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Variations in the Use of Perioperative Multimodal Analgesic Therapy

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Abstract

Objective—Practice guidelines for perioperative pain management recommend that multimodal analgesic therapy should be used for all post-surgical patients. However, the proportion of patients whom actually receive this evidence-based approach is currently unknown. The objective of this study was to describe hospital-level patterns in the utilization of perioperative multimodal analgesia.

Methods—Data for the study were obtained from the Premier Research Database. Patients undergoing below-knee amputation, open lobectomy, total knee arthroplasty and open colectomy between 2007 and 2014 were included in the analysis. Patients were considered to have multimodal therapy if they received one or more non-opioid analgesic therapies. Mixed-effects logistic regression models were used to estimate the hospital-specific frequency of multimodal therapy use while adjusting for the case-mix of patients and hospital characteristics and accounting for random variation.

Results—The cohort consisted of 799,449 patients who underwent a procedure at one of 315 hospitals. The mean probability of receiving multimodal therapy was 90.4%, with 95% of the hospitals having a predicted probability between 42.6% and 99.2%. In a secondary analysis, we examined whether patients received two or more non-opioid analgesics, which gave an average predicted probability of 54.2%, with 95% of the hospitals having a predicted probability between 9.3% and 93.2%.

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Conclusion—In this large nationwide sample of surgical admissions in the United States we observed tremendous variation in the utilization of multimodal therapy use not accounted for by patient or hospital characteristics. Efforts should be made to identify why there are variations in the use of multimodal analgesic therapy and to promote its adoption in appropriate patients.

Introduction

Postoperative pain is a significant issue for the millions of patients undergoing surgery in the United States each year. Effective treatment of post-surgical pain has been shown to decrease the incidence of chronic pain, improve patient satisfaction and decrease resource utilization[1–4]. Yet despite efforts to improve the provision of perioperative analgesia, the proportion of patients reporting moderate to severe pain after surgery has remained constant over the past decade[5,6].

While opioids provide effective analgesia, their use can be limited by side effects in the perioperative period[7]. Multimodal analgesia refers to the use of two or more drugs or non-pharmacologic interventions with differing mechanisms. Its use has been shown to limit the amount of opioids consumed and provide more effective pain control than opioids alone[8–10]. Component therapies of multimodal analgesia with substantial evidence to support efficacy in postoperative patients include gabapentinoids[11–13], acetaminophen[14,15], ketamine[16,17], non-steroidal anti-inflammatory drugs[18,19], and regional anesthesia[20,21].

The sum of the currently available evidence, even after the exclusion of numerous studies in this field that were found to be fraudulent, suggests that routine use of multimodal analgesia should be the standard of care[8,22]. Indeed, current practice guidelines for perioperative pain management recommend that multimodal therapy should be used in all post-surgical patients[23]. However, the proportion of patients whom actually receive this evidence-based approach is currently unknown. The objective of this study was to describe hospital-level patterns in the utilization of perioperative multimodal analgesia for four common non-cardiac surgeries: open colectomy, total knee arthroplasty, lobectomy and below the knee amputation. These operations were selected to represent major intra-abdominal, orthopedic, non-cardiac thoracic and vascular surgical procedures respectively. We hypothesized that there would be substantial variation in the use of multimodal therapy not explained by patient or hospital characteristics.

Methods

Data source

Data for the study were obtained from the Premier Research Database and included patients undergoing a surgical procedure from the fourth quarter of 2007 till the third quarter of 2014. Premier is a hospital-based database that includes *International Classification of Diseases, 9th revision, Clinical Modification* (ICD-9 CM) discharge diagnoses codes. The database also contains detailed information on all charges for procedures performed and medications administered during an inpatient hospitalization. The database has been previously used to evaluate the safety and patterns of use of inpatient medications[24–30]. The

use of these de-identified data for research was approved by the Partners Institutional Review Board (Boston, MA).

Cohort

Using ICD-9 codes we identified adult patients undergoing four types of surgical procedures: below-knee amputation, open lobectomy, total knee arthroplasty and open colectomy. The use of ICD-9 codes to differentiate between open and minimally invasive lobectomies and colectomies has been well established in the prior literature[31–35]. Additionally, we excluded patients with any codes or charges that suggested a laparoscopic or video-assisted thorascopic surgery since the smaller incisions might alter the approach to pain management. We also excluded patients under the age of eighteen, as pediatric pain management is a separate entity. We restricted our analysis to hospitals with greater than 10 procedures for each surgery type in the database as smaller numbers of procedures would yield unstable estimates of multimodal therapy use. The final cohort included 315 hospitals.

Exposure

Exposure was defined on the basis of charges generated at any time from the day of surgery till the day of discharge. We identified patients who received regional blockade with local anesthetics i.e. epidural placement and peripheral nerve blocks, oral cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), non-selective NSAIDs, calcium channel α-2-δ antagonists (gabapentinoids), ketamine and acetaminophen. The full list of medications included in these categories can be found in Supplemental Digital Content 1 and the complete set of codes can be obtained upon request from the corresponding author. Patients were considered to have multimodal therapy if they received one or more of these non-opioid analgesic therapies. In a secondary analysis, we examined the proportion of patients who received two or more non-opioid therapies.

Covariates

We considered five groups of covariates, which could relate to multimodal analgesia use. These included: (1) surgery type (2) patient demographics and year of procedure (3) medical co-morbidities, (4) pain related conditions, psychiatric co-morbidities and psychoactive medication use and (5) hospital characteristics. We assessed the following patient demographics: gender, age and race/ethnicity. Medical comorbidities were defined based on the presence of ICD-9 CM diagnosis codes during the surgical hospitalization[36]. These included renal disease, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, diabetes, coagulopathy, liver disease, AIDS/HIV, paralysis, peptic ulcer disease, valvular disease, pulmonary circulation disorders, seizure disorders and other neurological disorders. Pain conditions and psychiatric co-morbidities were assessed in a similar manner and included malignancy, back pain, fibromyalgia, chronic pain, rheumatoid arthritis, migraines, anxiety, depression, dementia, personality disorder and psychoses. Psychoactive medication usage during the surgical hospitalization was also assessed and included the use of anxiolytics, anti-depressants, anti-psychotics, and anti-convulsants (excluding gabapentioids). We also considered the following hospital characteristics: urban (versus rural) location, geographic region (categorized as Midwest, Northeast, South, and West), teaching status, and annual procedure volume tertile (based on

total procedure volume during the study time period, categorized as low [66–302], medium [303–509], or high [511–1838]). A full list of covariates and associated codes can be found in Supplemental Digital Content 1.

Statistical analysis

The proportion of patients who received multimodal therapy was determined for each hospital and hospitals were divided into quartiles based on the overall proportion of patients who received multimodal therapy. Patient and hospital characteristics that were likely to influence the use of multimodal therapy were described stratified by hospital quartile, and compared with a chi-square test.

We used mixed-effects logistic regression models to estimate the hospital-specific frequency of multimodal therapy while adjusting for patient case-mix and hospital characteristics as well as account for random variation. For each model, a variable identifying each hospital was added as a random intercept, and patient-level and hospital-level covariates were incorporated as fixed effects. The hospital-specific intercept represents the hospital-specific frequency for multimodal therapy use after adjusting for covariates[37,38].

We used sequential mixed effects models with increasing levels of adjustment to assess the relative influence of different patient and hospital characteristics for between-hospital variation in multimodal therapy use. After adjusting for all patient and hospital level characteristics, the hospital-specific intercepts represented the hospital-level tendency to utilize multimodal therapy independent of covariates.

Due to the large number of covariates, we used propensity scores as a data reduction technique[37,38]. For each stage of sequential adjustment, a separate propensity score was estimated to predict exposure to multimodal therapy and included in the mixed effects model. The propensity score was centered on the mean so that the random intercept for an individual hospital represented the probability that an average patient would be treated with multimodal therapy in a given hospital.

We performed two additional analyses in order to better interpret the trends discovered in the primary analysis. First, we repeated the analysis but varied the definition of the exposure based on two time periods: the day of surgery and the days after surgery until discharge. This was undertaken to investigate the dynamics of the perioperative period. Specifically, since anesthesiologists decide which analgesics are administered on the day of surgery this variation may be less compared to that found on subsequent days. Additionally, we repeated the primary analysis in sub-groups defined by surgical procedure. This was performed to ensure that the results of the primary analysis were not driven by the most common surgery i.e. total knee arthroplasty and to determine whether the use of multimodal therapy varied by procedure. As with the primary analysis, the propensity score was re-estimated for each model in the sub-group analyses. All analyses were performed in SAS (version 9.3; SAS, Carey, NC) and mixed effects model were run using the NLMIXED command.

Results

The cohort included 799,449 patients who underwent a procedure at any of the 315 hospitals of which 4% underwent a below-knee amputation, 22% underwent a colectomy, 3% percent underwent a lobectomy and 71% underwent a total knee arthroplasty. Of all the patients, 97% received an opioid, whereas 66% received acetaminophen. The usage of individual analgesics varied by surgery type. For example, the rate of regional anesthesia was 27% amongst patients undergoing lobectomy, but only 3% for those undergoing below-knee amputation. The usage of each analgesic by surgery type is displayed in table 1. The observed (crude) overall usage of multimodal therapy was 85.8% amongst all patients and the median hospital utilization rate was 89.5% (inter-quartile range 80.8% to 94.0%). We stratified hospitals based on the proportion of patients treated with multimodal therapy and differences between quartiles for each covariate were assessed. The lowest quartile had a greater proportion low volume centers and black patients when compared to the highest quartile. Patients in the highest in quartile were more likely to be using an anti-depressant and have chronic pain but less likely to have a solid tumor compared to the lowest quartile. Covariates and differences across quartiles are fully displayed in tables 2 and Supplemental Digital Content 2.

The results of the sequential mixed-effects logistic regression models with demographic, medical comorbidities, pain related conditions and psychiatric comorbidities, and hospital-level covariates added at each step are shown in table 3. The between-hospital variance in the use of multimodal therapy is described by σ_b^2. If the between-hospital variation in multimodal therapy use is fully explained by the covariates, σ_b^2 would be expected to approach zero and all hospitals would be predicted to have the same probability of multimodal therapy use. In the unadjusted model, the σ_b^2 (SE) was 1.75 (0.14) and when controlling for all covariates the σ_b^2 decreased slightly to 1.68 (0.14). Thus the variation observed was not explained by patient or hospital level factors. The unadjusted mixed effects model generated a mean predicted probability of exposure to multimodal of 87.9% and 95% of the hospitals had a predicted probability between 35.2% and 99.0%. These estimates remove random variation compared with the crude estimates, but do not account for potential between-hospital differences in patient and hospital characteristics. In the fully adjusted model (accounting for patient and hospital characteristics), the mean predicted probability was 90.4%, with 95% of the hospitals having a predicted probability between 42.6% and 99.2%.

The predicted probabilities of multimodal therapy use for each hospital in rank-order in the unadjusted and fully adjusted models are presented in Figure 1 (panel A). We observed little attenuation of the variation in use of multimodal therapy when accounting for a broad range of patient and hospital characteristics.

In a secondary analysis, we examined whether patients received two or more non-opioid analgesics, which may confer additional benefits to the patient by targeting additional pain pathways. Within the entire cohort, the observed proportion of patients who received more than one non-opioid analgesic was 55.7% and the median hospital utilization was 54.6% (inter-quartile range 37.5% to 68.2%). In the unadjusted model, the σ_b^2 (SE) was 1.54 (0.13)

and after adjustment for all covariates the σ_b^2 increased to 1.56 (0.13), again suggesting that the variation is not explained by the patient and hospital factors included in the model. In the unadjusted mixed-effects model, the predicted mean probability of receiving two ore more non-opioid analgesics was 51.1% (95% range of 8.4–92.3). In the fully adjusted model, the average predicted probability was 54.2%, with 95% of the hospitals having a predicted probability between 9.3% and 93.2%. The results from the sequential models in the secondary analysis are presented in Supplemental Digital Content 3. The predicted probabilities of receiving two or more non-opioid analgesics for each hospital in rank-order in the unadjusted and fully adjusted models are presented in figure 1 (panel B). Similar to the initial exposure definition, there was little change in the variation observed when controlling for covariates.

When the exposure definition was divided into two time periods (day of surgery and days after surgery), a greater proportion of patients received a non-opioid analgesic on the days after surgery compared to the day of surgery (80% vs 65%). The same trend, although less pronounced, occurred when examining the use of two or more non-opioid analgesics (38% vs 34%). The complete list of proportions for each individual analgesic separated by perioperative time period can be found in Supplemental Digital Content 4 (table S5). When using mixed effects models, there was little change in the variation between the unadjusted and fully adjusted models (Supplemental Digital Content 4, tables S6 and S7). Figure 2 displays the range of predicted proportions across hospitals for both time periods.

The mixed effects models were also run for each individual surgery type. The range of multimodal therapy usage did vary by surgical procedure. When examining the use of more than one non-opioid analgesic, the mean predicted probability of exposure to multimodal therapy in the fully adjusted model was 84.4% (95% range 40.6% – 97.7%) for patients undergoing below-knee amputations compared to 73.1% (95% range 32.4%–93.9%) for patients who had a colectomy. Similar to the primary analysis, there was little change in the variation between the fully adjusted and unadjusted models. The complete results from the models for each surgery type can be found in Supplemental Digital Content 5. Figure 3 displays the ranges of multimodal use for each surgical procedure from the fully adjusted mixed effects models. Of note, when examining the use of one or more non-opioid analgesics in patients undergoing total knee arthroplasty, the fully adjusted model did not converge and estimates could not be obtained.

Discussion

In this large nationwide sample of surgical admissions in the United States we observed tremendous variation in the use of multimodal therapy use. Adjustment for patient demographics, comorbidities and hospital characteristics did not mitigate this variation as the majority of hospitals had a utilization rate ranging from 43%–99% in the fully adjusted model. When extending the analysis to the use of two or more non-opioid analgesics the range was even wider with 95% of the hospitals ranging from 8% – 92%. This analysis suggests that the use of multimodal therapy is based on nonmedical and institution specific factors such as local hospital culture and individual physician preference independent of patient, surgical, or other hospital characteristics. We also found that the usage of

multimodal therapy varied by surgical procedure and multimodal analgesia was less prevalent on the day of surgery compared to the days following surgery.

This analysis represents, to the best of our knowledge, the first empiric description of the use of multimodal therapy in the United States. The use of multimodal therapy has been recommended by numerous societies, as a strategy that should be implemented whenever possible[23,39,40]. The results of our analysis demonstrate that these recommendations have not been universally adopted. In our cohort, nearly all patients received an opioid, however they did not consistently receive an additional non-opioid analgesic. The incidence of side effects due to opioids is high in the perioperative period with gastrointestinal and central nervous system related adverse event rates ranging as high as thirty percent[41]. These adverse reactions have been implicated in significant increases in mortality, cost, lengths of stay and readmission rates[7,42,43]. Several previous studies have demonstrated that combinations of analgesic agents lead to more effective pain control with fewer side effects[8–10]. Therefore expanding the use of non-opioid analgesics can potentially result in improved outcomes and patient satisfaction. Further research should be undertaken to better understand the barriers to administering these medications to all eligible patients.

It is important to note that the variation in practice was greater when examining the use of two or more non-opioid analgesics. Thus the real opportunity in decreasing variability may be in expanding the use of multiple types of medications, rather than just a single non-opioid analgesic. However additional study is required to determine the optimal combinations of medications that maximizes synergy of analgesia, while minimizing side effects from polypharmacy.

This study has certain limitations inherent to its design. We were unable to control for outpatient medication use prior to surgery. Patients who are opioid tolerant might be more prone to receiving multimodal therapy and certain hospitals may have a higher prevalence of these patients. However, the prevalence of patients with drug abuse or dependence (including opioid abuse/dependence) was similar across each of the hospital quartiles, suggesting this was not an important determinant of the observed patterns. Further, covariates are based on ICD-9 codes and the sensitivity of certain codes is limited for some conditions. However, this is unlikely to explain the tremendous variations in practice between institutions, particularly given that the predicted use did not shift significantly with adjustment for measured covariates.

We examined four surgeries, selected because they span across four different surgical specialties and there is an evidence base for the benefits of multimodal analgesia with these procedures[44]. However, even amongst these procedures, we observed differences in the use of multimodal therapy by surgery type. Thus, the variation across other surgical procedures, in which the evidence to support the use of multimodal analgesia is less robust, would likely be even greater than the amount observed in this study. Medication administration was determined by charge codes under the assumption that a patient actually received a medication if he or she was assigned a billing code for it. In our cohort 97% of patients had a billing code for an opioid suggesting that the rate of potential misclassification of medication administration was small and unlikely to significantly affect the results. Finally,

the unit of analysis in our study was the hospital and not individual providers since we did not have provider-level data. Given, the multitude of physicians and other healthcare providers that interact with a patient during the perioperative period, it is difficult to identify any single individual as responsible for providing perioperative analgesia. For this reason, the hospital may be the ideal level for action, through interventions such as the creation of an acute pain service[45] or the establishment of protocols.

There is no doubt that postoperative pain management should be tailored to individual patients and specific surgical procedures. For example, elderly patients with certain comorbidities may not be candidates to receive gabapentin or COX-2 inhibitors. However, the results of our study suggest that the non-opioid analgesics are under-utilized at many institutions. These medications provide a potential cost-effective strategy to improve outcomes and patient satisfaction with a side-effect profile that is superior to opioids alone. We see little reason why the utilization rate of multimodal therapy should not be dramatically higher across all hospitals. Efforts should be made to identify why there are variations in the use of multimodal analgesic therapy in patients undergoing surgery. This represents an opportunity for both surgeons and anesthesiologists to work together to ensure the delivery of multimodal analgesia to each and every patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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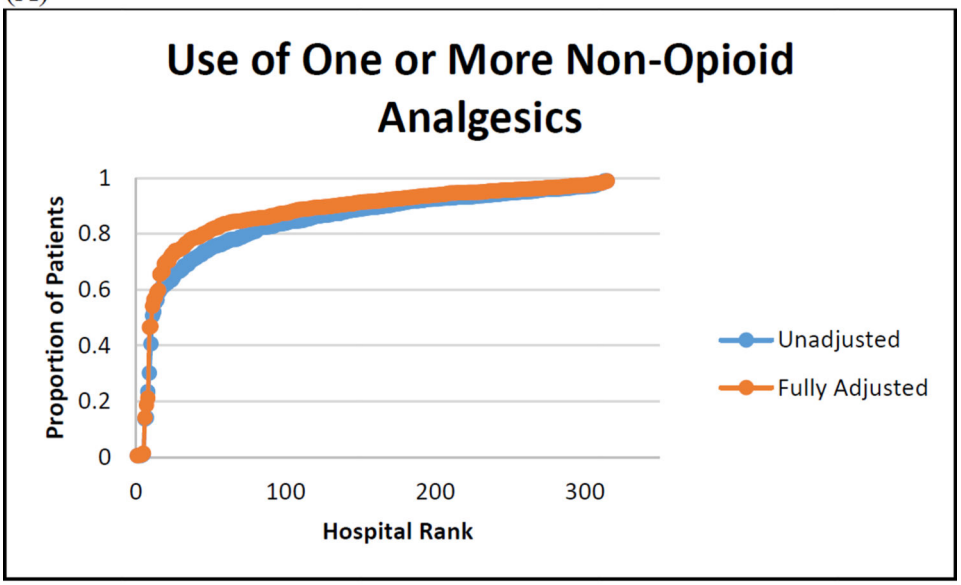


(B)

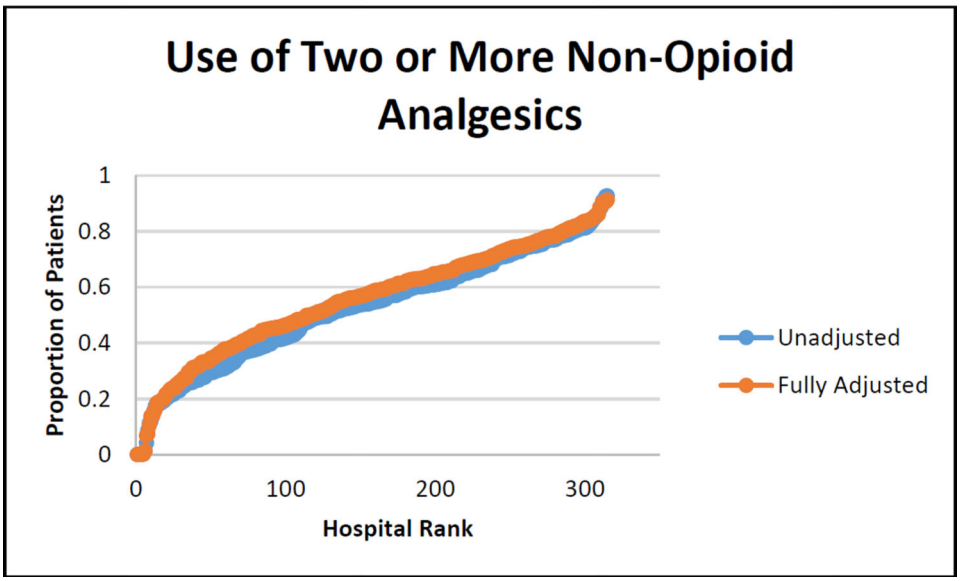


Figure 1.

Range of predicted proportions of the use of multimodal therapy obtained from unadjusted and fully adjusted mixed effects models in the entire cohort. Panel A shows the rate of use of one or more non-opioid analgesics. Panel B represents the estimated proportion of patients receiving two or more non-opioid analgesics at each hospital.

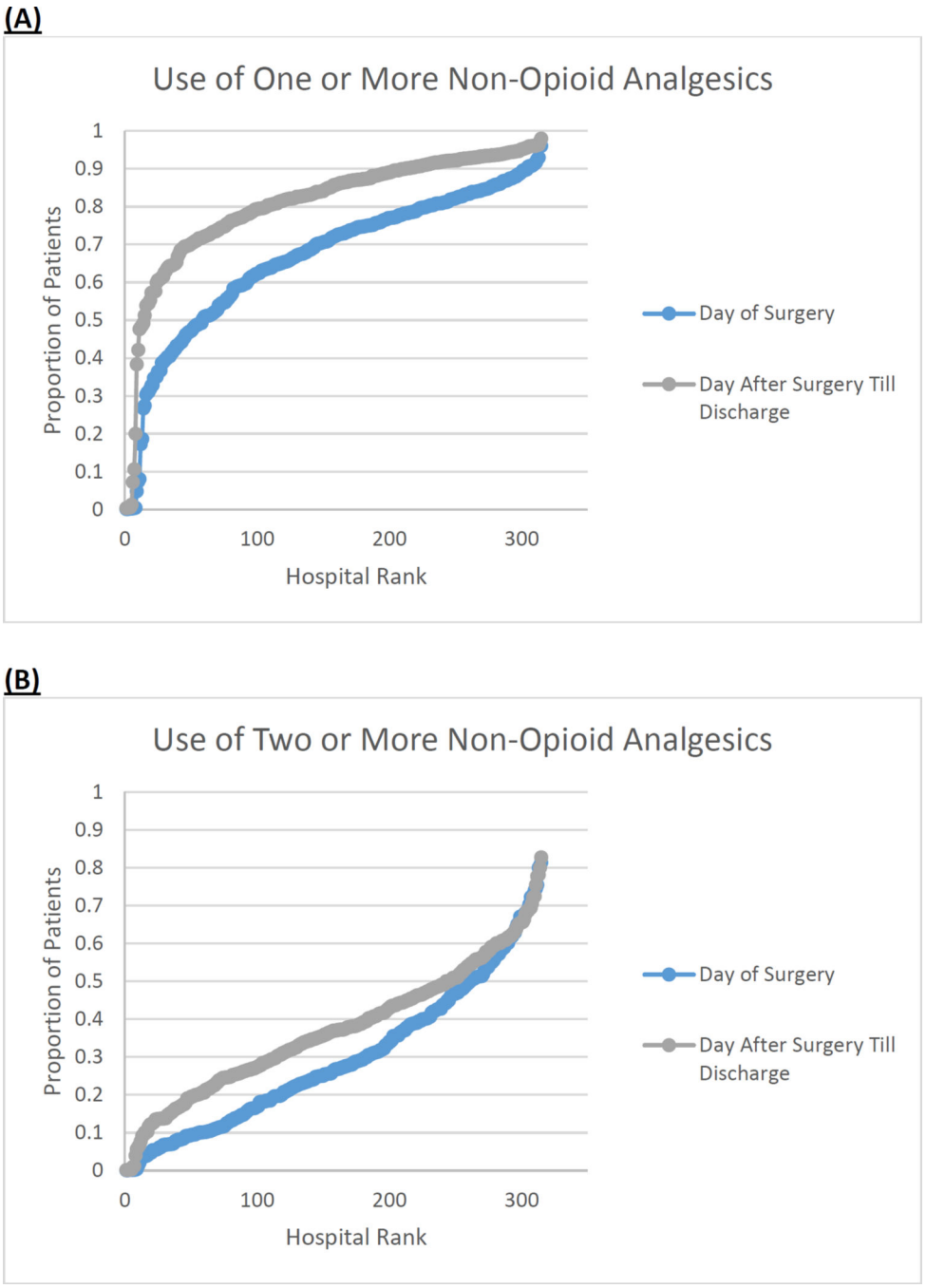
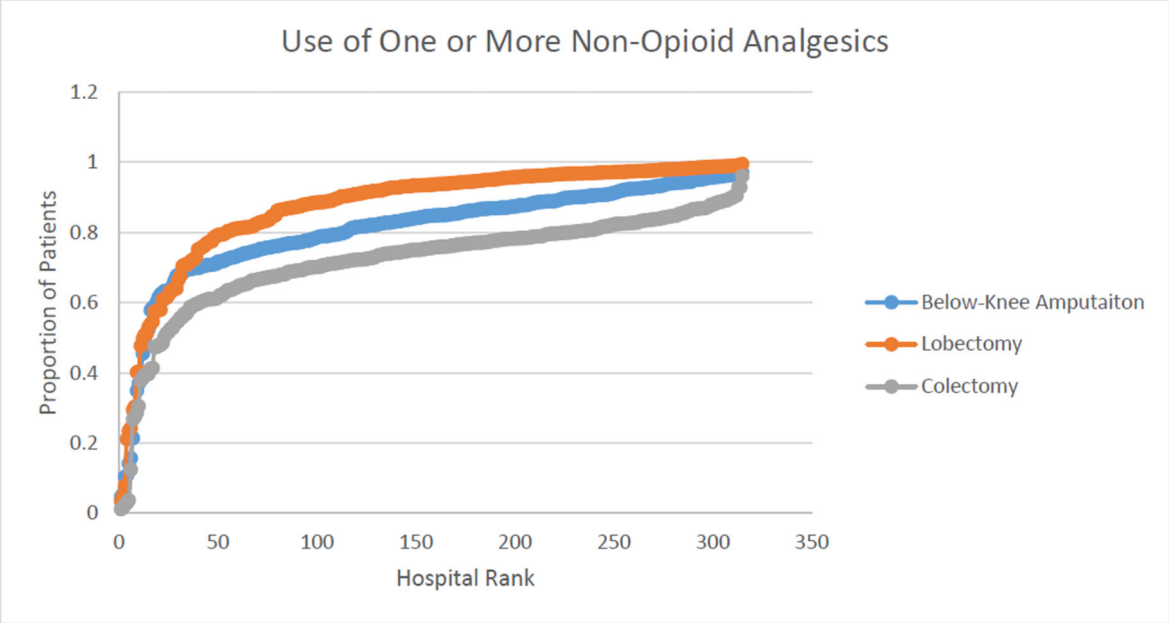


Figure 2.

Range of predicted proportions of the use of multimodal therapy obtained from fully adjusted mixed effects models grouped by perioperative time period. Panel A shows the rate of use of one or more non-opioid analgesics. Panel B represents the estimated proportion of patients receiving two or more non-opioid analgesics at each hospital.

(A)



(B)

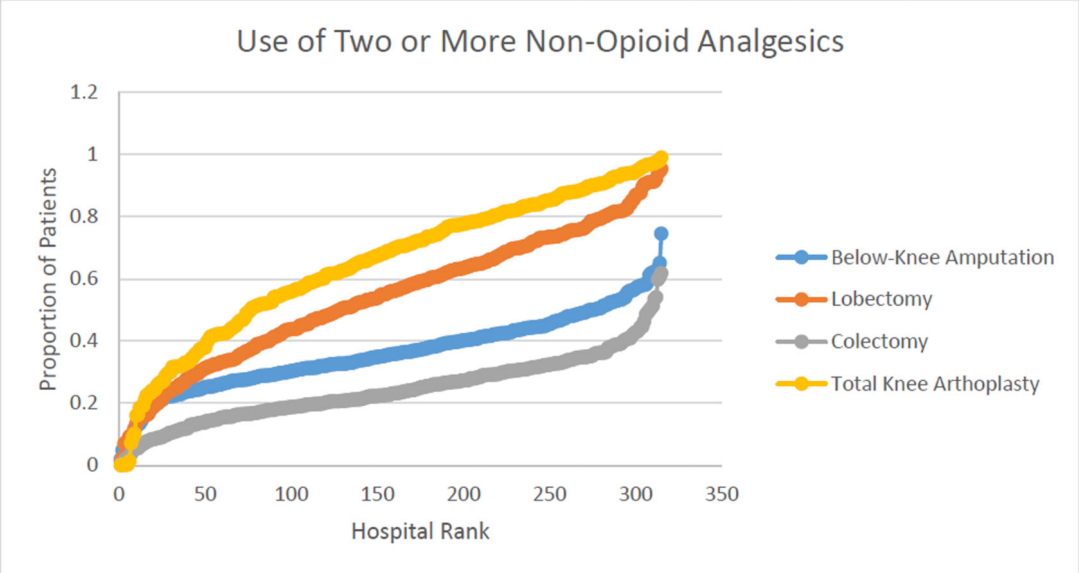


Figure 3.

Range of predicted proportions of the use of multimodal therapy obtained from fully adjusted mixed effects models grouped by type of surgery Panel A shows the rate of use of one or more non-opioid analgesics. Panel B represents the estimated proportion of patients receiving two or more non-opioid analgesics at each hospital. Of note, the model examining the use of one or more non-opioid analgesics in total knee arthroplasty did not converge and thus estimates could not be calculated.

Table 1

Usage of Analgesic Technique Across Surgical Procedures:

	Total	Any-Non Opioid Analgesic	More than One Non-Opioid Analgesic	Regional Anesthesia	Acetaminophen	COX-2 Inhibitors	Non-Specific NSAIDs	Gabapentinoids	Ketamine	Any Opioid
Below-Knee Amputation	32375	25920 (80.1)	11758 (36.3)	855 (2.6)	21329 (65.9)	420 (1.3)	4727 (14.6)	11562 (35.7)	1664 (5.1)	31217 (96.4)
Colectomy	171942	122533 (71.3)	44056 (25.6)	10083 (5.9)	96060 (55.9)	1579 (0.9)	53769 (31.3)	7348 (4.3)	4121 (2.4)	166241 (96.7)
Lobectomy	23696	20643 (87.1)	12870 (54.3)	6326 (26.7)	15070 (63.6)	494 (2.1)	13454 (56.8)	1909 (8.1)	628 (2.7)	22834 (96.4)
Total Knee Arthroplasty	571436	516770 (90.4)	376208 (65.8)	81871 (14.3)	398881 (69.8)	220191 (38.5)	285667 (50.0)	126178 (22.1)	23402 (4.1)	555209 (97.2)

Values displayed as n, (%)

NSAIDs – non-steroidal anti-inflammatory drugs
COX-2 – cyclooxygenase-2

Table 2

Selection of Patient and Hospital Level Characteristics According to Quartile of Multimodal Therapy Usage

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
Number of Patients	165966	184953	209969	238561	
Number of Hospitals	78	79	80	78	
Percentage of Patients Receiving Multimodal Therapy, median (min to max)	71.3 (0.1–80.7)	85.7 (80.8–89.4)	92.4 (89.5–94.0)	96.0 (94.0–99.0)	
Surgery Type					
Below Knee Amputation	8012 (4.8)	8339 (4.5)	8633 (4.1)	7391 (3.1)	<.0001
Open Colectomy	46419 (28.0)	43114 (23.3)	45554 (21.7)	36855 (15.5)	
Open Lobectomy	5474 (3.3)	5756 (3.1)	6264 (3.0)	6202 (2.6)	
Total Knee Replacement	106061 (63.9)	127744 (69.1)	149518 (71.2)	188113 (78.9)	
Demographic					
Male	67304 (40.6)	74491 (40.3)	86227 (41.1)	96669(40.5)	<.0001
Age					
18–30	2011 (1.2)	1728 (0.9)	1934 (0.9)	1444 (0.6)	<.0001
31–40	3501(2.1)	3267(1.8)	3489(1.7)	3096(1.3)	
41–50	13235 (8.0)	12937 (7.0)	14218 (6.8)	14492 (6.07)	
51–60	37297 (22.5)	40388 (21.8)	46807 (22.3)	51456(21.6)	
61–70	52462 (31.6)	61346 (33.2)	69448 (33.1)	81838 (34.3)	
71–80	40984 (24.7)	47738 (25.8)	53628 (25.5)	63600 (26.7)	
81 and over	16476 (9.9)	17549 (9.5)	20445 (9.7)	22635 (9.5)	
Race					
Other	34798 (21.0)	37584 (20.3)	27800 (13.2)	40205 (16.9)	<.0001
Black	20196 (12.2)	20437 (11.1)	16393 (7.8)	15243 (6.4)	
White	110972 (66.9)	126932 (68.6)	165776 (79.0)	183113 (76.8)	
Hospital Characteristics					
Teaching Hospital	72542 (43.7)	93153 (50.4)	93961 (44.8)	90678 (38.0)	<.0001
Procedure Volume					
Low	44075 (26.6)	35170 (19.0)	26507 (12.6)	18206 (7.6)	<.0001
Middle	51788 (31.2)	51971 (28.1)	68675 (32.7)	57765 (24.2)	

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
High	70103 (42.2)	97812 (52.9)	114787 (54.7)	162590 (68.2)	
Pain related conditions and psychiatric co-morbidities					
Alcohol Abuse	2905 (1.8)	3274 (1.8)	3700 (1.8)	3632 (1.5)	<.0001
Drug Abuse	2328 (1.4)	2677 (1.5)	2777 (1.3)	2637 (1.1)	<.0001
Tobacco Abuse	35354 (21.3)	46567 (25.2)	50080 (23.9)	59342 (24.9)	<.0001
Back Pain	9455 (5.7)	11030 (6.0)	13315 (6.3)	17801 (7.5)	<.0001
Chronic Pain	4646 (2.8)	5929 (3.2)	6283 (3.0)	9992 (4.2)	<.0001
Metastatic Cancer	8433 (5.1)	7488 (4.1)	7845 (3.7)	7079 (3.0)	<.0001
Solid Tumor	21510 (13.0)	20858 (11.3)	21316 (10.2)	19051 (8.0)	<.0001
Anxiety	12267 (7.4)	14683 (7.9)	13924 (6.6)	17678 (7.4)	<.0001
Depression	21040(12.68)	26053(14.09)	27882(13.28)	33696(14.12)	<.0001
Medication Usage					
Anxiolytic	40863(24.62)	49329(26.67)	55316(26.34)	60894(25.53)	<.0001
Anti-Depressant	31206(18.80)	42799(23.14)	51586(24.57)	57982(24.30)	<.0001
Medical Comorbidities					
Chronic Pulmonary Disease	31763(19.14)	35459(19.17)	37586(17.90)	40907(17.15)	<.0001
Diabetes	40972(24.69)	46684(25.24)	49883(23.76)	53607(22.47)	<.0001
Ischemic Heart Disease	8040(4.84)	9585(5.18)	10167(4.84)	10350(4.34)	<.0001
Renal Disease	14000(8.44)	15459(8.36)	15402(7.34)	16196(6.79)	<.0001

Additional covariates incorporated into the mixed effects models are listed in table S3

Table 3

Estimated Hospital Level Usage Rate of One or More Non-Opioid Analgesics Based on Mixed-Effects Models with Increasing Levels of Adjustment for Patient and Hospital-Level Factors

			Multimodal Therapy Usage Rate (%)		
Models	**β_0(SE)[a]**	**σ^2(SE)[b]**	**Average Hospital[c]**	**2.5 Percentile[d]**	**97.5 Percentile**
Unadjusted	1.98 (0.075)	1.75 (0.14)	87.87	35.20	98.97
Adjusted for:					
Surgery Type	2.18 (0.076)	1.80 (0.15)	89.92	39.04	99.20
Surgery Type, Demographics, Year of Hospitalization	2.18 (0.076)	1.80 (0.15)	89.86	38.91	99.19
Surgery Type, Demographics, Year of Hospitalization, Medical Co-Morbidities	2.18 (0.076)	1.80 (0.15)	89.84	38.88	99.19
Surgery Type, Demographics, Year of Hospitalization, Medical Comorbidities, Pain Related Conditions, Psychiatric Comorbidities, Medication Usage	2.18 (0.075)	1.74 (0.14)	89.83	39.91	99.16
Surgery Type, Demographics, Year of Hospitalization, Medical Comorbidities, Pain Related Conditions, Psychiatric Comorbidities, Medication Usage and Hospital Characteristics	2.24 (0.073)	1.68 (0.14)	90.43	42.64	99.18

[a] β_0 is the marginal (averaged across hospitals) odds of using multimodal therapy for a patient with the mean propensity score

[b] Estimate of the between-hospital variation. The random intercept b_j for each hospital is assumed to be normally distributed with mean 0 and variance σ^2. σ^2 represents the hospital-specific deviation from β_0. With increasing levels of adjustment, there is less unexplained variation and σ_b^2 is expected to decrease.

[c] Prescribing proportion for the "average" patient, defined as a patient with a mean propensity score. The average differs slightly between models since different factors are being adjusted for in the various models; it is estimated as $\exp(\beta_0)/[1 + \exp(\beta_0)]$.

[d] Range determined from observed predicted values