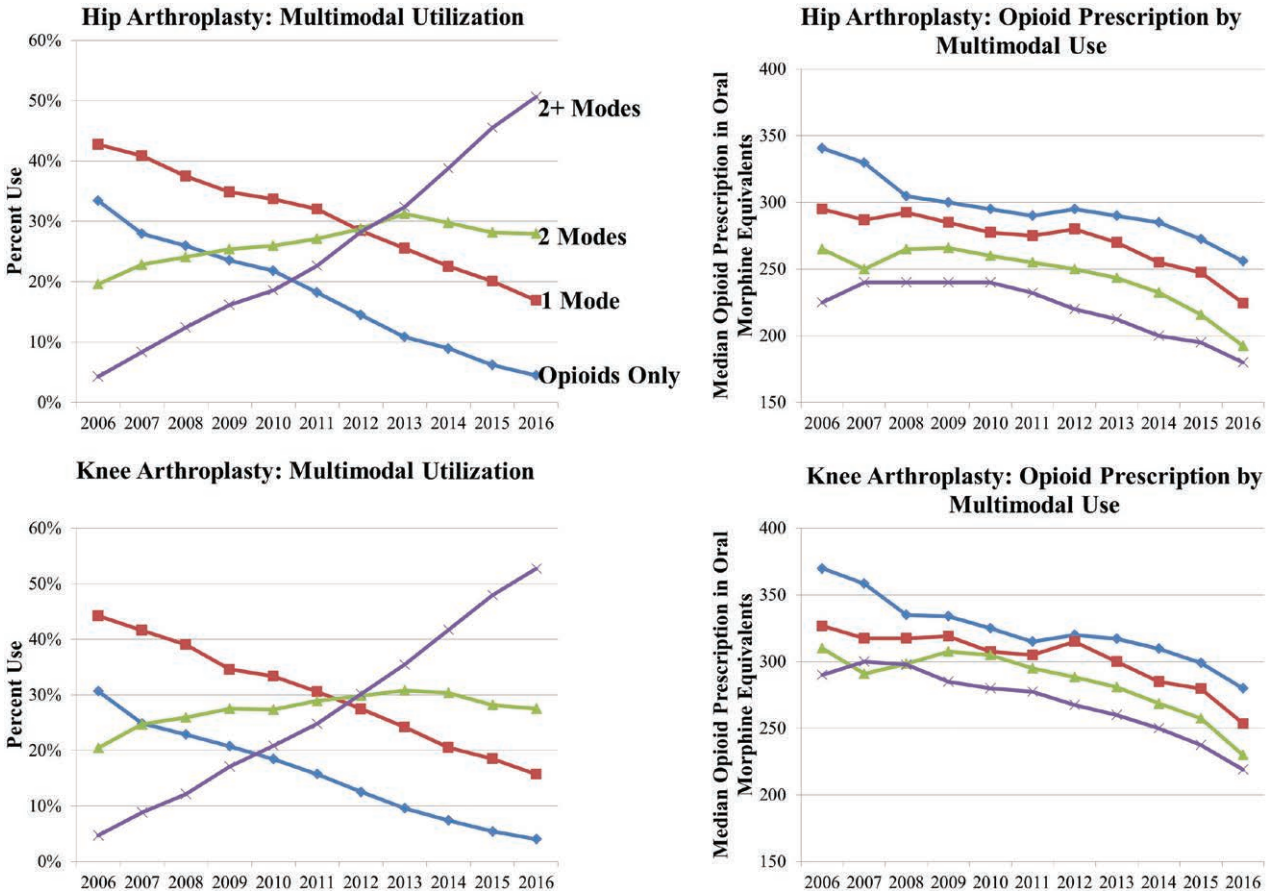


**Fig. 1.** Patterns in multimodal analgesia by number of modes used; utilization (*left*) and by median opioid prescription (*right*).

**Table 3.** Results from Multilevel Regression Models Providing Separate Effect Estimates for Multimodal Modalities

| | Total Opioid Prescription | Day 0 Opioid Prescription | Day 1 Opioid Prescription | Day 1+ Opioid Prescription |
|---|---|---|---|---|
| Hip arthroplasties, multimodal modality | | | | |
| NSAIDs | –5.5% (–5.9; –5.1%)* | –1.3% (–1.7; –0.9%)* | –10.9% (–11.3; –10.4%)* | –8.2% (–8.8; –7.6%)* |
| COX-2 inhibitors | –9.2% (–9.6; –8.8%)* | –4.8% (–5.2; –4.3%)* | –10.5% (–11.0; –10.0%)* | –16.6% (–17.2; –16.0%)* |
| Ketamine | 4.4% (3.6; 5.3%)* | 2.5% (1.5; 3.5%)* | 4.1% (3.0; 5.3%)* | 4.7% (3.1; 6.2%)* |
| Gabapentin/pregabalin | 0.3% (–0.2; 0.7%) | –1.9% (–2.4; –1.4%)* | 1.4% (0.7; 2.0%)* | 4.7% (3.9; 5.6%)* |
| Steroids | 3.0% (1.8; 4.2%)* | 2.4% (1.0; 3.8%)* | 0.1% (–1.4; 1.7%) | 5.4% (3.3; 7.5%)* |
| APAP | –3.1% (–3.5; –2.7%)* | 0.2% (–0.2; 0.7%) | –4.3% (–4.9; –3.8%)* | –3.4% (–4.1; –2.7%)* |
| Peripheral nerve block | –4.0% (–4.8; –3.1%)* | –5.1% (–6.0; –4.1%)* | –2.0% (–3.1; –0.8%)* | –5.3% (–6.7; –3.8%)* |
| Knee arthroplasties, multimodal modality | | | | |
| NSAIDs | –5.4% (–5.7; –5.2%)* | –2.1% (–2.4; –1.8%)* | –12.7% (–13.1; –12.4%)* | –4.7% (–5.1; –4.3%)* |
| COX-2 inhibitors | –6.1% (–6.4; –5.9%)* | –2.8% (–3.1; –2.5%)* | –8.6% (–8.9; –8.2%)* | –13.0% (–13.4; –12.6%)* |
| Ketamine | 3.6% (3.0; 4.2%)* | 1.7% (1.0; 2.4%)* | 2.2% (1.4; 3.0%)* | 4.8% (3.8; 5.7%)* |
| Gabapentin/pregabalin | 0.8% (0.5; 1.1%)* | 0.4% (0.1; 0.8%)* | 0.1% (–0.3; 0.5%) | 1.7% (1.2; 2.2%)* |
| Steroids | –0.2% (–1.0; 0.5%) | 2.3% (1.4; 3.2%)* | –4.3% (–5.3; –3.2%)* | 0.3% (–0.9; 1.5%) |
| APAP | –3.0% (–3.2; –2.7%)* | –0.1% (–0.5; 0.2%) | –3.8% (–4.2; –3.4%)* | –3.5% (–3.9; –3.1%)* |
| Peripheral nerve block | –3.0% (–3.4; –2.6%)* | –10.2% (–10.7; –9.7%)* | 6.0% (5.3; 6.7%)* | –0.4% (–1.1; 0.3%) |

Exponentiated coefficients from the log model depicting % change compared to reference (no use of each of the separate modalities). Models adjusted for: age, sex, race/ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific hip/knee arthroplasty volume, year of procedure, anesthesia type, patient-controlled analgesia use, individual Elixhauser comorbidities, history of substance use/abuse, pain conditions, psychiatric comorbidities, or opioid use disorder. 1+ indicates opioid prescription after postoperative day 1.

*$P < 0.05$.

APAP = acetyl-para-aminophenol/acetaminophen; COX-2 = cyclooxygenase-2; NSAIDs = nonsteroidal antiinflammatory drugs.

**Table 4.** Results from Multilevel Regression Models

| | Multimodal Use (Reference = Opioids Only) | | | |
|---|---|---|---|---|
| | 1 Mode | 2 Modes | 2+ Modes | *P* Value for Linear Trend |
| Hip arthroplasties | | | | |
| Opioid-related adverse effects | | | | |
| Respiratory | 0.95 (0.84, 1.07) | 0.97 (0.85, 1.10) | 0.81 (0.70, 0.94)* | 0.8400 |
| Gastrointestinal | 0.84 (0.76, 0.94)* | 0.78 (0.70, 0.88)* | 0.74 (0.65, 0.84)* | < 0.0001 |
| Genitourinary | 0.87 (0.79, 0.97)* | 0.89 (0.79, 0.99)* | 0.79 (0.70, 0.89)* | 0.0015 |
| Central nervous system | 1.03 (0.86, 1.22) | 1.05 (0.87, 1.26) | 0.94 (0.76, 1.16) | 0.2520 |
| Other | 0.97 (0.86, 1.09) | 0.84 (0.73, 0.96)* | 0.70 (0.60, 0.82)* | 0.5289 |
| Resource utilization | | | | |
| Total opioid prescription | –2.1% (–3.1; –1.2%)* | –6.9% (–7.9; –6.0%)* | –12.5% (–13.5; –11.5%)* | 0.7625 |
| Day 0 opioid prescription | –0.1% (–1.2; 1.1%) | –2.2% (–3.3; –1.0%)* | –5.8% (–7.0; –4.6%)* | 0.0004 |
| Day 1 opioid prescription | –6.9% (–8.1; –5.7%)* | –13.0% (–14.2; –11.8%)* | –18.5% (–19.7; –17.2%)* | < 0.0001 |
| Day 1+ opioid prescription | –6.8% (–8.3; –5.3%)* | –12.4% (–13.9; –10.9%)* | –18.4% (–20.0; –16.9%)* | < 0.0001 |
| Cost of hospitalization | 0.0% (–0.8; 0.7%) | –1.1% (–1.8; –0.3%)* | –2.1% (–2.9; –1.3%)* | 0.1753 |
| Length of stay | –3.6% (–4.3; –3.0%)* | –7.4% (–8.1; –6.8%)* | –12.1% (–12.8; –11.5%)* | < 0.0001 |
| Knee arthroplasties | | | | |
| Opioid-related adverse effects | | | | |
| Respiratory | 1.02 (0.94, 1.10) | 1.03 (0.95, 1.12) | 0.94 (0.85, 1.03) | 0.0422 |
| Gastrointestinal | 0.92 (0.85, 1.00)* | 0.90 (0.83, 0.98)* | 0.82 (0.75, 0.90)* | 0.0299 |
| Genitourinary | 0.87 (0.80, 0.94)* | 0.89 (0.81, 0.97)* | 0.84 (0.76, 0.92)* | < 0.0001 |
| Central nervous system | 0.99 (0.88, 1.12) | 1.01 (0.89, 1.16) | 1.02 (0.88, 1.18) | 0.8022 |
| Other | 0.98 (0.90, 1.07) | 0.93 (0.85, 1.02) | 0.82 (0.74, 0.91)* | 0.4347 |
| Resource utilization | | | | |
| Total opioid prescription | –3.2% (–3.9; –2.6%)* | –6.9% (–7.6; –6.3%)* | –10.1% (–10.8; –9.5%)* | < 0.0001 |
| Day 0 opioid prescription | –2.4% (–3.2; –1.6%)* | –4.6% (–5.4; –3.7%)* | –5.2% (–6.1; –4.3%)* | < 0.0001 |
| Day 1 opioid prescription | –8.0% (–8.9; –7.0%)* | –13.8% (–14.7; –12.9%)* | –18.5% (–19.5; –17.6%)* | < 0.0001 |
| Day 1+ opioid prescription | –6.4% (–7.3; –5.4%)* | –10.4% (–11.4; –9.4%)* | –15.0% (–16.1; –14.0%)* | < 0.0001 |
| Cost of hospitalization | –0.2% (–0.7; 0.3%) | –0.6% (–1.1; 0.0%)* | –1.3% (–1.9; –0.7%)* | 0.8009 |
| Length of stay | –3.1% (–3.5; –2.7%)* | –5.7% (–6.1; –5.3%)* | –9.3% (–9.7; –8.9%)* | < 0.0001 |

Odds ratios for opioid-related adverse effects and for continuous outcomes exponentiated coefficients from the log model depicting % change compared to reference ("opioids only"). Models adjusted for: age, sex, race/ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific hip/knee arthroplasty volume, year of procedure, anesthesia type, patient-controlled analgesia use, individual Elixhauser comorbidities, history of substance use/abuse, pain conditions, psychiatric comorbidities, or opioid use disorder. 1+ indicates opioid prescription after postoperative day 1. 2+ indicates more than two additional analgesic modes.

*$P < 0.05$.

The 85.6% multimodal utilization rate found in our study shows widespread acceptance of the concept. A previous population-based study demonstrated a 90.4% probability of receiving multimodal therapy, slightly higher than the utilization rate in the current study.[4] Nevertheless, while several professional societies have recommended multimodal analgesia to be implemented whenever possible,[17,18] these best practices do not appear to have fully penetrated daily clinical practice. Indeed, previous results suggest that the use of multimodal therapy may be driven by nonmedical and institution-specific factors such as local hospital culture and physician preference, independent of patient or hospital characteristics.[4] Understanding the barriers to changing clinical practice and developing the leadership skills to facilitate implementation of protocols based on emerging evidence are needed.[19,20]

We found that using an increasing number of modalities for pain management was associated with reduced rates of complications that are commonly associated with opioids.[8,21,22] The mechanism underlying these observations may very well be related to the opioid-sparing effects that other drug classes and analgesic procedures exert.[2,23–25] Supporting this concept, we found that decreased complications generally coincided with similar patterns of reduced postoperative opioid prescription. This, in turn, was reduced in a stepwise manner with an increased number of modalities used. A "dose-response" relationship adds strength to the notion of additive action of different pain management modalities and supports scientific robustness of results as "dose-response" patterns generally increase the quality of evidence rating.[26] Future studies should extend this "dose-response" pattern and assess whether there is a threshold after which additional analgesic modes do not result in more reduction of pain (and opioid prescription). While outside of the scope of the current manuscript, preliminary analyses (data not shown) suggest such a threshold may exist at four additional analgesic modes used; however, less than 2% of patients receive more than four analgesic modes.

We found that associations with reduced opioid prescription with increasing analgesic modes used was mainly driven

**Table 5.** Results from Additional Analyses Looking into Opioid Prescription Where an Alternative Multimodal Categorization Is Used That Separates Out the Use of Peripheral Nerve Blocks

| | Multimodal Use (Reference = Opioids Only) | | | | | |
|---|---|---|---|---|---|---|
| | Opioids + PNB | Opioids + PNB + 1 Mode | Opioids + PNB + > 1 Modes | Opioids + 1 Mode | Opioids + 2 Modes | Opioids + > 2 Modes |
| Hip arthroplasties | | | | | | |
| Total opioid prescription | 1.3% (−0.5; 3.2%) | −7.0% (−8.3; −5.7%)* | −14.1% (−15.1; −13.1%)* | −2.3% (−2.9; −1.7%)* | −7.0% (−7.5; −6.4%)* | −12.3% (−12.9; −11.7%)* |
| Day 0 opioid prescription | 0.8% (−1.4; 3.1%) | −6.0% (−7.5; −4.4%)* | −9.4% (−10.6; −8.3%)* | −0.1% (−0.8; 0.5%) | −1.9% (−2.6; −1.2%)* | −5.3% (−6.0; −4.6%)* |
| Day 1 opioid prescription | −3.1% (−5.5; −0.6%)* | −10.4% (−12.1; −8.7%)* | −17.0% (−18.2; −15.7%)* | −7.0% (−7.7; −6.3%)* | −13.2% (−13.9; −12.5%)* | −18.7% (−19.4; −18.0%)* |
| Day 1+ opioid prescription | −4.1% (−6.6; −1.6%)* | −10.3% (−12.1; −8.4%)* | −20.5% (−21.9; −19.2%)* | −6.9% (−7.6; −6.2%)* | −12.6% (−13.4; −11.8%)* | −17.9% (−18.7; −17.1%)* |
| Knee arthroplasties | | | | | | |
| Total opioid prescription | −3.1% (−3.9; −2.3%)* | −7.6% (−8.2; −7.0%)* | −10.7% (−11.2; −10.1%)* | −3.3% (−3.7; −2.9%)* | −6.8% (−7.2; −6.4%)* | −10.0% (−10.4; −9.6%)* |
| Day 0 opioid prescription | −10.7% (−11.6; −9.7%)* | −13.0% (−13.7; −12.2%)* | −12.6% (−13.3; −12.0%)* | −1.9% (−2.4; −1.4%)* | −3.3% (−3.8; −2.8%)* | −3.4% (−3.9; −2.8%)* |
| Day 1 opioid prescription | 3.2% (1.8; 4.5%)* | −5.9% (−6.9; −5.0%)* | −11.0% (−11.7; −10.2%)* | −8.5% (−9.0; −8.0%)* | −14.7% (−15.2; −14.2%)* | −20.2% (−20.7; −19.7%)* |
| Day 1+ opioid prescription | −1.3% (−2.6; 0.1%) | −8.6% (−9.6; −7.6%)* | −12.7% (−13.5; −11.8%)* | −6.7% (−7.3; −6.2%)* | −10.6% (−11.1; −10.0%)* | −15.6% (−16.3; −15.0%)* |

Multilevel regression models with exponentiated coefficients from the log model depicting % change compared to reference ("opioids only"). Models adjusted for: age, sex, race/ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific hip/knee arthroplasty volume, year of procedure, anesthesia type, patient-controlled analgesia use, individual Elixhauser comorbidities, history of substance use/abuse, pain conditions, psychiatric comorbidities, or opioid use disorder. 1+ indicates opioid prescription after postoperative day 1.

*$P < 0.05$.

PNB = peripheral nerve block.

by a decrease in opioid prescription starting the day after surgery. This may be explained by the nature of recording for this drug class in the Premier database. As this variable is derived from billing data, amounts are recorded for entire units (*i.e.*, vials, cartridges) dispensed. Thus, intra- and immediate postoperatively dispensed intravenous opioids given throughout the surgical procedure or *via* PCA equipment in the immediate postoperative period are most certainly counted in full, despite not being actually consumed by the patient. While we adjusted for PCA use in the multivariable models, we found that PCA use was more frequent in the "opioids only" group compared to the groups receiving multimodal analgesia. Another explanation pertains to the relative efficacy of nonopioid analgesics. As opioid utilization decreases in the days after surgery, the relative effect of nonopioid analgesics on reducing opioid utilization may be stronger.

Interestingly, length of stay reduction with increasing number of modalities used did not translate into equal reductions in cost of hospitalization. This could indicate that other drivers of hospitalization cost may be more important. Indeed, a recent population-based study demonstrated a decrease in length of stay for lower joint arthroplasties over time (4.1 to 3.0 days for knee arthroplasty and 4.1 to 2.8 days for hip arthroplasty from 2003 to 2013, respectively), while an increase was observed for inflation-adjusted cost of hospitalization ($14,988 to $22,837 for knees and $15,792 to $23,650 days for hips from 2003 to 2013, respectively).[27] This could be attributed to the increase in utilization of resources for monitoring and care in an increasingly comorbidity-ridden population.[27] In addition, our results may also indicate a minimum length of stay reduction needed for it to translate to cost of hospitalization reductions.

Our main study results are in support of perioperative analgesic protocols that combine multiple analgesic modalities. Crucial follow-up studies are needed and should focus on identifying optimal multimodal regimens and patient subgroups most likely to benefit from each combination. Greatly complicating any such study is the sheer number of potential multimodal combinations. Moreover, differential effects may exist for each specific mode; for example, table 5 shows peripheral nerve blocks to be particularly effective in reduction of opioid prescription on the day of surgery. In a preliminary analysis we found that NSAIDs are the most commonly used analgesic in hip arthroplasty patients, who receive just one additional mode (13.2% of all multimodal patients); in patients receiving two and three additional modes, this is NSAIDs plus acetaminophen (9.8% of all multimodal patients) and NSAIDs plus acetaminophen plus COX-2 inhibitors (7.7% of all multimodal patients), respectively. This leaves 69.3% of all hip arthroplasty patients with other combinations of multimodal analgesia. Identifying multimodal combinations with beneficial outcome patterns would inform targeted clinical investigations bypassing the current stalemate of numerous trials that include a wide

variety of control groups ranging from usual care to just opioids, placebo, and a multitude of multimodal combinations.

Our study has several limitations. Unfortunately, given the nature of the Premier database, we had to rely on ICD-9 coding to define complications and several covariates. Even though Premier performs regular quality checks[6] to identify and correct coding mistakes or falsely entered data, we cannot fully exclude data entry errors. Another limitation is the lack of several important (clinical) variables such as exact drug costs, preoperative opioid use, neuraxial analgesia (we were unable to distinguish between cases with neuraxial anesthesia and those continued as analgesia), and the use of enhanced recovery pathways, which may lead to confounding. We did, however, try to minimize the effect of preoperative opioid use by adjusting for substance use/abuse, pain conditions, psychiatric comorbidities, and preoperative opioid use disorder, given their link to preoperative opioid utilization. Multimodal analgesia and enhanced recovery protocols are correlated; thus, any effect we find could theoretically be due to other components of these protocols. However, multimodal analgesia directly targets pain and is therefore likely to affect opioid utilization and opioid-related adverse effects more so than potential other components. Confounding by indication and selection bias are further potential limitations that we feel have been addressed by our sensitivity analysis and by the fact that we find clear "dose-response" effects. The latter suggests that the difference between hospitals that use multimodal analgesia *versus* those that do not is less important than the difference between the number of multimodal analgesics used on a patient level (in hospitals where multimodal analgesia is used). A further limitation commonly found in population-based studies in respect to opioid-related issues, is the fact that we can only analyze data related to the prescription or dispensing of medication, and not actual consumption. As mentioned previously, this issue has to be taken into account especially in the context of intravenous opioids. These are frequently of high potency and get dispensed in vials with larger quantities on the day of surgery. To mitigate this problem, we have adjusted for PCA use in the multivariable models and distinguished opioid prescription by day of a patient's hospitalization, thus limiting the previously mentioned bias largely to the day of surgery. Moreover, this bias is likely independent of our treatment groups, further minimizing its effect.

In conclusion, in this large population-based study, we identified an association between the use of multimodal pain management approaches using an increasing number of modalities, and reduced postoperative complications and opioid prescription. Importantly, a stepwise improvement in associations for these outcomes was shown with an increasing number of modalities used both in hip and knee arthroplasty. These findings are important as they support the routine use of multimodal pain management approaches for medical and economic reasons, even though the optimal multimodal regimen is still not known. Especially in an era of increased awareness of detrimental opioid-related effects, our findings support making the multimodal analgesic approach ubiquitously available to patients undergoing joint arthroplasty.

## Research Support

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## Competing Interests

The authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Memtsoudis: Department of Anesthesiology, Hospital for Special Surgery, Weill Cornell Medical College, 535 East 70th Street, New York, New York 10021. memtsoudiss@hss.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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