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Utilization and effectiveness of multimodal discharge analgesia for postoperative pain management

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Abstract

Background: Although evidence-based guidelines recommend a multimodal approach to pain management, limited information exists on adherence to these guidelines and its association with outcomes in a generalized population. We sought to assess the association between discharge multimodal analgesia and postoperative pain outcomes in two diverse health care settings.

Methods: We evaluated patients undergoing four common surgeries associated with high pain in electronic health records from an academic hospital (AH) and Veterans Health Administration (VHA). Multimodal analgesia at discharge was characterized as opioids in combination with acetaminophen (O + A) and nonsteroidal antiinflammatory (O + A + N) drugs. Hierarchical models estimated associations of analgesia with 45-d follow-up pain scores and 30-d readmissions.

Results: We identified 7893 patients at AH and 34,581 at VHA. In both settings, most patients were discharged with O + A (60.6% and 54.8%, respectively), yet a significant proportion received opioids alone (AH: 24.3% and VHA: 18.8%). Combining acetaminophen with opioids was

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

associated with decreased follow-up pain in VHA (Odds ratio [OR]: 0.86, 95% confidence interval [CI]: 0.79, 0.93) and readmissions (AH OR: 0.74, CI: 0.60, 0.90; VHA OR: 0.89, CI: 0.82, 0.96). Further addition of nonsteroidal antiinflammatory drugs was associated with further decreased follow-up pain (AH OR: 0.71, CI: 0.53, 0.96; VHA OR: 0.77, CI: 0.69, 0.86) and readmissions (AH OR: 0.46, CI: 0.31, 0.69; VHA OR: 0.84, CI: 0.76, 0.93). In both systems, patients receiving multimodal analgesia received 10%−40% less opioids per day compared to opioids only.

Conclusions: A majority of surgical patients receive a multimodal pain approach at discharge yet many receive only opioids. Multimodal regimen at discharge was associated with better follow-up pain and all-cause readmissions compared to the opioid-only regimen.

Introduction

Postprocedure pain is a key component of surgical care.[1] If poorly managed, it is not only associated with reduced quality of life and higher costs[2] but also increased opioid use,[3] risk of chronic pain, and opioid dependence.[4–6] Regimens using multiple agents that target different pain-relieving mechanismsdso called “multimodal analgesia”dhave been associated with improved pain outcomes and reduced opioid consumption in clinical trials.[7–14] More specifically, the addition of nonsteroidal antiinflammatory drugs (NSAIDs) and/or acetaminophen to postoperative analgesic regimens reduces early pain intensity and morphine consumption.[15,16] For these reasons, postoperative pain management guidelines including those issued by the American Pain Society and the American Society of Anesthesiologists recommend multimodal analgesia for postoperative pain.[17,18] These guidelines have resulted in frequent implementation of multimodal analgesia in inpatient postoperative care.[19]

However, to date, there is limited published data on guideline adherence for multimodal analgesia, specifically at discharge. Furthermore, the evidence of effectiveness of adherence to multimodal analgesic strategies outside of controlled trials is limited. Finally, the effectiveness of such strategies to improve important pain-related outcomes not typically evaluated in controlled clinical trials such as pain severity at follow-up visits or subsequent hospital readmissions also remains unknown. In addition, because postoperative opioid exposure for pain treatment has been implicated as a significant factor contributing to prolonged opioid use and even misuse,[5,6,20,21] identification of opportunities such as those attributed to multimodal analgesic regimens to further limit opioid exposure could potentially positively impact the opioid-use epidemic in the US.[22,23]

To address these shortcomings, we conducted a retrospective study using electronic health records (EHRs) in two diverse settings to test three key questions: (1) are multimodal guidelines being implemented at discharge following key surgeries known for intense postoperative pain?, (2) does the multimodal approach improve pain compared to opioids alone outside of controlled clinical trials?, and (3) do the benefits of multimodal analgesic regimens extend to important pain-related outcomes such as pain at follow-up visits and subsequent hospital readmissions. To answer these questions, we developed hierarchical models at a large academic hospital (AH) and then tested the generalizability of these results

within the US Veterans Health Administration (VHA) data, which include 168 medical centers across all four US geographic regions.

Methods

Data sources

Academic hospital—In the AH, surgical patients were identified in the EHR, which used the EPIC system (Epic Systems, Verona WI) between 2009 and 2016. Specifically, data were extracted from Epic's Clarity relational database, which is updated nightly with the latest data from hospital and clinics.

VHA data—In the VHA cohort, data were obtained from the VA Corporate Data Warehouse, a national data repository from several VA clinical and administrative systems between 2009 and 2015. The Corporate Data Warehouse outpatient domains were queried for preoperative and postoperative outpatient visits including urgent care and emergency room visits. Medication information was obtained using both the bar code medication administration data and the Decision Support System National Data Extract pharmacy data set.

Patient population

We identified inpatients and outpatients undergoing four common surgical procedures using International Classification of Diseases-9-Clinical Modification, International Classification of Diseases-10-CM, and Current Procedural Terminology codes (Supplemental Table 1). The procedures included distal radial fracture, mastectomy, thoracotomy, and total knee replacement, which are reported to be associated with high postoperative pain and often the focus of randomized control trials to try and reduce the pain profile.[24–26] We captured patient demographics, diagnosis, medications, and type of insurance coverage (in the AH). Patients were excluded if age at surgery was less than 18 y or death occurred during the hospitalization. For patients with multiple surgeries, only first surgery was included. Patients with concurrent procedures were included in the analysis.

Study variables

Pain medications—The drug formulary and vocabularies were mapped to a 2016 version of RxNorm, which is part of the Unified Medical Language System and produced by the National Library of Medicine.[27] Prescription orders were distilled to the ingredient level. The algorithm used for data extraction accounted for any combination medications and trade names. The average daily oral morphine consumption for the inpatient stay and discharge medications were calculated using oral morphine equivalent conversion factors.[28,29]

Drug modality—The main indicator variable "drug modality" categorized patients based on discharge pain medications combinations prescribed: opioids only; opioids and NSAIDs (O + N); opioids and acetaminophen (O + A); and opioids, acetaminophen, and NSAIDs (O + A + N). The most commonly prescribed discharge medications (>20 patients receiving medication) were included in the classification. The class of opioids included codeine, hydrocodone, oxycodone, hydromorphone, methadone, fentanyl, meperidine, morphine,

oxymorphone, propoxyphene, and tramadol. The class of NSAIDs included diclofenac, naproxen, ibuprofen, nabumetone, ketorolac, celecoxib, and aspirin.

Patient and clinical characteristics—Patient variables included gender, race/ethnicity (white, Hispanic, black, Asian, and other), age at surgery, insurance type for the AH (private, Medicaid, Medicare and Other). Clinical variables included Charlson comorbidity index (no comorbidity, Charlson score one, and a Charlson score two or more),[30] year of surgery, and days to follow-up. Pain scores were routinely collected on a scale ranging from 0 to 10, where 0 indicates “no pain” and 10 indicates “worst pain”. Preoperative pain (0–10) was included as the last reported pain score up to 45 d before date of surgery. Inpatient oral morphine equivalence was calculated to account for amount of opioids used during the inpatient stay. Opioid-tolerant (nonnaïve) patients were defined as any patient with an outpatient opioid prescription 6 mo before the admission of the surgical procedure. Finally, unique provider/prescriber identification numbers were also obtained from both systems.

Primary outcomes

This study focused on two main outcome measures. First follow-up pain was the pain score recorded at the first follow-up visit within 45 d after surgery. At both the AH and VHA, pain scores were collected by a variety of people, including clinicians, nurses, medical assistants, and trainees/fellows. Pain scores are routinely captured during the health care encounter. Pain scores are stored as structured data within the EHR. These data are time stamped and associated with a health care encounter. This variable was dichotomized to low pain score (0–5) and high pain score (6–10) to aid interpretation according to previously used cutoffs to indicate severity.[31–33] Readmission 30 d after discharge was the second outcome of interest, which included emergency department readmissions and urgent care visits. This variable was dichotomized to yes/no readmission within 30 d after discharge.

Statistical analysis

For this study, models were first developed in the AH, as data are more readily available, easily accessed, and include a diverse population. As models developed at a single hospital are often not generalizable to other populations, we next tested the generalizability of the models in the national VA health care system.

Descriptive statistics were used to examine all independent and outcome variables reported as frequency (%) and means with standard deviations (*T*SD), as appropriate. Bivariate analysis was carried out with each independent variable and outcome variable using Chi square tests, Fisher exact test, and analysis of variance. *P* values less than 0.05 were considered to indicate statistical significance.

Hierarchical logistic regression models were used to examine the association of different drug modalities at discharge with the outcome variables while clustering within individual providers/prescribers and adjusting for other patient and clinical factors: gender, race/ethnicity, age at surgery, insurance, type of surgery, Charlson comorbidity index, preoperative pain, year of surgery, days to follow-up, and the average daily oral morphine

consumption during inpatient stay. All b coefficients for models were reported as odds ratios (ORs) with 95% confidence interval (CI).

The models were first created and tested using AH data. Sensitivity analyses were conducted in the AH cohort to determine the robustness of our models. Outcome variable first follow-up pain score was tested as continuous variables and with different cutoffs based on literature for severe pain (≤8) and using maximum follow-up pain score instead of first follow-up pain score. Next, we compared the multimodal therapy among opioid-naïve *versus* nonnaïve patients. Finally, we assess multimodal therapy in total knee arthroplasty only. Based on the results on the sensitivity analyses in the AH, the most robust models were then replicated using the VHA data. Processing of EMR data was done using Structured Query Language, which enabled us to query all tables within the EHR containing relevant data. Once the patient cohort and associated variables were identified, data were exported for further analyses. Statistical analysis was performed using STATA 13. This study was approved by both the AH internal review board and the local VA institutional review board.

Results

The AH cohort included 7893 patients, and the VHA cohort include 34,581 patients who had undergone one of our four surgeries of interest (Table 1). In both populations, patients were predominantly white (AH: 62.5%, VHA: 81.7%) and about 59–62 y old at time of surgery. The AH cohort included 57.6% women and the VHA cohort included 7% women. In the AH cohort, 46.5% patients had private health coverage.

Most patients in both settings were prescribed opioids + acetaminophen at discharge (AH: 58%, VHA: 50.9%); however, a large proportion was prescribed opioids alone (AH: 29.8%, VHA: 21.2%) (Table 1). In the AH cohort, 898 (11.7%) patients were discharged with a high pain score (6–10) of which 229 (38.2%) reported a high pain score at first follow-up also. A total of 2449 patients (32%) were lost to follow-up; hence, no first follow-up pain score was recorded. In the VHA cohort, 8617 (24.8%) patients were discharged with a high pain score (6–10) of which 3613 (44.7%) reported a high pain score at first follow-up also. In the AH, 925 (17.8%) patients reported high pain score (≤6) at first follow-up visit of which 32% were readmitted within 30 d of discharge. In the VHA, 9820 (30.3%) patients reported high pain score (≤6) at first follow-up visit of which 26.3% were readmitted within 30 d of discharge. A total of 5465 (70.1%) patients at the AH were opioid naïve compared to 22,223 (64.1%) at the VHA (Table 2.).

Table 3 presents data on first follow-up pain score and all-cause readmissions in the AH and VHA. In general, patients receiving any combination of a multimodal therapy at discharge had significantly lower rates of both events compared to those receiving opioids alone, with the exception of first follow-up pain score for opioids + NSAIDs (AH: 22.06% and 19.15%, $P = 0.005$; VHA: 36.68% and 36.71%, $P < 0.0001$, respectively) and 30-d all-cause readmissions in the AH (16.63% and 16.35%, $P < 0.0001$).

Modeled estimates suggest that patients on the multi-modal regime of opioids + acetaminophen (O + A) had lower odds of high pain at first follow-up in VHA (VHA OR:

0.86, 95% CI: 0.79–0.93) and lower odds of readmissions in both systems (AH OR: 0.74, CI: 0.60–0.90 and VHA OR: 0.89, CI: 0.82–0.96) compared to opioids alone (Table 4). Also, the addition of NSAIDs to the regimen of opioids + acetaminophen (O + A + N) also had lower odds of a severe pain at first follow-up (AH OR: 0.71, CI: 0.53–0.96 and VHA OR: 0.77, CI: 0.69–0.86) (Table 4) and lower odds of readmissions (AH OR: 0.46, CI: 0.31–0.69 and VHA OR: 0.84, CI: 0.76–0.93) compared to opioids only. Patients on drug modalities of opioids and acetaminophen received 24% (AH) and 40% (VHA) less opioids daily compared to those receiving opioids alone. The addition of NSAIDs to this combination also resulted in a 10% (AH) and 37% (VHA) reduction in the amount of opioids prescribed daily compared in comparison to those receiving opioids only.

Sensitivity analyses

Sensitivity analyses conducted in the AH cohort to determine most robust fit for models, showed similar associations with the indicator variable regardless of specifications of the first follow-up pain score. (Supplemental Tables 2–4).

Conclusions

In two different health care systems, most surgical patients receive some drug combination at discharge; however, significant proportions receive opioids alone. Discharge multimodal postoperative pain management therapy, which includes a combination of opioids and acetaminophen or opioids, acetaminophen, and NSAIDs, was associated with a significant reduction in follow-up pain scores and 30-d all-cause readmissions compared with opioids alone in two health care settings and among both opioid-tolerant and opioid-naïve patients. This nationwide study is one of the first to demonstrate the effectiveness of the multimodal analgesic outside of a controlled trial. The multimodal regime led to clinically meaningful reductions that extend beyond early pain intensity, including reduced postoperative opioid useda potential gateway to opioid misuse.[6]

Although recommendations exist to use multimodal therapies for postoperative pain,[17,18] a large proportion of postoperative patients receive only opioids, and few patients receive the most effective therapy at discharge suggesting limited adherence to guidelines or awareness of the clinical evidence underlying the recent guidelines.[34] These trends did not differ for opioid-naïve patients, which could be an opportunity to reduce opioid prescriptions for postoperative pain. Diffusion of innovations or guidelines reaching the point of care often take many years and barriers to the effective implementation of guidelines often range from organizational factors to individual patient/provider factors.[35,36] In this surgical population, barriers to widespread adoption of evidence-based guidelines could be due to a number of factors, including unclear or changing guidelines, stronger focus on keeping up to date on the main surgical undertaking compared to pain management, or simply habitual prescribing patterns undeterred by organizational intrusion or concern over potential contraindications of NSAIDs or coprescribing acetaminophen.[36] Recommendations in current guidelines focus predominantly on multimodal use during perioperative/postoperative phase, and few explicitly mention continued used of a multimodal regimen at discharge.[37] In addition, our study found the combination of opioids and acetaminophen was the most commonly

prescribed multimodal approach. This may be due to market availability of ready drug formulations with the combination.[38] Given the overabundance of clinical guidelines and literature, alongside relatively separate channels for pain and surgical publications, it is likely that many surgeons prescribing pain management medications are unaware of existing guidelines. Overcoming these barriers and increasing clinical awareness can be improved by focusing on organizational-level dissemination and enforcement strategies for postoperative pain management.[39]

These findings, although similar to smaller clinical efficacy studies,[40,41] contribute to evidence substantiating the real-world effectiveness of the multimodal approach by using EHR-based data for patients undergoing different types of surgeries under different conditions, in two diverse settings (AH and VA hospital). Moreover, previous studies have focused on effectiveness during the inpatient postoperative phase,[16] while this study exposes longer-term benefits of multimodal including lower amounts of opioids prescribed for those receiving this regime. As research progresses in developing standardized multimodal regimens in terms of the dosing, administration, application routes, times, etc., policy makers can potentially consider the use of multimodal regimen as a quality metric for postoperative pain management, similar to the quality metric assessing the administration of a prophylactic antibiotic before surgery or antithrombotic therapy (Aspirin) for cardiovascular care.[42]

It is well known that prolonged opioid use postsurgery may result in opioid dependence.[43] Studies have found that about 3%−10% of surgical patients prescribed an opioid postoperatively continue to use opioids after 3 mo to a year of the surgery.[43,44] Multiple governmental agencies, including the Food and Drug Administration and Centers for Disease Control and Prevention, have joined forces to tackle the opioid epidemic.[17,45,46] Hence, efforts must be made to provide optimal analgesia using evidence-based regimens such as multimodal analgesia that reduce opioid exposure while enhancing pain control. Stronger efforts should be made to offer multimodal analgesia to opioid-naïve patients, as they generally require less opioids to manage their pain.[47] This study supports these efforts by establishing generalizable evidence to support current guidelines. Using effective postoperative pain management strategies is an essential step to combat this fight against opioid abuse and related side effects.

It is important to understand the dramatic differences in amounts and medication combinations prescribed across surgical specialties.[48] Many studies have shown that orthopedic patients are often prescribed the greatest amounts of opioids.[49,50] Looking within surgical specialties, our work suggests a multimodal pain regime that was associated with improved pain outcomes, even among patients receiving total knee replacement, and these trends were consistent across both health care settings. Importantly, we investigate this hypothesis in two health care systems, the AH and the VA. We specifically included the VA to account for the fact that NSAIDS are available over the counter and would likely be missed in the AH, but not in the VA as they are a documented medication available for veterans. This work highlights opportunities to curb opioid prescriptions following painful surgical procedures.

Several limitations should be considered in interpreting our results. First, our findings are from two health care systems and therefore not necessarily generalizable to the U.S. population. However, the hypothesis was tested in two unique cohorts, and the VHA data represent patients across all four US geographic regions. Our study is unique in that we developed models in the AH and tested the generalizability in the VHA. At the AH, we developed our models with clinical guidance from providers on documentation of key information and important confounders stored within the EHRs. We then extrapolated this knowledge to the VHA and tested our hypothesis for generalizability. The AH has fewer patients than VHA, which may contribute from a sample perspective to the multimodal regimen of O + A not being statistically significant in improving follow-up pain scores. Furthermore, approximately one-third of patients were lost to follow-up in the AH, a common limitation at large tertiary academic centers. Second, our findings are based on existing data taken from EHRs using tailored algorithms for data extraction. There are multiple known caveats in using EHRs for comparative effectiveness research,[51] and efforts were made to check accuracy of selection and extractions of variables based on completeness, clinical meaningfulness, and distributions. Third, acetaminophen and NSAIDs prescribed at discharge might be underreported, since our records included only prescriptions dispensed at hospital pharmacy. NSAIDs and acetaminophen are commonly used as over-the-counter medications, and surgeons may instruct patients verbally to use alternatives available at home which would not be captured in the EHR. However, the generally higher dosage of opioids prescribed at discharge for patients with opioid only compared to multimodal therapy patients contradicts this concern (Table 2). Finally, when we stratified our outcomes by surgical subspecialty, the cohorts became very small, particularly for distal radial fracture and mastectomy. Among the models that did converge, CIs were wide and significance was minimal. Some of these results were inconsistent with our larger cohorts and could represent an inherent bias in the sample. Certainly, further studies are needed to understand these observed differences.

It is important to note that multimodal treatment is not appropriate for all patients. For example, acetaminophen could be contraindicated in patients with liver dysfunction. This study did not capture variations in prescribing patterns based on patient comorbidities. This variation represents an important next step of study to ensure patients receive appropriate pain management. Finally, our cohort includes only the medications that were prescribed to the patients and not the medication that was actually taken. This is a limitation of the study and should be taken into consideration when interpreting the results.

In our study, a significant portion of surgical patients did not receive a multimodal regimen for postoperative pain management. Our results are the first to study the effectiveness of this regimen outside of limited clinical trials, and we demonstrate that a regimen specifically including both NSAIDs and acetaminophen prescribed at discharge is associated with improved follow-up pain scores and fewer read-missions. An important step in combating the US opioid epidemic is to reduce prescription opioids while maintaining adequate pain control, which we show can be accomplished when multimodal analgesic regimens are implemented. Opioid addiction is a national concern, and evidence-based pain management is essential to incorporate into clinical practice to curb this epidemic. More efforts need to be

placed on improving and disseminating evidence-based guidelines for pain management at discharge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Joshi GP, Beck DE, Emerson RH, et al. Defining new directions for more effective management of surgical pain in the United States: highlights of the inaugural Surgical Pain Congress™. Am Surg 2014;80:219–228. [PubMed: 24666860]
2. Sinatra R. Causes and consequences of inadequate management of acute pain. Pain Med 2010;11:1859–1871. [PubMed: 21040438]
3. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003;97:534–540. [PubMed: 12873949]
4. VanDenKerkhof EG, Hopman WM, Goldstein DH, et al. Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study. Reg Anesth Pain Med 2012;37:19–27. [PubMed: 22157741]
5. Gawande AA. It's time to adopt electronic prescriptions for opioids. Ann Surg 2017;265:693–694. [PubMed: 28067675]
6. Waljee JF, Li L, Brummett CM, et al. Iatrogenic opioid dependence in the United States: are surgeons the gatekeepers? Ann Surg 2017;265:728–730. [PubMed: 27429023]
7. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1048–1056. [PubMed: 8105724]
8. Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. Anesthesiol Clin 2010;28:217–224. [PubMed: 20488391]
9. Brubaker L, Kendall L, Reina E. Multimodal analgesia: a systematic review of local NSAIDs for non-ophthalmologic postoperative pain management. Int J Surg 2016;32:158–166. [PubMed: 27394406]
10. Wang J, Liu GT, Mayo HG, et al. Pain management for elective foot and ankle surgery: a systematic review of randomized controlled trials. J Foot Ankle Surg 2015;54:625–635. [PubMed: 24954920]

11. Maund E, McDaid C, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 2011;106:292–297. [PubMed: 21285082]
12. Ong CK, Seymour RA, Lirk P, et al. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010;110:1170–1179. [PubMed: 20142348]
13. Elia N, Tramer MR. Ketamine and postoperative painea quantitative systematic review of randomised trials. Pain 2005;113:61–70. [PubMed: 15621365]
14. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002;96:725–741. [PubMed: 11873051]
15. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005;94:505–513. [PubMed: 15681586]
16. Elia N, Lysakowski C, Tram MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005;103:1296–1304. [PubMed: 16306743]
17. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of regional anesthesia and pain medicine, and the American Society of anesthesiologists' Committee on regional anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131–157. [PubMed: 26827847]
18. American Society of Anesthesiologists. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of anesthesiologists task force on acute pain management. Anesthesiology 2012;116:248–273. [PubMed: 22227789]
19. Ladha KS, Patorno E, Huybrechts KF, et al. Variations in the use of perioperative multimodal analgesic therapy. Anesthesiology 2016;124:837–845. [PubMed: 26835644]
20. Wunsch H, Wijeysundera DN, Passarella MA, et al. Opioids prescribed after low-risk surgical procedures in the United States, 2004–2012. JAMA 2016;315:1654–1657. [PubMed: 26978756]
21. Alam A, Juurlink DN. The prescription opioid epidemic: an overview for anesthesiologists. Can J Anaesth 2016;63:61–68. [PubMed: 26507535]
22. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med 2015;372:241–248. [PubMed: 25587948]
23. Tedesco D, Asch SM, Curtin C, et al. Opioid abuse and poisoning: trends in inpatient and emergency department discharges. Health Aff (Millwood) 2017;36:1748–1753. [PubMed: 28971919]
24. Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain 2010;26:381–385. [PubMed: 20473044]
25. Yazigi A, Abou-Zeid H, Srouji T, et al. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. Ann Card Anaesth 2012;15:32–38. [PubMed: 22234019]
26. Zollinger PE, Tuinebreijer WE, Kreis RW, et al. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354:2025–2058. [PubMed: 10636366]
27. Liu S, Ma W, Moore R, et al. RxNorm: prescription for electronic drug information exchange. IT Prof 2005;7:17–23.
28. Nielsen S, Degenhardt L, Hoban B, et al. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. Pharmacoepidemiol Drug Saf 2016;25:733–737. [PubMed: 26693665]
29. Control NCfIPa. CDC compilation of opioid analgesic formulations with morphine milligram equivalent conversion factors, 2015 version September 19 2016; 2015. Available at: http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf. Accessed August 17, 2017.

30. de Groot V, Beckerman H, Lankhorst GJ, et al. How to measure comorbidity: a critical review of available methods. J Clin Epidemiol 2003;56:221–229. [PubMed: 12725876]
31. Maharaj CH, Kallam SR, Malik A, et al. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. Anesth Analg 2005;100:675–682. [PubMed: 15728051]
32. Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013;118:934–944. [PubMed: 23392233]
33. Zaslansky R, Rothaug J, Chapman C, et al. PAIN OUT: the making of an international acute pain registry. Eur J Pain 2015;19:490–502. [PubMed: 25132607]
34. Kim N, Matzon JL, Abboudi J, et al. A prospective evaluation of opioid utilization after upper-extremity surgical procedures: identifying consumption patterns and determining prescribing guidelines. J Bone Joint Surg Am 2016;98:e89. [PubMed: 27869630]
35. Davis DA, Taylor-Vaisey A. Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997;157:408–416. [PubMed: 9275952]
36. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458–1465. [PubMed: 10535437]
37. McGrory B, Weber K, Lynott JA, et al. The American Academy of orthopaedic surgeons evidence-based clinical practice guideline on surgical management of osteoarthritis of the knee. J Bone Joint Surg Am 2016;98:688–692. [PubMed: 27098328]
38. Barkin RL. Acetaminophen, aspirin, or ibuprofen in combination analgesic products. Am J Ther 2001;8:433–442. [PubMed: 11704782]
39. Brolliar SM, Moore M, Thompson HJ, et al. A qualitative study exploring factors associated with provider adherence to severe pediatric traumatic brain injury guidelines. J Neurotrauma 2016;33:1554–1560. [PubMed: 26760283]
40. Schug SA, Sidebotham DA, McGuinnety M, et al. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesth Analg 1998;87:368–372. [PubMed: 9706932]
41. Plummer JL, Owen H, Ilsley AH, et al. Sustained-release ibuprofen as an adjunct to morphine patient-controlled analgesia. Anesth Analg 1996;83:92–96. [PubMed: 8659772]
42. National Quality Forum. NQF endorses cardiovascular measures Available at: http://www.qualityforum.org/News_And_Resources/Press_Releases/2012/NQF_Endorses_Cardiovascular_Measures.aspx ; 2012. Accessed October 10, 2016.
43. Clarke H, Soneji N, Ko DT, et al. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ 2014;348:g1251. [PubMed: 24519537]
44. Alam A, Gomes T, Zheng H, et al. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med 2012;172:425–430. [PubMed: 22412106]
45. Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med 2016;374: 1480–1485. [PubMed: 26845291]
46. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic paindUnited States, 2016. JAMA 2016;315:1624–1645. [PubMed: 26977696]
47. Patanwala AE, Jarzyna DL, Miller MD, et al. Comparison of opioid requirements and analgesic response in opioid-tolerant versus opioid-naive patients after total knee arthroplasty. Pharmacotherapy 2008;28:1453–1460. [PubMed: 19025426]
48. Hill MV, McMahon ML, Stucke RS, et al. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. Ann Surg 2017;265:709–714. [PubMed: 27631771]
49. Chen JH, Humphreys K, Shah NH, et al. Distribution of opioids by different types of medicare prescribers. JAMA Intern Med 2016;176:259–261.
50. Waljee JF, Zhong L, Hou H, et al. The use of opioid analgesics following common upper extremity surgical procedures: a national, population-based study. Plast Reconstr Surg 2016;137:355e–364e.

51. Hersh WR, Weiner MG, Embi PJ, et al. Caveats for the use of operational electronic health record data in comparative effectiveness research. Med Care 2013;51:S30–S37. [PubMed: 23774517]

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Table 1

Baseline demographic characteristic of patients at time of surgery[*,‡].

Characteristic	Total cohort	Drug modality[†]			
	Total	Opioids	Opioids + NSAID	Opioids + aceta[§]	Opioids + NSAID + aceta[§]
Academic hospital					
No. (%)	7893	1921 (24.34)	375 (4.75)	4779 (60.55)	818 (10.36)
Age—y	59.91 ± 15.84	58.71 ± 15.27	63.75 ± 12.52	59.56 ± 16.20	62.96 ± 15.76
Gender—n (%)					
Women	4552 (57.67)	1033 (22.69)	209 (4.59)	2806 (61.64)	504 (11.07)
Men	3341 (42.33)	888 (26.58)	166 (4.97)	1973 (59.05)	314 (9.40)
Race/Ethnicity—n (%)					
White	4916 (62.28)	1194 (25.77)	244 (4.96)	2917 (59.34)	561 (11.41)
Hispanic	943 (11.95)	243 (25.77)	44 (4.67)	590 (62.57)	66 (7.00)
Black	267 (3.38)	72 (26.97)	14 (5.24)	153 (57.30)	28 (10.49)
Asian	1018 (12.90)	205 (20.14)	38 (3.73)	681 (66.90)	94 (9.23)
Other/Unknown	749 (9.49)	207 (27.64)	35 (4.67)	438 (58.48)	69 (9.21)
Charlson comorbidity—no. (%)					
0	4024 (50.98)	1013 (25.17)	265 (6.59)	2247(55.84)	499 (12.40)
1	1021 (12.94)	276 (27.03)	49 (4.80)	574 (56.22)	122 (11.95)
2+	2848 (36.08)	632 (22.19)	61 (2.14)	1958 (68.75)	197 (6.92)
Insurance type—n (%)					
Private	3504 (44.39)	883 (25.20)	159 (4.54)	2137 (60.99)	325 (9.28)
Medicaid	759 (9.62)	196 (25.82)	27 (3.56)	478 (62.98)	58 (7.64)
Medicare	3398 (43.05)	767 (22.57)	169 (4.97)	2038 (59.98)	424 (12.48)
Other	232 (2.94)	75 (32.33)	20 (8.62)	126 (54.31)	11 (4.74)
Veteran health administration data					
No. (%)	34,581	6504 (18.81)	1847 (5.34)	18,943 (54.78)	7287 (21.07)
Age—y	62.96 ± 9.08	62.58 ± 9.14	62.44 ± 8.36	63.10 ± 9.31	63.06 ± 8.57
Gender—n (%)					
Men	32,158 (92.99)	488 (20.14)	120 (4.95)	1412 (58.27)	403 (16.63)

Characteristic	Total cohort	Drug modality[†]			
	Total	Opioids	Opioids + NSAID	Opioids + aceta[§]	Opioids + NSAID + aceta[§]
Women	2423 (7.01)	6016 (18.71)	1727 (5.37)	17,531 (54.52)	6884 (21.41)
Race/Ethnicity—n (%)					
White	27,339 (81.72)	5301 (19.39)	1447 (5.29)	14,893 (54.48)	5698 (20.84)
Hispanic	142 (0.42)	46 (32.39)	8 (5.63)	61 (42.96)	27 (19.01)
Black	5143 (15.37)	779 (15.15)	283 (5.50)	2934 (57.05)	1147 (22.30)
Other/Unknown	831 (2.48)	152 (18.77)	1781 (5.32)	18,354 (54.86)	7042 (21.05)
Charlson comorbidity—no. (%)					
0	21,668 (62.66)	3820 (17.63)	1209 (5.58)	11,751 (54.23)	4888 (22.56)
1	7219 (20.88)	1295 (17.94)	392 (5.43)	3871 (53.62)	1661 (23.01)
2+	5694 (16.47)	641 (24.39)	246 (4.32)	3321 (58.32)	738 (12.96)

[*] Plus-minus values are means ± SD.

[†] Drug modality-drug combination regime provided at discharge.

[‡] Significant at $P < 0.05$ unless stated otherwise.

[§] Acetaeacetaminophen.

Table 2

Clinical characteristics of patients[*,†].

Characteristic	Total cohort (%)	Drug modality[‡] (%)			
		Opioids	Opioids + NSAID	Opioids + aceta[§]	Opioids + NSAID + aceta[§]
Academic hospital					
No. (%)	7893	1921 (24.34)	375 (4.75)	4779 (60.55)	818 (10.36)
Type of surgery—no. (%)					
Distal radial fracture	735 (9.31)	234 (31.84)	2 (0.27)	491 (66.53)	10 (1.36)
Mastectomy	1049 (13.29)	117 (11.15)	7 (0.67)	897 (85.51)	28 (2.67)
Knee replacement	3422 (43.35)	951 (27.79)	304 (8.88)	1621 (47.37)	546 (15.96)
Thoracotomy	2687 (34.04)	619 (23.04)	62 (2.31)	1772 (65.95)	234 (8.71)
Pain at discharge—no. (%)					
Low pain (0–5)	6738 (88.24)	1599 (23.73)	328 (4.87)	4093 (60.75)	718 (10.66)
High pain (6–10)	898 (11.76)	268 (29.84)	40 (4.45)	521 (58.02)	69 (7.68)
Days to first follow-up[‖]—no. (%)					
0–30 d	4397 (85.78)	1129 (25.68)	171 (3.89)	2753 (62.61)	344 (7.82)
31–45 d	729 (14.22)	243 (33.33)	31 (4.25)	387 (53.09)	68 (9.33)
Length of stay–d	6.60 (±14.25)	7.81 (±21.13)	4.30 (±8.12)	6.75 (±12.08)	3.95 (±3.87)
Inpat. oral morphine equivalence[¶]—mg/d	60.33 (±70.13)	73.56 (±84.53)	60.31 (±53.69)	55.76 (±65.97)	55.93 (±58.27)
Preoperative pain score[#]	2.74 (±3.28)	3.22 (±3.30)	4.08 (±3.50)	2.44 (±3.21)	2.57 (±.27)
Discharge oral morphine equivalence [**]—mg/d	72.40 (±63.81)	86.00 (±86.18)	85.02`(±58.02)	67.70 (±53.81)	78.07 (±50.56)
Opioid naïve					
Yes	5465 (70.06)	1184 (21.67)	275 (5.03)	3352 (61.34)	654 (11.97)
No	2336 (29.94)	714 (30.57)	96 (4.11)	1376 (58.90)	150 (6.42)
Veterans health data					
No. (%)	34,581	6504 (18.81)	1847 (5.34)	18,943 (54.78)	7287 (21.07)
Type of surgery—no. (%)					
Distal radial fracture	819 (2.37)	167 (20.39)	9 (1.10)	595 (72.65)	48 (1.36)
Mastectomy	701 (2.03)	113 (16.12)	7 (1.00)	552 (78.74)	29 (4.14)

Characteristic	Total cohort (%)	Drug modality‡ (%)			
		Opioids	Opioids + NSAID	Opioids + aceta§	Opioids + NSAID + aceta§
Knee replacement	25,939 (75.01)	4491 (17.31)	1553 (5.99)	13,613 (52.48)	6282 (24.22)
Thoracotomy	7122 (20.60)	1733 (24.33)	278 (3.90)	4183 (58.73)	928 (13.03)
Pain at discharge—no. (%)					
Low pain (0–5)	25,985 (75.14)	4678 (18.00)	1279 (4.92)	14,562 (56.04)	5466 (21.04)
High pain (6–10)	8596 (24.86)	1826 (21.24)	568 (6.61)	4381 (50.97)	1821 (21.18)
Days to first follow-up§–no. (%)					
0–30 d	21,751 (62.90)	4117 (18.93)	1008 (4.63)	12,503 (57.48)	4123 (18.96)
31–45 d	12,830 (37.10)	2387 (18.60)	839 (6.54)	6440 (50.19)	3164 (24.66)
Length of stay—d	6.48 (±8.35)	7.34 (±8.98)	6.40 (±8.62)	6.41 (±8.05)	5.89 (±8.33)
Inpat. oral morphine equivalence‖—mg/d	60.50 (±55.45)	72.94 (±68.04)	76.40 (±68.40)	54.29 (±47.37)	61.65 (±55.93)
Preoperative pain score¶	3.80 (±3.32)	3.92 (±3.31)	4.18 (±3.30)	3.63 (±3.34)	4.04 (±3.26)
Discharge oral morphine equivalence#—mg/d	45.24 (±46.42)	60.51 (±73.46)	58.30 (±54.78)	40.16 (±35.81)	41.52 (±31.40)
Opioid naïve					
Yes	22,223 (64.12)	3899 (17.58)	1186 (5.35)	12,307 (55.48)	4789 (21.59)
No	12,438 (35.88)	2605 (21.01)	661 (5.33)	6636 (53.52)	2498 (20.15)

*Plus-minus values are means ± SD.

†Significant at $P < 0.05$ unless stated otherwise.

‡Drug modality-drug combination regime provided at discharge.

§Aceta–acetaminophen.

‖Days until first follow-up visit.

¶Calculated average oral morphine equivalence in milligrams during the inpatient stay.

#Preoperative pain score.

**Calculated average oral morphine equivalence in milligrams given at discharge.

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Table 3

Characteristics of drug modality according to first follow-up pain score and readmissions[*].

Drug modality[†]	AH (*n* = 5187)		VHA (*n* = 24,485)	
	Low pain (0–5)	**High pain (6–10)**	**Low pain (0–5)**	**High pain (6–10)**
First follow-up pain score				
Opioids—no. (%)	1127 (80.85)	267 (19.15)	2915 (65.75)	1691 (36.71)
Opioids and NSAID—no. (%)	159 (77.94)	45 (22.06)	707 (65.16)	446 (38.68)
Opioids and aceta[‡]—no. (%)	2624 (82.72)	548 (17.28)	9660 (70.96)	4257 (30.58)
Opioids and NSAID and aceta[‡]—no. (%)	352 (84.41)	65 (15.59)	3321 (70.97)	1488 (30.94)
TOTAL—no. (%)	4262 (82.17)	925 (17.83)	16,603 (67.80)	7882 (32.20)
Drug modality[†]	AH (*n* = 7893)		VHA (*n* = 34,581)	
	No	Yes	No	Yes
30-d all-cause readmissions				
Opioids—no. (%)	1607 (83.65)	314 (16.35)	5244 (80.63)	1260 (19.37)
Opioids and NSAID—no. (%)	340 (90.67)	35 (9.33)	1537 (83.22)	310 (16.78)
Opioids and aceta[‡]—no. (%)	3970 (83.07)	809 (16.93)	15,809 (83.46)	3134 (16.54)
Opioids and NSAID and aceta[‡]—no. (%)	747 (91.32)	71 (8.68)	6251 (85.78)	1036 (14.22)
TOTALdno. (%)	6664 (84.43)	1229 (15.57)	28,898 (83.37)	5763 (16.63)

[*] Significant at $P < 0.05$ unless stated otherwise.

[†] Drug modality-drug combination regime provided at discharge.

[‡] Acetaeacetaminophen.

Table 4

The estimated association between drug modality and first follow-up pain and readmissions.

Drug modality	**AH (*n* = 3810)**		**VHA[†] (*n* = 23,773)**	
	Adjusted analysis odds ratio (95% CI)	***P* value**	**Adjusted analysis odds ratio (95% CI)**	***P* value**
First follow-up Pain score[*]				
Opioids	1 (Ref)		1 (Ref)	
Opioids and NSAID	0.95 (0.61, 1.47)	0.83	1.00 (0.87, 1.15)	0.97
Opioids and acetaminophen	0.97 (0.78, 1.20)	0.91	0.86 (0.79, 0.93)	0.001
Opioids and NSAID and acetaminophen	0.71 (0.53, 0.96)	0.02	0.77 (0.69, 0.86)	<0.001
Drug modality	AH (*n* = 4791)		VHA (*n* = 32,739)	
	Adjusted analysis odds ratio (95% CI)	*P* value	Adjusted analysis odds ratio (95% CI)	*P* value
Readmissions[†]				
Opioids	1 (Ref)		1 (Ref)	
Opioids and NSAID	0.84 (0.53, 1.32)	0.46	0.97 (0.85, 0.10)	0.66
Opioids and acetaminophen	0.74 (0.60, 0.90)	0.004	0.89 (0.82, 0.96)	0.007
Opioids and NSAID and acetaminophen	0.46 (0.31, 0.69)	<0.001	0.84 (0.76, 0.93)	0.001

[*] First pain score recorded within 45 d of discharge date. Models controlled for gender, age at surgery, race/ethnicity, insurance, Charlson comorbidity, surgery type, days to follow-up, preoperative pain, discharge pain, inpatient oral morphine equivalence, and year of surgery by provider/prescriber.

[†] All-cause readmissions within 30 d of discharge date. Models controlled for gender, age at surgery, race/ethnicity, insurance, Charlson comorbidity, surgery type, preoperative pain, discharge pain, inpatient oral morphine equivalence, and year of surgery by provider/prescriber.