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Preoperative Predictors of Prolonged Opioid Use in the 6 Months Following Total Knee Arthroplasty

Daniel B. Larach, M.D., M.S.T.R., M.A.[1], **Miklos D. Kertai, M.D., Ph.D.**[1], **Frederic T. Billings IV, M.D., M.S.C.I.**[1], **Sara B. Anderson, B.A.**[1], **Gregory G. Polkowski, M.D., M.S.C.R.**[2], **Andrew A. Shinar, M.D.**[2], **Ginger L. Milne, Ph.D.**[3], **Puneet Mishra, M.D.**[1], **Stephen Bruehl, Ph.D.**[1]

[1]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA.

[2]Department of Orthopaedic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA.

[3]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

Abstract

Objectives—Prolonged postoperative opioid use increases risk for new post-surgical opioid use disorder. We evaluated preoperative phenotypic factors predicting prolonged postoperative opioid use.

Methods—We performed a secondary analysis of a prospective observational cohort (n=108) undergoing total knee arthroplasty (TKA) for osteoarthritis with 6-week and 6-month follow-up. Current opioid use and psychosocial, pain, and opioid-related characteristics were assessed at preoperative baseline. Primary outcomes were days/week of opioid use at follow-up.

Results—At 6 weeks, preoperative opioid use and greater cumulative opioid exposure, depression, catastrophizing, anxiety, pain interference, sleep disturbance, and central sensitization were significantly associated with more days/week of opioid use after controlling for contemporaneous pain intensity. These predictors, and prior euphoric response to opioids, were also significant predictors at 6 months. All 6-week predictors except anxiety remained significant after controlling for preoperative opioid use; at 6 months, cumulative opioid exposure, catastrophizing, pain interference, and sleep disturbance remained significant after this adjustment (p's <0.05). In multivariable models, a psychosocial factor reflecting negative affect, sleep, and pain accurately predicted 6-week opioid use (AUC=0.84). A combined model incorporating psychosocial factor scores, opioid-related factor scores, and preoperative opioid use showed near-perfect predictive accuracy at 6 months (AUC=0.97).

Discussion—Overall, preoperative psychosocial, pain-related, and opioid-related phenotypic characteristics predicted prolonged opioid use following TKA.

Keywords

persistent postoperative opioid use; pain; opioid; psychosocial; precision medicine

CORRESPONDING AUTHOR: Daniel B. Larach, M.D., M.S.T.R., M.A., Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN (daniel.larach@vumc.org; phone 615-875-8795; fax 615-875-5511).

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Introduction

About 25% of the nearly 70,000 U.S. opioid overdose deaths in 2020 involved prescription opioids.[1] Post-surgical care is often patients' first opioid exposure,[2] and 4–10% of opioid-naïve surgical patients receiving postoperative opioids develop new persistent opioid use.[3–7] Opioid overdose or a new OUD diagnosis occurs in 0.1–0.7% of surgical patients prescribed opioids during the first postoperative year.[8, 9] Extrapolating based on surgical and dental prescribing estimates, 1.8–4.5 million U.S patients develop post-procedural new persistent opioid use and 45,000–315,000 develop post-procedural OUD annually.[10] Persistent postoperative opioid use increases risk for OUD (88% increased hazard) and overdose (78% increased hazard).[9]

Although large electronic health record and insurance database studies examining persistent post-surgical opioid use rates are available,[11] the dearth of systematic prospective data examining risk factors for persistent opioid use represents a significant research gap.[12] Prospective studies of well-phenotyped patients are needed to examine predictors of prolonged postoperative opioid use in granular detail, potentially enabling future risk stratification algorithms and personalized postsurgical care (e.g., minimizing opioids and maximizing non-opioid therapies for at-risk patients, increased surveillance for opioid misuse). Preoperative opioid use is a well-known predictor of delayed opioid cessation postoperatively.[5, 13–22]. *Distant* prior opioid use also predicts persistent postoperative opioid use.[23]

Biopsychosocial factors also may drive persistent postoperative opioid use. For example, persistent postoperative pain (incidence up to 50% depending on surgery[24]) is a predictor of persistent postoperative opioid use.[12, 25–27] Central sensitization, which may drive postoperative pain intensity and chronicity, may also affect postoperative opioid use, but has been little studied in this context.[28, 29] Beyond preoperative opioid use and postoperative pain, prior prospective work has identified psychosocial factors associated with prolonged postoperative opioid use, including catastrophizing,[5, 16, 17, 30, 31] anxiety,[25, 31, 32] and depression.[15, 31] These studies often comprise heterogeneous samples reflecting surgeries varying in degree of tissue trauma and expected postoperative pain course, potentially confounding interpretation. Moreover, absence of prior prospective work evaluating history of positive subjective responses to opioids (e.g., euphoria) as a risk factor for persistent postoperative opioid use is a potentially important gap, as these responses may drive continued opioid use due to operant reinforcement mechanisms.[33–35]

Given heterogeneous post-surgical pain trajectories,[36] known relationships between preoperative and persistent postoperative opioid use, and evidence that phenotypic characteristics unrelated to pain may contribute to prolonged postoperative opioid use, we comprehensively evaluated preoperative phenotypic factors predicting extent of subacute and chronic postoperative opioid use while (1) controlling for contemporaneous pain intensity (a confound rarely addressed) and (2) with and without controlling for preoperative opioid use. This approach permits evaluating whether psychosocial and pain/opioid-related phenotypes (including central sensitization and euphoric response to opioids) predict prolonged opioid use beyond what can be accounted for by preoperative opioid use and pain intensity

itself. This is critical for developing optimal precision pre-surgical opioid risk stratification approaches. The current sample was a homogeneous cohort of patients undergoing unilateral total knee arthroplasty (TKA) for osteoarthritis, a population with substantial rates of prolonged postoperative opioid use (20%)[5, 13, 14, 16, 37] and persistent pain (25%),[38]

Materials and Methods

Design

A mixed between/within-subjects longitudinal design was used including assessment of pain/opioid-related and psychosocial phenotypes at preoperative baseline, and assessment of opioid use outcomes at 6 weeks and 6 months post-TKA. These are secondary analyses of data from a project examining perioperative oxidative stress mechanisms of post-TKA pain.[39–41]

Participants

Participants (n=108) were individuals of both sexes, age ≥55, undergoing primary unilateral TKA for osteoarthritis by one of the two surgeon co-authors (GGP, AAS). Participants were recruited in-person during preoperative group education sessions or (post-COVID) telephone calls to potentially qualifying patients by the research coordinator. Individuals who were interested in study participation were then screened for eligibility and consented. All procedures were Institutional Review Board-approved. Participants enrolled between August 2017-June 2021. The n=120 sample size for the parent study was chosen to achieve >0.80 power to detect associations between the primary oxidative stress measure (F2-isoprostanes) and pain outcomes.

Inclusion criteria were: 1) intact cognitive status and ability to provide informed consent (Mini Mental State Examination score ≥24),[42] 2) ability to understand English sufficiently to complete study questionnaires, 3) age ≥55 years, 4) undergoing unilateral TKA, 5) osteoarthritis diagnosis. Exclusion criteria were: 1) complex regional pain syndrome diagnosis, 2) TKA revision, 3) presence of lower extremity vascular disease, inflammatory or autoimmune disorders, or malignancy, and 4) presence of other conditions making participation unsafe. Participants received $200 for completing the study.

There were 985 potential participants identified, with 303 interested and screened. Of these, 120 qualified and consented, with 7 subsequently disqualified due to other medical issues noted (cognitive dysfunction, medical exclusions). The final sample was n=113 (no participants withdrew or were lost to follow-up). The final analyzed sample included all participants (n=108) with primary opioid outcome data available at follow-up. Table 1 summarizes sample characteristics.

Measures

Preoperative Phenotype—Preoperative phenotype measures were chosen based on prior work suggesting associations of each construct with opioid responsiveness or opioid use.[28, 43–49]

Prior Euphoric Responses to Opioids and Cumulative Opioid Exposure: The Euphoric Response and Cumulative Opioid Exposure subscales of the History of Opioid Medical Exposure measure (HOME) were used to assess prior positive subjective responses to opioids as well as the lifetime amount of opioid taken by subjects.[43]

Negative Affect: The Center for Epidemiological Studies-Depression scale (CES-D; 20 item version) was used to assess depressive symptoms. This is a widely used standardized measure validated for use in older populations[50, 51] and those with chronic medical conditions including arthritis.[52] Higher scores indicate greater depressive symptoms.

Anxiety symptoms were assessed using the trait form of the State-Trait Anxiety Inventory (STAI), a commonly used self-report measure with well-established psychometric properties.[53] Higher STAI scores denote an increased tendency toward anxiety symptoms.

Pain Catastrophizing: Pain catastrophizing was assessed using the Pain Catastrophizing Scale (CATS).[54] This is a 13-item measure that assesses the degree to which individuals have negative thoughts and feelings when experiencing pain. Higher scores indicate greater pain catastrophizing.

Centralized Pain: The Michigan Body Map (MBM) assesses how many of 19 discrete sites subjects experience pain at. It is one of two components of the Fibromyalgia Survey Criteria used for fibromyalgia diagnosis. The MBM is used in the research setting to evaluate the degree of widespread pain (a marker of centralized pain) experienced by subjects.[55]

We also included results of a dynamic quantitative sensory testing (QST) protocol, temporal summation of punctate pain (TSP), that indexes central nervous system pain facilitation (i.e., central sensitization).[56] TSP to punctate mechanical stimuli was assessed using procedures based on Goodin *et al.*[56] The stimulus used was a 100g monofilament, with this stimulus weight determined based on weights shown to elicit TSP in prior literature (e.g., ranging from 25g to 300g).[56, 57] A single stimulus was first applied for one second to the affected knee (4 cm above the patella, 8 cm towards the midline), with pain intensity rated using a 0–10 Numeric Rating Scale (NRS) anchored with "*no pain*" and "*worst possible pain.*" Then, using the same procedures as above, a series of 10 punctate stimuli were delivered at a rate of one stimulus per second to the affected knee, with an NRS pain intensity rating then obtained to describe the highest pain intensity experienced. This procedure was repeated twice. The change in pain intensity between the first stimulus and the stimulus eliciting the highest pain rating (mean of the two trials) was used to index preoperative TSP in the affected knee (larger positive values indicated greater TSP). This punctate TSP measure was the only QST measure used to maximize clinical feasibility of the protocol.

Sleep Disturbance: The PROMIS Sleep Disturbance – Short Form 8a instrument assesses sleep quality, sleep depth and restoration associated with sleep over the past week. Higher scores indicate greater levels of sleep disturbance. This measure has been found to have superior precision compared with other commonly used self-reported sleep measures.[58]

Function: The PROMIS Pain Interference– Short Form 8a instrument (PROMIS Interference) assesses pain-related life interference over the prior week (the impact of pain on the ability to carry out daily social, emotional, physical, and recreational activities).[59] Higher scores indicate greater levels of interference.

Opioid Use—Opioid use outcomes were self-reported number of days (0–7) of opioid use in the week prior to each assessment (6-week and 6-month follow-up). Self-reported opioid use over 2-week periods corresponds highly (intraclass correlation=0.85) with opioid use determined via electronic pill cap.[60] For use in exploratory combined predictor models evaluating Receiver Operating Characteristic (ROC) curves, a dichotomous opioid use outcome was created reflecting daily vs. non-daily opioid use at each follow-up (1/0). This secondary dichotomous outcome is clinically relevant and maintains adequate statistical power. Opioid use immediately before surgery (yes/no; confirmed against patient medication list) was also assessed for inclusion as a preoperative predictor.

Postoperative Pain—Postoperative pain was assessed using an 11-point numeric rating of past 24-hour worst pain intensity in the operative knee at each postoperative assessment (0 = “No Pain” and 10 = “Worst Possible Pain”).

Procedure

After providing informed consent, baseline preoperative assessments were conducted by the research coordinator in the participant’s home (median=3.0 days preoperatively). Assessment included demographics and opioid use, phenotype measures, and standardized TSP assessment using established protocols.[61] Anesthesia and postoperative care protocols are described in Supplemental Digital Content 1. At 6 weeks (6–8-week window) and 6 months (24–28-week window) postoperatively, the research coordinator assessed opioid use and postoperative pain outcomes in person in the participant’s home.

Statistical Analysis

Analyses were conducted using SPSS (IBM SPSS Statistics for Windows, Version 28.0, Armonk, NY). Except where noted, sample descriptive statistics included mean (SD) and percentages for continuous and categorical variables, respectively. Associations among preoperative predictors were examined using Spearman nonparametric correlations. Given the right-skewed and highly dispersed nature of the opioid use outcomes, primary analyses used generalized linear models (GLM) specifying a negative binomial distribution. All GLM models adjusted for sex, age, body mass index (BMI), and past 24-hour worst pain intensity contemporaneous with opioid use outcomes at follow-up (the latter to evaluate predictive effects beyond that attributable to postoperative pain intensity). Primary analyses examined preoperative opioid use and phenotype measures as predictors of days per week of opioid use at both follow-ups. Then, these analyses were repeated, including preoperative opioid use as an additional control variable to evaluate phenotype predictive effects beyond those accounted for simply by preoperative opioid use.

To evaluate combined predictor models in exploratory analyses while addressing multicollinearity issues, significant phenotype predictors in primary analyses were subjected

to principal components analysis (varimax rotation) resulting in extraction of two factors accounting for 57.1% of variance across measures: 1) a *psychosocial* factor (negative affect, sleep, and pain-related), and 2) an *opioid-related* factor (past euphoric opioid responses and cumulative opioid exposure from the HOME). Two factor scores (regression method) reflecting the factors above were generated for each patient and then tested (in addition to preoperative opioid use) as predictors of daily versus non-daily opioid use in ROC curve analyses, with area under the curve (AUC) the predictive accuracy criterion. All analyses included the maximum number of cases available. A two-sided $p<0.05$ significance level defined statistical significance. The sample size resulted in power of 0.80 to detect effect sizes of $r \geq 0.27$ (i.e., moderate or larger effects).[62]

Results

Opioid Use Outcomes Post-TKA

Preoperatively, 9.3% (n=10) of patients had recently used an opioid analgesic. The standard discharge analgesic, oxycodone 10 mg, was received by 96.3% (n=104) of patients, with 2.8% (n=3) receiving hydrocodone and 0.9% (n=1) receiving hydromorphone for continuity with presurgical opioid regimens. Changes in state law regarding postoperative opioid prescribing that occurred in early 2019 did not significantly alter discharge prescription size or our primary opioid use outcome. Refills were provided as clinically indicated. Postoperatively, 54.2% (n=58) of patients requested opioid refills. Median (IQR) number of refills was 1.0 (1.0), with number of refills ranging from 0–4. Median days per week of opioid use at both post-TKA follow-ups was zero, with wide variability at both follow-ups (range: 0–7 days; see Figures, Supplemental Digital Content 2–3). At 6-week follow-up, 11.3% (n=12) were using opioids daily with 79.2% (n=84) no longer using any opioids. At 6-month follow-up, 5.6% (n=6) were using opioids daily with the remainder using no opioids.

Associations Among Preoperative Predictors

Table 2 displays intercorrelations among preoperative predictors. Preoperative opioid use was associated with higher HOME Cumulative Opioid Exposure scores, and greater widespread pain (MBM) and sleep disturbance. Greater cumulative opioid exposure was associated with higher depression (CES-D), pain interference and sleep disturbance (PROMIS measures), and more widespread pain. Depression, anxiety (STAI), and catastrophizing (CATS) were significantly intercorrelated, reflecting a common underlying negative affect (NA) construct. Greater TSP was correlated with higher depression, catastrophizing, and sleep disturbance. The HOME Euphoric Response subscale that assesses prior positive subjective opioid responses was not associated with any other measures.

Prospective Predictors of Postoperative Opioid Use

Table 3 summarizes GLM analyses examining preoperative predictors of subsequent postoperative opioid use at 6-week and 6-month follow-up (controlling for contemporaneous pain intensity). As expected, preoperative opioid use significantly predicted days per week of postoperative opioid use at both follow-ups. At 6-week follow-up, a variety of

preoperative phenotype characteristics predicted greater extent of opioid use, including greater cumulative opioid exposure; higher depression, anxiety, and catastrophizing; more pain-related life interference and sleep disturbance; and greater TSP (central sensitization). All predictors of postoperative opioid use at 6 weeks were also significant at 6-month follow-up. In addition, at 6 months post-TKA, higher scores on the Euphoric Response subscale of the HOME also predicted more prolonged opioid use. All of the predictors above remained significant after applying the Benjamini-Hochberg procedure to address Type I error rate inflation (FDR = 0.25).

To evaluate extent to which phenotype measures predicted postoperative opioid use beyond that accounted for simply by preoperative opioid use, we repeated the analyses above in second analyses, adjusting for preoperative opioid use (see Table, Supplemental Digital Content 4). At 6-week follow-up, all phenotype predictors identified above except anxiety remained significant even after controlling for preoperative opioid use. At 6-month follow-up, cumulative opioid exposure, catastrophizing, pain interference, and sleep disturbance remained significant predictors after adjusting for influence of preoperative opioid use.

Potential for Clinical Utility

To address issues of potential clinical utility in precision pain medicine algorithms, we evaluated in exploratory analyses the accuracy of combined models reflecting the two factor scores described above (*psychosocial* and *opioid-related* factors), as well as preoperative opioid use, for predicting daily versus non-daily use of opioids at each follow-up. At 6-week follow-up (Figure 1), scores on the *psychosocial* factor were the most accurate predictor of daily opioid use (AUC=0.84). Both preoperative opioid use (AUC=0.64) and *opioid-related* factor scores (AUC=0.59) displayed similar but lower accuracy. Only scores on the *psychosocial* factor produced a good predictive model (i.e., AUC>0.70). A combination of all three predictors (standardized) did not improve accuracy (AUC=0.83) beyond the *psychosocial* factor alone.

At 6-month follow-up (Figure 2), preoperative opioid use was the most accurate predictor (AUC=0.90). Scores on the *psychosocial* factor (AUC=0.83) and *opioid-related* factor (AUC=0.77) displayed somewhat lower accuracy, but all resulted in good predictive models. Combining all three predictors improved accuracy of predicting daily opioid use at 6-month follow-up to near-perfect prediction (AUC=0.97).

Discussion

Multiple studies have highlighted the high incidence of persistent postoperative opioid use.[3–7] However, much of this work has been carried out utilizing insurance claims databases and other large-scale retrospective cohorts. Progressing from problem identification to clinical precision medicine approaches to opioid risk mitigation requires prospective studies with more granular data.[12] In this study, we identified a preoperative phenotype that identifies patients at risk for prolonged opioid use following TKA. As the heterogeneity of definitions for persistent postoperative opioid use has been criticized,[11] we utilized a granular outcome of days per week of opioid use to identify phenotypic predictors in

univariate models and a stringent definition of daily opioid use to construct ROC curves in exploratory combined predictor models.

As in many prior studies,[5, 13–22] preoperative opioid use predicted extent of opioid use postoperatively. Our results further indicated that even when controlling for contemporaneous pain intensity, phenotypic characteristics including cumulative prior opioid exposure, depression, anxiety, catastrophizing, pain interference, sleep disturbance, and central sensitization all independently predicted extent of opioid use at 6 weeks post-TKA. These same predictors, as well as past euphoric subjective opioid responses, predicted opioid use at 6 months (all of which represented *daily* opioid use). Several of these predictors replicate findings from prior studies, including catastrophizing,[5, 16, 17, 30, 31] anxiety,[25, 31, 32] and depression.[15, 31] However, our results are inconsistent with findings from a recent single-center cohort study of similar size that only preoperative patient fatigue, but not pain catastrophizing, depression, or anxiety, were associated with duration of subacute opioid use following total knee and hip arthroplasty. Reasons for this discrepancy are unclear but may potentially be related to differences in opioid outcomes or the specific measures of negative affect examined.[63] Our finding of an association between self-reported cumulative lifetime opioid use and prolonged postoperative use is similar to the association between distant prior opioid use and persistent opioid use reported recently.[23] Central sensitization has been previously associated with immediate postoperative opioid utilization; we extend this finding to a much longer timeframe.[28, 29] Surprisingly, we did not identify the expected association between prolonged opioid use and extent of widespread pain.[55] The reasons for this finding are unclear. Finally, our novel finding that preoperative patient report of a euphoric response to first-ever opioid exposure was significantly associated with persistent daily opioid use at 6 months suggests a potential role for subjective opioid reinforcing effects in the transition from routine postoperative opioid use to persistent use. While this association is consistent with reinforcement models of OUD, this study did not directly assess OUD.[33–35] The role of reinforcing subjective opioid effects has been little studied in the perioperative context and warrants further investigation.

In a secondary analysis controlling for influence of preoperative opioid use, all predictive factors above (except anxiety) remained significant at 6 weeks, with cumulative opioid exposure, catastrophizing, pain interference, and sleep disturbance remaining significant at 6 months. Many large cross-sectional predictive algorithm studies confirm that prior opioid use is frequently the strongest predictor of prolonged postoperative use.[64–67] Our prospective findings indicate that patient psychosocial and pain phenotypic characteristics predict greater opioid use at postoperative follow-up above and beyond that accounted for by preoperative opioid use. These findings have implications for developing clinically useful opioid stratification algorithms.

Our factor analytic-derived combined phenotype measures (*psychosocial* and *opioid-related*) as well as preoperative opioid use each displayed high accuracy for predicting daily opioid use at 6 months postoperatively. Combining all three predictors yielded an AUC approaching 1.0 for this outcome, implying that we are unlikely to have missed unstudied patient characteristics that drive extent of persistent postoperative use. For the shorter-term

6-week daily use outcome, the *psychosocial* factor was a more accurate predictor than either preoperative opioid use or the *opioid-related* factor, and a combined model did not improve accuracy. These data may point to a potential transition in factors driving prolonged use between the subacute and chronic periods and warrant further study in larger cohorts. Previously published predictive models for extended postoperative opioid use—all based on retrospective data—show an average AUC of 0.76 for preoperative opioid use.[64–75] Our prospective models show that at 6 weeks post-TKA, preoperative opioid use is a less accurate predictor (AUC=0.64) than prior retrospective models indicate, highlighting the importance of psychosocial and pain-related predictors at this time point. In contrast, at 6-month follow-up, preoperative opioid use is an even better prospective predictor than prior work would suggest (AUC=0.90), and the addition of the above phenotypic characteristics improves it even further.

Our study findings can be interpreted in context of our prior laboratory work indicating that elevated depression, anxiety, catastrophizing, and pain-related disability are each associated with increased analgesic responsiveness to a weight-adjusted opioid dose (morphine).[44] These associations are mediated in part by low endogenous opioid analgesic activity observed in individuals with higher levels of these phenotypic characteristics.[44] In light of these prior mechanistic findings, the current results suggest the possibility that risk for more extensive and persistent postoperative opioid use may be elevated in those with lower ability to naturally inhibit pain (i.e., low endogenous opioids). Notably, our prior work also indicates that low endogenous opioid function is associated with elevated drug liking and euphoric responses to opioids,[76] factors linked to OUD risk. These issues merit further exploration.

Clinical utility of the current findings remains to be proven. However, the risk factors identified in this study for more extensive opioid use could potentially serve as preoperative indicators for increased monitoring of patients' postoperative opioid use. Surgeons and anesthesiologists could consider adjusting standard perioperative analgesic techniques in such patients to incorporate alternative strategies such as careful expectation-setting for postoperative pain, the use of regional techniques, and more frequent follow-up in the weeks after surgery. The potential clinical value of this precision pain medicine approach warrants further investigation.

This study has several limitations. Our rate of persistent opioid use at 6 months (5.6%) was substantially lower than that observed at 6 months post-TKA in some prior studies (11–32%).[37] This may be due to differences in the stringency of the persistent use definition (daily use in our study versus filling a single subsequent prescription 3–6 months postoperatively in some studies) or possibly heightened opioid prescribing caution related to the opioid crisis. While this low number of patients (n=6) using opioids at 6 months could potentially result in unreliable predictive models, the fact that the same predictors were significant at 6 weeks with a sample twice as large argues against this possibility. It is possible that negative findings for some predictors (widespread pain at 6 weeks and 6 months; euphoric response to opioids at 6 weeks) would have been positive had our study had greater statistical power. Reported accuracy of combined models may be inflated; these data should be used solely for comparing relative accuracy across models. Our cohort was

also overwhelmingly non-Hispanic white, which limits generalizability of our data. These data require replication in more diverse samples. We also did not have data on the quantity and duration of preoperative opioid use in patients taking opioids prior to surgery (i.e., daily oral morphine equivalent dose), which may have influenced observed associations between preoperative and postoperative opioid use. Finally, reliance on participant self-reporting of postoperative opioid use may have led to over- or under-reporting of actual consumption at the two postoperative assessment points.

Conclusion

Utilizing a prospective design in a homogeneous population of patients undergoing primary unilateral TKA, we: (1) replicated preoperative opioid use as a predictor of prolonged postoperative opioid use and (2) identified multiple psychosocial and pain/opioid-related phenotypic characteristics that prospectively predict persistent postoperative opioid use independent of pain intensity. Our findings warrant replication, and future risk stratification algorithms should use both sources to predict risks for persistent postoperative opioid use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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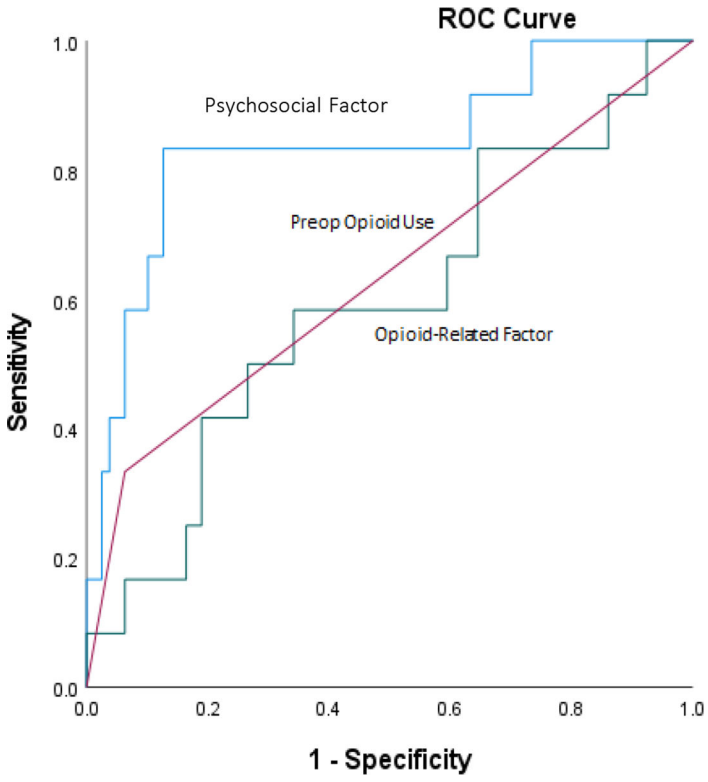

Figure 1.
ROC curves displaying classification accuracy of preoperative opioid use and factor analysis-derived combined phenotype predictors of subsequent daily opioid use versus non-daily opioid use at 6 weeks post-TKA.

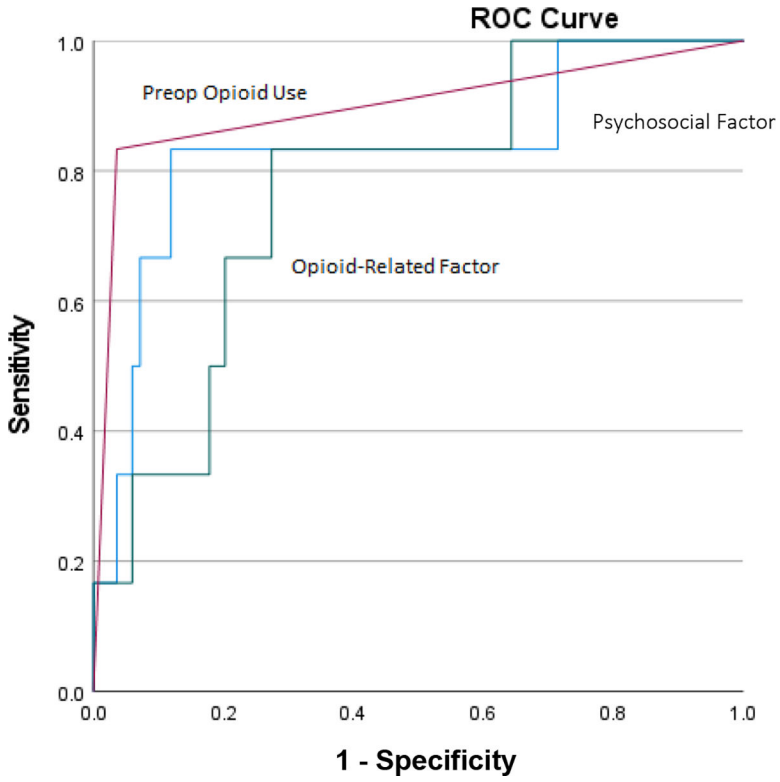

Figure 2.

ROC curves displaying classification accuracy of preoperative opioid use and factor analysis-derived combined phenotype predictors of subsequent daily opioid use versus non-daily opioid use at 6 months post-TKA.

Table 1.

Summary of preoperative demographic, clinical characteristics, and phenotype predictors.

	Mean (SD) or % (n = 108)
Demographic Characteristics:	
Age (years)	67.4 (6.91)
Gender (% female)	63.9
Race/Ethnicity:	
Non-Hispanic White	96.3
African-American	3.7
BMI	31.9 (5.30)
Diabetes Status (% yes)	19.8
Anesthesia Type (% spinal)	87.0
ASA Status:	
2	32.4
3	67.6
Current Smoking Status (% yes)	3.7
Kellgren and Lawrence Grade	
2	1.1
3	7.4
4	91.6
Preoperative Phenotype Predictors:	
Preoperative Opioid Use (% Yes)	9.3
HOME-Euphoric Response	3.1 (1.22)
HOME-Opioid Exposure	2.4 (1.44)
CES-D	18.9 (7.14)
CATS	14.2 (11.53)
STAI	32.4 (9.47)
MBM	4.5 (3.44)
PROMIS Pain Interference	61.9 (7.50)
PROMIS Sleep Disturbance	52.7 (9.14)
Temporal Summation of Pain	1.7 (1.39)

Note: BMI = Body Mass Index, HOME = History of Opioid Medical Exposure, CES-D = Center for Epidemiological Studies-Depression Scale, CATS = Catastrophizing Scale, STAI = State Trait Anxiety Inventory, MBM = Michigan Body Map. Temporal summation of pain values reflect the greatest increase in 0–10 NRS pain ratings after 10 repeated punctate stimuli (100g von frey hair) relative to a single stimulus.

Table 2.

Zero-order Spearman nonparametric correlations among preoperative predictors of postoperative opioid use.

Preoperative Predictor	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Preoperative Opioid Use	0.11	0.39***	0.08	0.13	0.02	0.20*	0.15	0.28**	0.12
2. HOME-Euphoric Response	--	0.09	−0.10	−0.01	−0.17	0.00	0.00	−0.03	−0.11
3. HOME-Opioid Exposure	--	--	0.26**	0.19†	0.14	0.24*	0.25*	0.26**	0.00
4. CES-D	--	--	--	0.66***	0.53***	0.14	0.52***	0.52***	0.28**
5. CATS	--	--	--	--	0.59***	0.22*	0.63***	0.42***	0.31**
6. STAI	--	--	--	--	--	0.22*	0.38***	0.38***	0.13
7. MBM	--	--	--	--	--	--	0.22*	0.18†	0.15
8. PROMIS Pain Interference	--	--	--	--	--	--	--	0.39***	0.12
9. PROMIS Sleep Disturbance	--	--	--	--	--	--	--	--	0.21*
10. Temporal Summation of Pain	--	--	--	--	--	--	--	--	--

† p<.10

* p<.05

** p<.01

*** p<.001

Note: TKA = Total Knee Arthroplasty, HOME = History of Opioid Medical Exposure, CES-D = Center for Epidemiological Studies Depression Scale, CATS = Catastrophizing Scale, STAI = State Trait Anxiety Inventory, MBM = Michigan Body Map

Table 3.

GLM analyses of prospective preoperative predictors of days per week of opioid use at post-TKA follow-up.

	6-Week Follow-Up					6-Month Follow-Up				
Preoperative Predictor	**Beta**	**SE**	**P value**	**Adj OR**	**95% CI**	**Beta**	**SE**	**P value**	**Adj OR**	**95% CI**
Preoperative Opioid Use	**1.344**	**0.452**	**.003**	**3.83**	**1.58, 9.31**	**5.727**	**1.283**	**<.001**	**307.19**	**24.86, 3796.07**
HOME-Euphoric Response	−0.020	0.163	.902	0.98	0.71, 1.35	**0.615**	**0.276**	**.026**	**1.85**	**1.08, 3.18**
HOME-Opioid Exposure	**0.417**	**0.113**	**<.001**	**1.52**	**1.22, 1.89**	**2.958**	**0.892**	**<.001**	**19.26**	**3.36, 110.54**
CES-D	**0.101**	**0.022**	**<.001**	**1.11**	**1.06, 1.15**	**0.130**	**0.035**	**<.001**	**1.14**	**1.06, 1.22**
CATS	**0.053**	**0.013**	**<.001**	**1.05**	**1.03, 1.08**	**0.091**	**0.024**	**<.001**	**1.10**	**1.05, 1.15**
STAI	**0.031**	**0.015**	**.035**	**1.03**	**1.01, 1.06**	**0.060**	**0.023**	**.009**	**1.06**	**1.02, 1.11**
MBM	−0.030	0.047	.520	0.97	0.89, 1.06	0.095	0.071	.183	1.10	0.96, 1.26
PROMIS Pain Interference	**0.065**	**0.023**	**.005**	**1.07**	**1.02, 1.12**	**0.108**	**0.040**	**.007**	**1.11**	**1.03, 1.21**
PROMIS Sleep Disturbance	**0.063**	**0.020**	**.001**	**1.07**	**1.03, 1.11**	**0.163**	**0.039**	**<.001**	**1.18**	**1.09, 1.27**
Temporal Summation of Pain	**0.360**	**0.105**	**<.001**	**1.43**	**1.17, 1.76**	**0.786**	**0.204**	**<.001**	**2.20**	**1.47, 3.28**

Note: Analyses of the continuous days per week of opioid use outcome specified a negative binomial distribution.

Significant results are highlighted in bold text. TKA = Total Knee Arthroplasty, HOME = History of Opioid

Medical Exposure, CES-D = Center for Epidemiological Studies Depression Scale, CATS = Catastrophizing

Scale, STAI = State Trait Anxiety Inventory, MBM = Michigan Body Map