



Original research

The interaction of depression and prior opioid use on pain and opioid requirements after total joint arthroplasty

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ABSTRACT

Background: Preoperative opioid use causes increased pain and opioid requirements after total joint arthroplasty (TJA), but the effect of depression on this relationship is not well defined.

Methods: We conducted a retrospective review of primary TJA patients using an institutional database. Demographic variables, inpatient opioid requirements, and discharge prescription quantities were collected and compared between patients with and without a prior diagnosis of depression in both the prior opioid-using and nonusing cohorts.

Results: Four hundred and three patients were analyzed between August 1, 2016, and July 31, 2017. Among prior opioid users, patients with depression experienced higher inpatient pain levels (4 vs 3; $P = .001$), required more inpatient opioids (117 oral morphine equivalents [OMEs] vs 70 OMEs; $P = .022$), were prescribed more opioids at discharge (1163 OMEs vs 750 OMEs; $P = .02$), and required more long-term opioid refills (57.7% vs 15.4%; $P < .001$) than patients without depression. However, depression was not associated with increased pain, opioid requirements, prescription quantities, or refill rates among opioid-naïve patients.

Conclusions: Depression is not associated with increased pain or opioid requirements among opioid-naïve patients after TJA but is associated with significantly higher pain and opioid requirements among patients who use opioids preoperatively. The interaction of these variables may highlight a target for preoperative counseling and risk modification in the arthroplasty population.

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Introduction

The United States is in the midst of a prescription opioid crisis. Between 1999 and 2012, the sales and related overdose deaths from prescription opioid medications quadrupled [1–3]. Although opioids are an essential element of pain management after surgery, surgeons and perioperative providers play an important role in controlling usage and dissemination of these addictive medications. Studies estimate that between 3% and 7% of patients who were previously opioid naïve continue to take prescription pain

medication more than 1 year later [4,5]. In addition, physicians frequently discharge patients with more opioid medication than required, risking opioid diversion [6]. Studies also show that for many heroin users, addiction started with prescription pain medication, often prescribed to other patients [7].

With the increasing focus from physicians, government officials, and public policy-makers on the clinical utilization of perioperative opioids, it is important for orthopedic surgeons to consider specific patient characteristics that increase pain and opioid consumption after surgery, particularly to target patients for risk modifications. One such subset of patients comprised those with depression. The prevalence of depression in the general population is estimated to be 9.1% [8], and it has a major impact on public health and global disease burden [9]. The prevalence of depression in the orthopedic population is believed to be even higher [10–13]. With respect to opioid use, depression has been shown to be strongly associated with chronic pain, and the prevalence of opioid use among patients

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with depression doubles compared with that of an appropriate control population [14]. This relationship between depression and opioid use potentially puts patients with depression at risk for increased dependence on opioids in the perioperative period.

To our knowledge, there has been limited study on how depression affects postoperative pain, opioid requirements, and opioid prescriptions after total joint arthroplasty (TJA) and whether this relationship changes among prior opioid users and nonusers. The purpose of this study was to compare postoperative pain, opioid requirements, and prescriptions in TJA patients with and without depression and to assess how this relationship changes among patients who are using and not using opioids preoperatively.

Material and methods

Patient cohort

The authors performed a retrospective review of an institutional clinical database from a single large tertiary referral center over a 1-year period from August 1, 2016, to July 31, 2017. Patients were included if they underwent a primary hip or knee replacement requiring hospital admission. Exclusion criteria included discharge from a nonorthopedic service and admission duration less than 24 hours. Patients undergoing joint replacement for hip fractures were also excluded. Patient factors including age, active opioid use (defined as having an opioid on their admission medication reconciliation), and an active diagnosis of depression (defined as having an International Classification of Diseases-10 code of one or more of F33.9, F33.0, F33.1, F33.2, F33.3, F33.41, F33.42, F32.8, F32.9 on the active problem list) were collected along with operative time and length of hospitalization.

Power analysis

An a priori power analysis was performed using effect sizes previously reported on predischARGE opioid consumption between depressed and nondepressed patients. A study by Etcheson et al. [15] found among total knee arthroplasty (TKA) patients that opioid consumption on the third hospitalization day was 23.2 oral morphine equivalents (OMEs) for those with depression vs 10.2 OMEs for those without depression (although they did not specifically distinguish between opioid users and nonusers). Using this effect size in a two-tailed test with power set to 0.8 and significance set to 0.05, a total of 30 patients would be required with at least 15 in each group.

Perioperative pain control

The perioperative pain control protocol was constant over this time period and included a multimodal regimen. This included preoperative and postoperative scheduled doses of oral acetaminophen, celecoxib, and neurotin with oral oxycodone as needed and intravenous hydromorphone for breakthrough pain. All patients received a periarticular injection as described by Kelley et al. [16] that includes ropivacaine, epinephrine, ketorolac, and clonidine. Total knee patients also underwent placement of an adductor canal catheter preoperatively by the anesthesiology service, dosed with 0.5% ropivacaine. This catheter was removed on the morning of the first postoperative day.

Postoperative pain, opioid consumption, and discharge prescriptions

Pain levels as measured on the Visual Analog Scale were obtained for the first postoperative day, as were the types, amounts, and regimens of opioids both prescribed at discharge and

consumed by the patient the day before discharge. Using the institution's opioid conversion table, all opioids taken by the patient on the last full calendar day (24 hours) of their hospitalization (including opioids administered orally, intravenously, or transdermally) were converted into OMEs, according to standard reporting of opioid dosing [17]. Similarly, both the total and daily discharge opioid prescription regimens were converted into OMEs. In the setting of multiple discharge opioid prescriptions, each was independently converted to OMEs and then added together to create a single total OME amount prescribed for each patient. Opioid prescription refills were also recorded if they occurred at our institution between 0 to 30 days, 31 to 60 days, and 61 to 90 days after discharge.

Statistical analysis

Pain levels, inpatient opioid requirements, discharge prescription quantities, and length of stay were shown to involve non-normal distributions using the Shapiro-Wilk test. These variables were subsequently compared between patients with and without a prior diagnosis of depression using the Mann-Whitney U test for variables with skewed distributions, and this comparison was stratified by prior opioid use. Categorical variables (surgery type, depression diagnosis, refills) were compared using the chi-square test. All statistical analyses were performed on the STATA software (version 15.0; StataCorp, College Station, TX), with significance set to $P < .05$.

This study was approved by the medical center's institutional review board.

Results

Demographics

A total of 403 patients admitted after primary hip ($n = 234$) or knee ($n = 169$) replacement were analyzed. For patients, their age ranged from 22 to 95 years, the rate of depression was 10.7%, the rate of prior opioid use was 45.2%, and the median discharge opioid prescription was 675 OMEs (interquartile range, 450-960). Patients with and without prior opioid use were found to be comparable with respect to age, gender, procedure, and operative time, but patients with prior opioid use had a higher rate of depression and longer hospitalizations (Table 1). In the non-opioid-using cohort, there were 17 patients with depression and 204 patients without depression, whereas there were 25 patients with depression and 156 patients without depression in the opioid-using cohort. These groups satisfied the minimum of 15 patients per group required for adequate power in this analysis. Within both the prior opioid-using and non-opioid-using cohorts, demographic, surgical, and inpatient characteristics

Table 1
Patient, surgery, and inpatient characteristics by prior opioid use and depression.

Patient Characteristics	Without prior opioid use (N = 221)	With prior opioid use (N = 182)	P value
Age (y)	64 (IQR, 59-67)	64 (IQR, 57-71)	.93
Male	45.7%	37.4%	.09
Primary THA	132 (59.7%)	102 (56.0%)	.46
Primary TKA	89 (40.3%)	80 (44.0%)	
Operative time (min)	104.5 (IQR, 82-126)	111 (89-126)	.27
Prior diagnosis of depression	17 (7.7%)	26 (14.3%)	.033
Length of stay (d)	1.5 (IQR, 1.3-2.3)	2.2 (1.3-2.4)	.037

IQR, interquartile range.

Values are listed as median (IQR) or number (percent total). Items in bold are statistically significant.

were comparable between those with and without depression (Table 2).

Pain level comparison

Among prior opioid users, patients with depression experienced significantly higher pain levels on the first postoperative day (4 vs 3; $P = .001$) and on the final hospitalization day (4 vs 3; $P = .003$) than patients without depression. However, depression was not associated with higher pain levels on the first postoperative day (2 vs 3; $P = .33$) or the final hospitalization day (2 vs 2; $P = .28$) among nonopioid users (Table 3).

Inpatient opioid requirements

Among prior opioid users, patients with depression required more opioids 24 hours before discharge (117 OMEs vs 70 OMEs; $P = .022$) than patients without depression (Table 3; Fig. 1). Among nonopioid users, depression was not associated with differences in the pre-discharge day opioid requirements (38 OMEs vs 30 OMEs; $P = .73$) (Table 3; Fig. 1).

Discharge prescription comparison

Patients with a diagnosis of depression were given a larger total opioid prescription at discharge (1163 OMEs vs 750 OMEs; $P = .02$) and a larger daily discharge prescription regimen (150 OMEs vs 120 OMEs; $P = .02$) than patients without depression among prior opioid users. In contrast, depression was not associated with differences in total discharge prescription quantities (675 OMEs vs 600 OMEs; $P = .60$) or daily discharge prescription regimens (95 OMEs vs 90 OMEs; $P = .44$) between depressed and nondepressed patients in the opioid-naïve cohort (Table 3; Fig. 2).

Prescription refill rates

Among prior opioid users, patients with and without a diagnosis of depression required similar opioid refill rates from 0 to 30 days after discharge (61.5% vs 47.4%; $P = .18$). However, those with depression required significantly more refills from 31 to 60 days (76.9% vs 39.1%; $P < .001$) and 61 to 90 days (57.7% vs 15.4%; $P < .001$) after discharge among prior opioid users. Depressed and nondepressed patients who did not use opioids preoperatively required similar refill rates at all time points after discharge (Table 3; Fig. 3).

Discussion

The results of this study suggest that the effect of depression on postoperative pain and opioid consumption differs among those who are and those who are not using opioids preoperatively. In particular, depression was associated with significantly higher pain

levels on the first postoperative day, pain levels on the last hospitalization day, opioids consumed in the 24 hours before discharge, opioids prescribed at discharge, and refill rates among prior opioid users but not for opioid-naïve patients. Although the link between depression and pain has been studied, to our knowledge, this is the first study to stratify the impact of depression on postoperative pain and opioid usage by prior opioid use. This trend suggests that depression is a significant risk factor for increased postoperative pain and opioid use among patients who use opioids preoperatively, which may highlight a cohort of patients who warrant targeted risk modification preoperatively.

The neurobiological changes that occur in depression have been previously shown to have significant overlap with those occurring in acute pain, suggesting these conditions share similar pathways and may not be entirely separate processes [18–21]. Bistolfi et al. [22] studied the influence of mild depressive symptoms on postoperative pain perception after TKA. Though there was no difference in pain perception before surgery, the mildly depressed cohort patients were more likely to report pain and have lower Hospital for Special Surgery scores at 1 year postoperatively. Furthermore, Singh and Lewallen analyzed predictors of pain medication use in TJA, finding links between depression and pain medication use at 2-year follow-up [23,24]. These studies collectively suggest that total joint patients with depression may have increased opiate requirements and increased pain in the postoperative period.

The present study aimed to further define the role of depression as a predictor of postoperative pain and opioid consumption by controlling for preoperative opioid use, which is a known risk factor for increased postoperative pain and opioid requirements. The results suggest that preoperative opioid use and depression interact as risk factors, with depression playing a more significant role in postoperative pain and opioid requirements among prior opioid users. While preoperative opioid use was defined as having an opioid on the active preoperative medication list, some preoperative opioid users may also have had chronic pain, which is linked to depression in a number of studies [25,26]. In a longitudinal analysis of 500 primary care patients with persistent back, hip, or knee pain, Kroenke et al. [27] found that changes in pain severity were a strong predictor of subsequent depression severity, and changes in depression severity also predicted changes in pain severity. The interplay between pain, opioid use, and depression is therefore complex, and it is important to better define this relationship to optimize patients for surgery and to educate them on the expected pain and recovery in the postoperative period.

Patients who are using opioids before surgery will likely have more difficulty controlling pain in the postoperative period because of opioid tolerance, but there may be other factors impacting opioid use as well. One term useful in this discussion is pain catastrophization, which can impact how patients interpret and respond to pain. It is believed to be an exaggerated negative mindset and inability to cope, which can contribute to more intense pain [28]. A

Table 2
Patient, surgery, and inpatient characteristics by prior opioid use and depression.

Patient Characteristics	Without prior opioid use (N = 221)			With prior opioid use (N = 182)		
	With depression (N = 17)	Without depression (N = 204)	P value	With depression (N = 26)	Without depression (N = 156)	P value
Age (y)	64 (62–70)	63 (59–67)	.39	61 (57–68)	64 (57–71)	.76
Male	35.3%	46.6%	.37	23.1%	39.7%	.10
Primary THA	9 (52.9%)	123 (60.3%)	.55	10 (38.5%)	92 (59.0%)	.051
Primary TKA	8 (47.1%)	81 (39.7%)		16 (61.5%)	64 (41.0%)	
Operative time (min)	100 (81–125)	104.5 (82–127)	.80	113.5 (104–128)	109.5 (86–125)	.20
Length of stay (d)	2.2 (1.4–3.3)	1.5 (1.3–2.3)	.12	2.3 (2.1–3.3)	2.1 (1.3–2.4)	.02

IQR, interquartile range.

Values are listed as median (IQR) or number (percent total). Items in bold are statistically significant.

Table 3
Pain scores, length of stay, opioids consumed, and opioids prescribed.

Pain and prescription detail	Without prior opioid use (N = 221)			With prior opioid use (N = 182)		
	With depression (N = 17)	Without depression (N = 204)	P value	With depression (N = 26)	Without depression (N = 156)	P value
VAS pain score on POD1	2 (1-4)	3 (2-4)	.33	4 (4-6)	3 (2-4)	.001
VAS pain score on final hospitalization day	2 (1-3)	2 (2-4)	.28	4 (3-4.5)	3 (2-4)	.003
Opioids taken 24-h before discharge (OMEs)	38 (23-53)	30 (15-60)	.73	117 (75-153)	70 (38-137)	.022
Daily opioid regimen prescribed at discharge (OMEs)	95 (90-135)	90 (90-128)	.44	150 (120-240)	120 (90-180)	.02
Total opioids prescribed at discharge (OMEs)	675 (450-750)	600 (450-750)	.60	1163 (675-1600)	750 (563-1350)	.02
Refills 0-30 d after discharge	41.2%	29.4%	.31	61.5%	47.4%	.18
Refills 31-60 d after discharge	17.7%	10.8%	.39	76.9%	39.1%	<.001
Refills 61-90 d after discharge	4.4%	0%	.38	57.7%	15.4%	<.001

IQR, interquartile range; POD, post-operative day; VAS, Visual Analog Scale. Values are listed as median (IQR) or number (percent total). Items in bold are statistically significant.

study by Riddle et al. [29] analyzed a variety of psychologic factors including depression and pain catastrophization to predict knee pain at 6 months after a TKA. They found that pain catastrophization, not depression, was the only consistent predictor of a poor outcome.

Although we did not assess specifically for pain catastrophization in our study, our findings suggest that it is not preexisting depression alone that results in increased postoperative pain and opioid requirements but that depression in the setting of prior opioid use markedly increases these challenges. This shows the possibility that there may be a need to better target and optimize patients with both depression and prior opioid use. It may be possible to find alternative ways to treat these patients aside from increasing opioids in the postoperative period, and preoperative opioid reduction may impact postoperative usage. One randomized controlled trial took a group of primary care patients with depression and comorbid hip, back, or knee pain with the intervention arm consisting of 12 weeks of optimized antidepressant therapy followed by 6 sessions of a pain self-management program [30]. At 1 year, the patients in the intervention arm had a reduced

prevalence of depression, as well as a clinically and statistically significant reduction in pain. These results suggest alternatives to opioid therapy in a depressed patient which ultimately may prove more effective and would allow the patients to fully realize the benefits of their joint replacement.

While much of the conversation surrounding the use and prescription of opioids is focused on long-term dependence and addiction, there is also a question of whether there are any short-term impacts from increased use of opioids in the postoperative period. Namba et al. [31] studied 24,105 TKA patients of whom 41% continued to use opioids after the initial 90-day postoperative period. The patients who continued to use medium-low to high opioids during this time period were at a higher risk of revision at 1 year postoperatively. Expanding these results to our study, the subset of depressed patients with prior opioid use may be at increased risk for revision, considering the dramatically increased opioid consumption seen in this subgroup. This further emphasizes the need for preoperative counseling and intervention to minimize the use of opioids and risk of adverse complications in the postoperative period. In addition, minimizing the

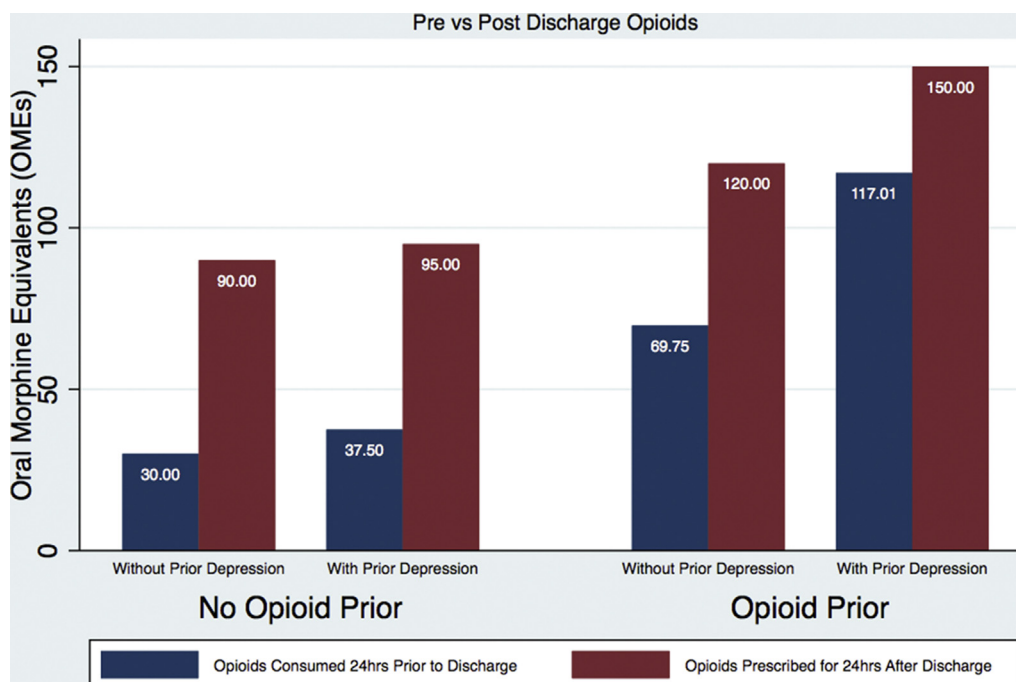


Figure 1. Pre vs post discharge opioids.

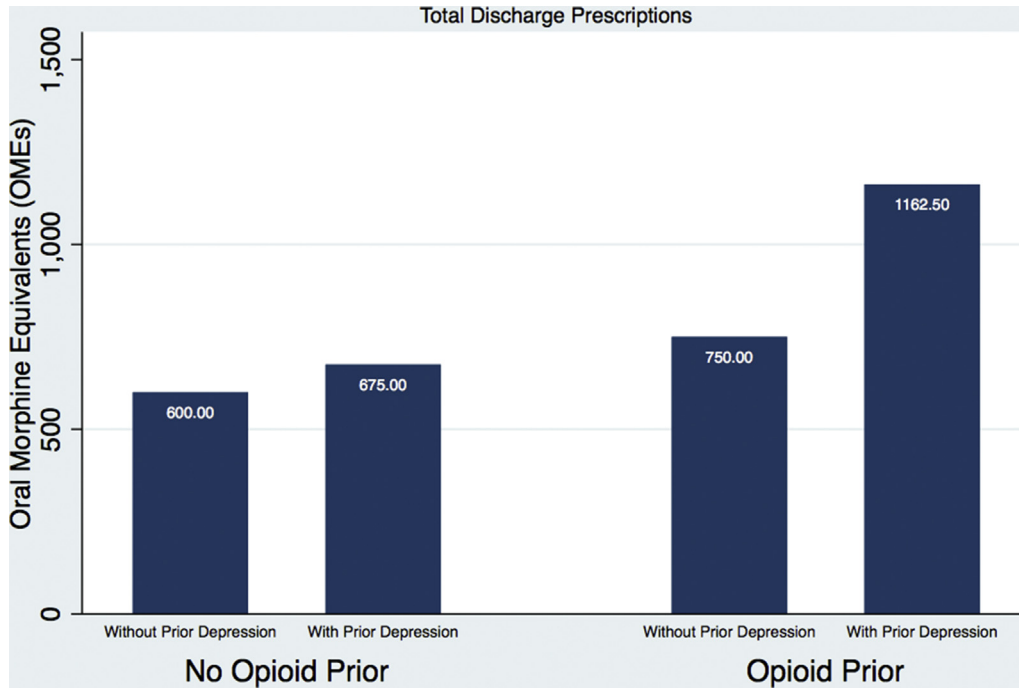


Figure 2. Total discharge prescriptions.

number of opioids distributed into the general population is an important goal.

There are a number of limitations with our study. It is subject to the inherent biases and limitations present in any retrospective review. With respect to the collection of opioid data, this study used prescriptions to estimate number of opioids taken after discharge. This is a proxy, and it likely does not exactly match the number of pills taken by the patients. However, we were able to identify higher refill rates among patients with prior opioid use and depression up

to 3 months after surgery. This finding implies that not only are these patients being prescribed more opioids upon discharge but also that they are using this medication and requiring further refills. Another key piece of this study was the identification of patients with depression. This identification was made through a chart review and was not undertaken through the completion of screenings or controlled instruments. Thus, there is no way to determine the degree of depressive symptoms, status of treatment, or time since diagnosis. More granular detail related to a patient's depression

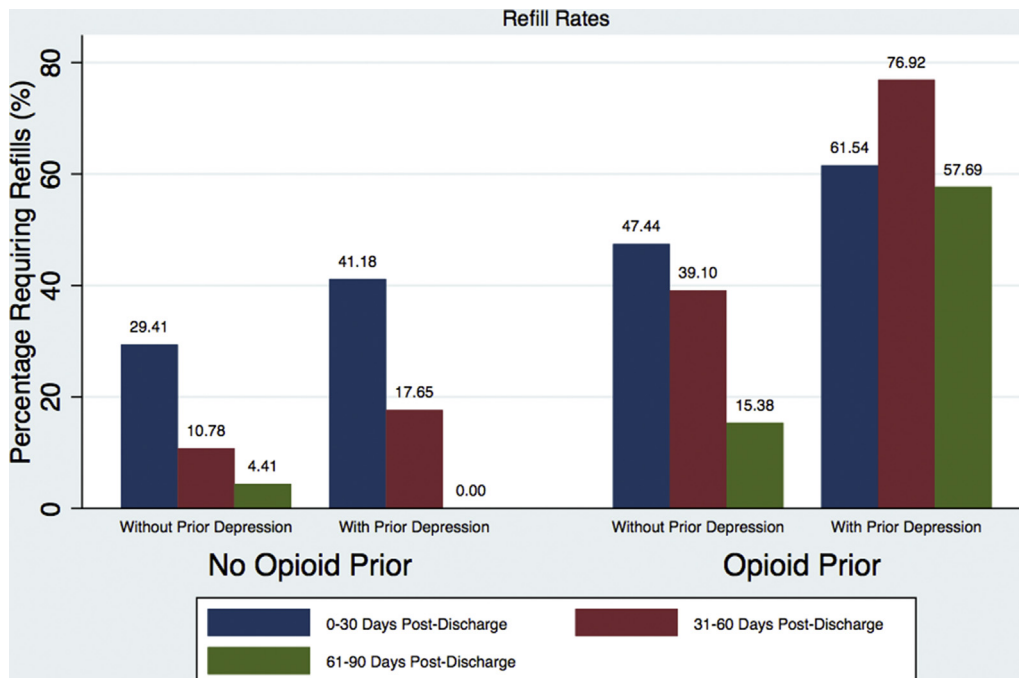


Figure 3. Refill rates.

status would be useful in future studies to determine if there are differences in opioid use within subsets of the population related to severity and treatment status. Similarly, we do not have any baseline data related to preoperative pain scores or amount of opioids taken. It would be preferable to have baseline data so as to assess any preoperative differences between and/or within the groups and to be able to quantify postoperative changes. That being said, every patient undergoes an in-person review of their medication list with a nurse immediately before surgery so as to be confident that any patients in the opioid group truly were actively taking an opioid medication preoperatively. Even with this limitation, our findings including the refill data show that 3 months after surgery, there remains a difference in amount of pain medication being taken among those with prior opioid use and depression—a significant finding despite the inability to quantify the exact change from before surgery. Finally, this study looked only at opioid consumption up to 3 months postoperatively, and we are therefore unable to assess whether this increased usage in the short term translates to long-term use and dependence; however, prior studies suggest that this is the case. Future study should focus on long-term outcomes to determine if depression in patients with preoperative opioid usage is linked to longer term opioid use after TJA.

Conclusions

Depression alone is not associated with increased pain levels or opioid requirements among opioid-naïve patients after primary hip or knee arthroplasty, but it significantly increases these outcomes in patients who use opioids preoperatively. Orthopedic surgeons should focus on identifying these patients preoperatively for appropriate risk stratification and counseling. Most importantly, this study identifies a target for possible risk modification, warranting further study into preoperative opioid reduction, particularly in patients with a history of depression.

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