Survey Criteria for Fibromyalgia Independently Predict Increased Postoperative Opioid Consumption after Lower-extremity Joint Arthroplasty

A Prospective, Observational Cohort Study

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ABSTRACT

Background: Variance in pain after total knee and hip arthroplasty may be due to a number of procedural and peripheral factors but also, in some individuals, to aberrant central pain processing as is described in conditions like fibromyalgia. To test this hypothesis, the authors conducted a prospective, observational cohort study of patients undergoing lower-extremity joint arthroplasty.

Methods: Five hundred nineteen patients were preoperatively phenotyped using validated self-reported pain questionnaires, psychological measures, and health information. In addition to being assessed for factors previously found to be associated with poor outcomes in arthroplasty, participants also completed the American College of Rheumatology survey criteria for fibromyalgia. Previous studies have suggested that rather than being "present" or "absent," features of fibromyalgia as measured by this instrument, occur over a wide continuum. Postoperative pain control was assessed by total postoperative opioid consumption.

Results: Preoperatively, patients with higher fibromyalgia survey scores were younger, more likely to be female, taking more opioids, reported higher pain severity, and had a more negative psychological profile. In the multivariate analysis, the fibromyalgia survey score, younger age, preoperative opioid use, knee (*vs.* hip), pain severity at baseline, and the anesthetic technique were all predictive of increased postoperative opioid consumption.

Conclusions: The use of the survey criteria for fibromyalgia led to the finding of distinct phenotypic differences, and the measure was independently predictive of opioid consumption. This self-report measure may provide an additional

What We Already Know about This Topic

- Lower-extremity joint arthroplasty is increasing in frequency and is associated with severe acute pain
- Whether patients with symptoms consistent with fibromyalgia experience more pain or require more opioids after lower-extremity joint arthroplasty is unknown

What This Article Tells Us That Is New

- Even though less than 9% of participants met "criteria" for fibromyalgia, increasing degrees of fibromyalgia-like symptoms were independently predictive of increased postoperative opioid requirements.

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simple means of predicting postoperative pain outcomes and analgesic requirements. Future studies are needed to determine whether tailored therapies can improve postoperative pain control in this population.

THE estimated lifetime risk for symptomatic knee osteoarthritis is approximately 45%.[1] Predominately due to trends in aging and obesity, it is estimated that the number of total knee arthroplasties (TKAs) and total hip arthroplasties (THAs) will increase by 673 and 174%, respectively, between the years of 2005 and 2030.[2] Although TKA and THA have been shown to improve chronic pain and function,[3] both surgeries are associated with moderate to severe acute postoperative pain. Younger age, female sex, increased body mass index, preoperative surgical site pain severity, preoperative use of opioids, TKA compared with THA, and general anesthesia (GA) were described by a multicentered, retrospective study as risk factors for moderate to severe acute pain.[4] Extreme thinking patterns and beliefs about pain such as pain catastrophizing and mood disorders like depression and anxiety have also been shown to influence acute pain.[5] Despite the work to date, there is still a large amount of variance that is unknown when trying to understand an individual's acute pain response.

Studies have identified aberrant central nervous system processing and modulation of pain along with comorbid symptoms in multiple chronic pain states.[6–8] The most commonly studied pain disorder associated with aberrant central pain processing is fibromyalgia; however, there are other conditions such as irritable bowel syndrome and interstitial cystitis that have shown similar pathophysiology, including widespread body pain and symptoms like fatigue, sleep problems, and difficulties with thinking. Fibromyalgia is associated with higher levels of central nervous system neurotransmitters that facilitate pain and lower levels of those that down-regulate pain.[6,9] Paradoxically, patients with fibromyalgia have higher endogenous opioid levels with lower opioid receptor availability and this could hypothetically make them less responsive to opioids.[10,11] In 2010, the American College of Rheumatology (ACR) accepted a new set of clinical criteria for the diagnosis of fibromyalgia that can be used *in lieu* of the 1990 criteria, which included a tender point examination.[12] These clinical survey criteria have also been modified to appear in a self-report questionnaire that can be used in epidemiologic studies[12,13] and have demonstrated good reliability, convergent validity, and discriminant validity.[14] Although the survey criteria cannot be used to make the diagnosis of fibromyalgia, this simple, self-report measure provides an index of the likelihood that an individual suffers from fibromyalgia. Using this measure as a continuous variable (*i.e.*, rather than "yes" or "no") for the diagnosis of fibromyalgia, Wolfe *et al.*[13,15] have shown that an earlier version of this measure predicts pain and disability levels across many rheumatic diseases, such as rheumatoid arthritis.

There are currently no data regarding the impact of the fibromyalgia-like state on postoperative opioid consumption. The objective of this prospective, observational cohort study was to assess the impact of the fibromyalgia survey score on acute pain outcomes in TKA and THA. We hypothesized that higher scores on the 2011 ACR survey criteria for fibromyalgia would predict higher postoperative opioid consumption after arthroplasty.

Materials and Methods

Institutional Review Board (University of Michigan, Ann Arbor, Michigan) approval was obtained. The reporting of this study conforms to the STrengthening the Reporting of OBservational studies in Epidemiology Statement (STROBE).[16] Adult patients (≥18 yr old) scheduled for primary, unilateral TKA and THA between March 2010 and March 2012 were prospectively recruited from a preoperative arthroplasty workshop or from the preoperative waiting area on the day of surgery. Exclusion criteria included bilateral arthroplasty, inability to provide written informed consent, non-English speakers, and prisoners. For the current article, any patient having an additional surgery during the postsurgical admission period was excluded from the analyses of postoperative opioid consumption. Written informed consent was obtained from all participants.

Phenotyping Battery

Patients were phenotyped preoperatively using a battery of validated self-report questionnaires of pain and psychological status administered in pen-and-paper format. The measures included the following:

- *Pain severity*: The four pain severity questions from the Brief Pain Inventory (worst, least, average, and right now; numeric rating scale, 0 = no pain, 10 = pain as bad as you can imagine) were used to create a single composite score (0–10) for pain severity, using published methods.[17,18] Pain severity at the surgical site (knee or hip) was measured separately from overall body pain.
- *Duration of pain in the surgical site*: Patients were asked to estimate the duration of pain in the joint scheduled for replacement (knee or hip). Patients could rate the duration in years, months, weeks, days, or a combination of all four. The values were then converted to a single variable measured in days.
- *Widespread pain*: The Michigan Body Map was used to assess the location(s) of chronic pain complaints and widespread body pain.[19] The Michigan Body Map is a one-sided body image with check-box responses for 35 potential body areas where chronic pain (defined as pain ≥3 months' duration) might exist and a box for "No pain." The Michigan Body Map contains the subset of body regions needed to score the 2011 ACR survey criteria for fibromyalgia (described in the "American

College of Rheumatology Fibromyalgia Survey Criteria" measure given below).

- *Neuropathic pain descriptors:* The PainDETECT is a nine-item screening tool used to detect descriptors of neuropathic pain. Scores greater than or equal to 19 suggest a neuropathic component is likely.[20] The neuropathic pain assessment was specific to the surgical site (knee or hip).
- *Depressive Symptoms, Anxiety, and Positive Affect:* The Hospital Anxiety and Depression Scale was used for the assessment of depressive symptoms and anxiety. It contains seven questions about anxiety and seven questions about depression, with a 0–3 score for each question (score 0–21 for each measure, higher scores indicate more depressive symptoms and anxiety).[21] Positive affect was measured using the six positivity questions, with a 0–3 score for each question (0–18, higher scores indicate lower positive affect).[22] This measure was introduced later in the study, hence the first 117 patients did not receive the measure.
- *Catastrophizing:* The Coping Strategies Questionnaire contains a subscale for pain catastrophizing, which is a valid and reliable measure of this form of thinking.[23,24] This measure was introduced later in the study, hence the first 162 patients did not receive the measure.
- ACR *Fibromyalgia Survey Criteria:* The 2011 ACR survey criteria for fibromyalgia is a validated self-report measure consisting of widespread pain and comorbid symptomatology.[12,25] The Widespread Pain Index was calculated using the Michigan Body Map to assess the 19 specific body areas described in the ACR survey criteria (score 0–19). The second aspect of the criteria was evaluated using the comorbid Symptom Severity scale (score 0–12). The total score for the measure ranges from 0 to 31. Survey scores of 13 or more have been described to best separate individuals "with" from those "without" fibromyalgia (*e.g.*, categorical fibromyalgia);[25] however, it can also be used as a continuous measure.

Preoperative pain medications were recorded by the research assistant using a list from the medical records. All drugs, dosages, and average daily consumption (24-h totals) were confirmed with the patient. The average daily dose of preoperative opioids (24-h total) was converted to a single oral morphine equivalent (OME) variable using previously described conversions.**[26,27]

Specific elements of the preoperative anesthesia history and physical and intraoperative record were queried from the electronic medical record (Centricity; General Electric Healthcare, Waukesha, WI), including sex, age, race, body mass index, American Society of Anesthesiologists (ASA) physical status score, and primary anesthetic technique (GA, GA plus peripheral nerve block [femoral nerve block], GA plus neuraxial anesthesia [spinal or epidural], or neuraxial anesthesia).

Acute Pain Outcomes Assessment

Postoperative opioid consumption was obtained from the institutional electronic order entry system (Carelink†† for all oral and intravenous boluses of medications) and nursing records (patient-controlled analgesia) throughout time in the postanesthesia care unit and the inpatient course. Total postoperative opioid consumption was the sum of all opioids administered in the postanesthesia care unit and the remainder of their inpatient admission converted to OMEs. The length of stay was measured in days both as a secondary outcome and as a covariate of postoperative opioid consumption.

The cohort was also prospectively followed longitudinally at 1, 3, and 6 months after surgery to assess for chronic pain outcomes (data not included). The data derived from the longitudinal assessment will be the focus of a separate article, and this article is the primary analysis for acute pain outcomes from this cohort. Measures of physical function were not included in the current analysis, as they were intended to assess chronic postoperative outcomes.

Statistical Analysis

Data were entered into the Assessment of Pain Outcomes Longitudinal Electronic Data Capture system.[28] Missing data for the validated instruments were handled as described by instrument authors.[20,21,29] Patients who did not complete all the components of the ACR survey criteria for fibromyalgia were not included in the analysis. Additionally, patients missing more than one item on the Brief Pain Inventory subscales and the PainDETECT were excluded. For the Hospital Anxiety and Depression Scale, when six of the seven questions were answered, a single value for the missing item was inferred by imputation of the mean of the other six values as recommended. For the other instruments, only one missing question was allowed; however, other completed questionnaires were allowed (*e.g.*, patients were not completely excluded from the analysis for having one incomplete questionnaire). Data were analyzed using R 2.15.2 and SPSS (version 19; SPSS Inc., Chicago, IL).

The cohort was divided into tertiles based on the estimates of one third and two third percentiles of the distribution of the fibromyalgia survey score for between-group analyses. Between-groups comparisons were based on multivariate models specific to the scale of the variable being considered (linear regression with continuous data, logistic with binary data, multinomial logistic with nominal data, and proportional odds regression with ordinal data), and adjusted for preoperative overall body pain and surgical site pain. Holm adjustment for multicomparisons was used in reporting the test results.[30] D'Agostino test of skewness was used to flag skewed variables.[31] Mean and SDs are presented for descriptive data, and median and interquartile range for skewed data are presented in Supplemental Digital Content

** The Hopkins Opioid Program. Available at: www.hopweb.org. Accessed February 20, 2013.

†† UM CareLink. Available at: http://www.med.umich.edu/carelink/. Accessed February 18, 2013.

1, http://links.lww.com/ALN/A982, and Supplemental Digital Content 2, http://links.lww.com/ALN/A983. Tests based on linear regression (*t* tests, continuous data), proportional odds model (Wilcoxon tests, ordinal data), logistic regression (chi-square tests, binary data, proportions), multinomial logistic model (likelihood ratio tests, nominal categorical data) were used to report on descriptive analysis of differences in preoperative phenotype, clinical care variables, and opioid consumption by time period defined by surgery type and fibromyalgia status.

Total postoperative opioid consumption converted into OMEs was used as the primary outcome measure. Multivariate linear regression models were used to analyze postoperative opioid consumption. Multivariate linear mixed models were used to analyze the whole longitudinal profile of postoperative consumption. A Gaussian random intercept term was included to model the subject-specific effects. Explanatory variables included demographics (age, sex), body mass index, home opioid use (OME), surgical site (Brief Pain Inventory knee or hip), preoperative overall body pain severity (Brief Pain Inventory), neuropathic pain (PainDETECT), psychological variables (depressive and anxiety symptoms, catastrophizing, and positive affect), fibromyalgia survey score, ASA physical status score, anesthesia type (GA, GA + block, GA + neuraxial, neuraxial), and length of stay. Model-based hypotheses testing and a search for the best parsimonious model (variable selection) was done using likelihood ratio tests and the Akaike information criterion. Models were conducted with missing data on relevant data excluded. Backward search for the best model was conducted starting from all variables included in the initial full model (Supplemental Digital Content 3, http://links.lww.com/ALN/A984, and Supplemental Digital Content 4, http://links.lww.com/ALN/A985) and supervised by medical experts within the limits of uncertainty allowed by the technical procedure. Interactions were tested by the likelihood ratio tests. Two-sided tests and 0.05 significance level were used throughout.

Results

Recruitment and Retention

A total of 754 patients were approached, and 536 agreed to participate (71.1%; fig. 1). Twelve patients recruited before the day of surgery withdrew on the day of their operation, and five patients had additional surgeries during the same admission and were excluded from the analyses. The final data set included 519 patients, including 233 TKAs and 286 THAs. There were no significant differences between participants and those declining study participation for age (participants 62.7 yr *vs.* nonparticipants 62.9 yr; $P = 0.85$), sex (59.4 *vs.* 52.1% female; $P = 0.088$), or race (85 *vs.* 89.9% Caucasian; $P = 0.074$).

ACR Survey Criteria for Fibromyalgia

The distribution of the ACR survey criteria for fibromyalgia scores is shown in figure 2 (score range, 0–31). For the overall

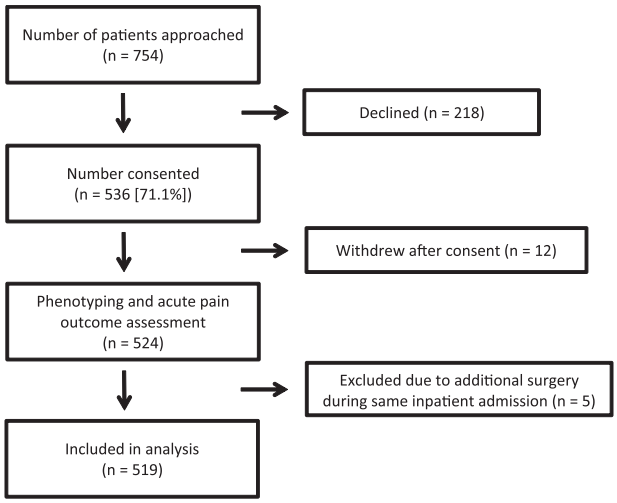

Fig. 1. Recruitment and retention flowchart.

group, 44 (8.5%) met previously defined survey criteria for a categorical "diagnosis" of fibromyalgia (survey score ≥13),[25] including 16 (6.9%) for TKA and 28 (9.8%) for THA. On the basis of the distribution's one third and two third percentiles estimates, the cohort was divided into tertiles for "Low," "Moderate," and "High" fibromyalgia survey scores. Scores for the groups were as follows: Low = 0–4 (n = 170), Moderate = 5–8 (n = 199), and High = 9–31 (n = 147). The tertiles described were used for the subsequent between-group

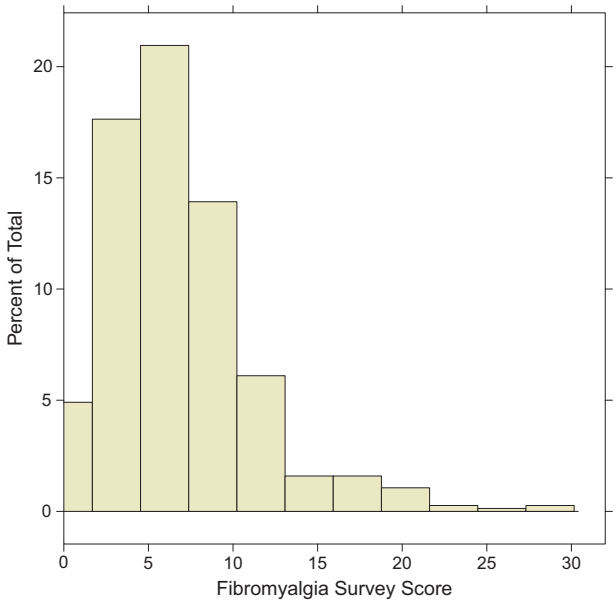

Fig. 2. Histogram of the score for the American College of Rheumatology survey criteria for fibromyalgia. This self-report questionnaire consists of a measure of widespread pain (Widespread Pain Index) assessed from a checklist body map of 19 potential predefined body areas (0–19) plus a Symptom Severity Index of questions about fatigue, trouble thinking or remembering, waking up tired, pain or cramps in the lower abdomen, depression, and headache (0–12). The two scores are summed for a total score between 0 and 31.

analyses to confirm a monotonic trend in phenotype and response variables with the increase in fibromyalgia score. Multivariate models emerging from this analysis incorporated the continuous fibromyalgia survey scores.

Preoperative Phenotypic Difference

Distinct preoperative phenotypic differences were demonstrated when the cohort was divided by tertiles (table 1). All descriptive analyses in table 1 were adjusted for preoperative pain levels (preoperative surgical site and overall body pain), except for the pain variables themselves. Higher scores on fibromyalgia survey were associated with younger age ($P = 0.022$), and when compared with the Low group, the High group had a larger proportion of women, although the difference was not significant. There were no differences for body mass index, ASA physical status score, or duration of pain in the surgical hip or knee. Patients in higher tertile groups were more likely to be taking opioids preoperatively ($P < 0.001$), and the total daily opioid dose (OME) showed an upward trend with tertile group ($P < 0.001$).

Measures of pain and psychological status were significantly different in the between-group analyses (table 1). Preoperatively, patients in the higher tertiles reported higher pain severity at the surgical site and overall body, more neuropathic pain, higher depressive and anxiety symptoms, lower positive affect, and more catastrophizing ($P < 0.001$ for all variables).

Differences were also noted for the type of surgery. A smaller proportion of the Moderate and High fibromyalgia tertiles underwent TKA; however, this effect did not reach significance. In addition, there were significant between-group differences in the primary anesthetic, as shown in table 1.

Length of Stay and Postoperative Opioid Consumption

Patients in the High fibromyalgia score group showed a trend for longer lengths of stay when compared with those in the Low group ($P = 0.13$; table 2). There were no significant between-group differences for length of stay. There was an overall association for postanesthesia care unit ($P = 0.0092$) and total postoperative opioid consumption ($P < 0.00001$), with the higher fibromyalgia groups consuming more opioids. *Post hoc* analyses demonstrated that patients in the High fibromyalgia score group required significantly more opioids in the postanesthesia care unit and throughout the remainder of their inpatient course when compared with either the Moderate or Low groups. There were no between-group differences when comparing the Low and Moderate groups for opioid consumption. As in table 1, these results were adjusted for preoperative surgical site and overall body pain.

Multivariate Models for Postoperative Opioid Consumption

Using a multivariate general linear model which adjusted for all of the variables in Table 1 and the length of stay (covariate to account for the time in the hospital), preoperative patient characteristics were analyzed for their independent effects on total postoperative opioid consumption. Opioid consumption showed significant skewness, and was log transformed to improve model fit. The full model fit is shown in Supplemental Digital Content 3, http://links.lww.com/ALN/A984. A backward variable selection procedure using the likelihood ratio test and Akaike information criterion, starting from the full model was conducted in search for the best model reported in table 3. The set of significant variables is the same in the best and full models. Younger age, preoperative opioid use, primary anesthetic technique, TKA (compared with THA), and the length of stay were all associated with increased opioid consumption after adjusting for other covariates. The pain or mood self-report measures significantly positively associated with the primary outcome was the ACR survey criteria for fibromyalgia, with an increased opioid consumption of 0.022 log-mg on the log-OME scale for every 1-point increase on the 31-point measure, and preoperative overall body pain, with an increase of 0.051 log-mg on the log-OME scale for every 1-point increase in pain (table 3). The best model on the original OME scale (not log transformed) showed increased opioid consumption of 9.1 mg (SE = 2.57; $P < 0.001$) for every 1-point increase in the fibromyalgia score. Overall body pain was not significant in the original model before log transformation with a 1.43 mg (SE = 5.74; $P = 0.8$) OME increase for every 1-point increase in preoperative overall body pain. For clinical context, the estimates for other associate covariates in the original model (not log transformed) showed a reduction in opioid consumption of 6.9 mg for every one increase in year of age and a 71.7 mg for neuraxial anesthesia when compared with GA. Conversely, opioid consumption increased by 3.3 mg for every mg OME preoperatively (home opioids), 78.9 mg for TKA when compared with THA, and 64.9 mg for each additional day in the hospital.

A second model was created eliminating all patients on opioids before surgery (n = 122 taking opioids preoperatively eliminated), and the results were similar (table 4). Despite the exclusion of the opiate-tolerant patients, the ACR survey criteria score was still predictive of postoperative opioid consumption showing about the same magnitude of effect (estimate, 0.018; SE = 0.009; $P = 0.048$ for the log OME scale; estimate, 7.5, SE = 2.06; $P = 0.0003$, on the original OME scale). Except for race, the set of significant variables is the same in the best and full models, as well as in models for the full data set.

Missing Data

With the exception of the Hospital Anxiety and Depression Scale and Catastrophizing measures, which were introduced later in the study (see Materials and Methods), missing data were relatively rare. There were no missing data for race, home opioid dose, surgery performed, or duration of inpatient stay. There were some missing data for age 0.4%, sex 0.4%, body mass index 0.4%, ASA physical status score 0.4%, surgical site pain intensity 0.6%, overall

Table 1. Preoperative Phenotype between Patients Categorized as Reporting a Low, Moderate, or High Score on the American College of Rheumatology Survey for Fibromyalgia

	Low n = 170	Moderate n = 199	High n = 147	*P* Value (Overall Regression)	*P* Value (Low = Moderate)	*P* Value (Low = High)	*P* Value (Moderate = High)
Fibromyalgia survey score	0–4	5–8	9–31				
Demographics							
Age (yr)	65.5 (10.3)^	62.2 (11.8)^	60.6 (11.6)^	0.022	0.050	0.034	0.55
Sex (% female)	47.9	50.0	59.9	0.31	0.91	0.52	0.52
Caucasian	88.8	94.0	89.8	0.062	0.039	0.63	0.31
African American	3.5	4.5	4.8				
Other	7.7	1.5	5.4				
Medical phenotype							
BMI (kg/m^2)	30.1 (10.8)^	31.3 (5.72)^	30.6 (6.2)	0.34	0.54	0.88	0.54
ASA 1	5.4	4.0	4.2	0.51	1	1	1
ASA 2	61.7	63.1	52.8				
ASA 3	32.3	32.8	43.0				
ASA 4	0.6	0.0	0.0				
Preoperative home opioid use (% on opioids)	10.0	23.1	38.1	0.00001	0.396	0.00003	0.000172
Home opioid dose (24-h OME)	1.19 (5.01)^	6.69 (19.7)^	27.2 (74.6)^	0.00002	0.40	0.00003	0.00001
Preoperative pain phenotype							
Surgical site pain severity (0–10)	4.28 (2.21)	4.72 (1.94)	5.61 (2.05)	<0.00001	0.041	<0.00001	0.00008
Overall body pain severity (0–10)	4.12 (2.06)	4.74 (1.83)	5.73 (1.96)	<0.00001	0.0023	<0.00001	<0.00001
Duration of pain in surgical site (days)	1,593 (1,790)^	1,692 (2,380)^	1,529 (1,711)^	0.8	1	1	1
Neuropathic pain ([−1]–[+38])	7.74 (5.05)^	8.98 (5.66)^	12.6 (6.74)	<0.00001	0.26	<0.00001	0.00006
Depressive symptoms (0–21)	3.06 (2.22)^	4.43 (2.62)	7.2 (3.89)	<0.00001	0.0002	<0.00001	<0.00001
Anxiety symptoms (0–21)	3.89 (2.81)^	5.44 (3.1)	7.71 (4.19)	<0.00001	0.0002	<0.00001	<0.00001
Catastrophizing (0–36)	2.52 (3.49)^	4.15 (4.55)^	9.11 (7.59)^	<0.00001	0.035	<0.00001	<0.00001
Positive affect (0–18)	1.96 (1.93)^	3.17 (2.49)^	5.62 (3.62)	<0.00001	0.00044	<0.00001	<0.00001
Surgery and anesthesia							
Surgery (% TKA)	52.9	41.2	39.5	0.15	0.21	0.25	0.94
GA (%)	34.9	42.9	50.3	0.15	0.55	0.095	0.45
GA + block (%)	4.8	4.0	6.5				
GA + neuraxial (%)	15.7	15.2	13.7				
Neuraxial (%)	44.6	37.9	29.5				

Data presented as mean (SD) if continuous, or proportions (%) if categorical. Skewed data marked by ^ as determined by the Agostino test at 5% significance level. Median and interquartile ranges for nonnormally distributed data marked by ^ are displayed in the table in Supplemental Digital Content 1, http://links.lww.com/ALN/A982. Statistics and *P* values are regression model based with fibromyalgia tertile group as a categorical covariate, and pain at surgical site and overall pain as continuous covariates for all variables except themselves. Model is linear for continuous response, logistic for binary, multinomial logistic for nominal, and proportional odds for ordinal. First *P* value represents the overall regression result, and the individual between-group comparisons are noted in the *P* values to follow, adjusted for multicomparisons (Holm method). Scales for the self-report measures in the "Preoperative Pain Phenotype" section are noted in parentheses.

ASA = American Society of Anesthesiologists; BMI = body mass index; GA = general anesthesia; OME = oral morphine equivalents measured in mg; TKA = total knee arthroplasty.

body pain 1.7%, duration of pain 6.7%, neuropathic pain 8.3%, and primary anesthetic 0.4%. The total missing data for the depression, anxiety, and positive affect scales were 25% for the overall data set; however, after the measure was introduced, only 5.5% of the data were missing. Similarly, the catastrophizing measure was missing in 32.9% of the overall data set, but there were only 5.7% missing data after the including the measure.

Table 2. Length of Stay and Postoperative Opioid Consumption between Patients Categorized as Reporting a Low (0–4), Moderate (5–8), or High (9–31) Score on the American College of Rheumatology Survey for Fibromyalgia

	Low	Moderate	High	*P* Value (Overall Regression)	*P* Value (Low = Moderate)	*P* Value (Low = High)	*P* Value (Moderate = High)
Duration of postoperative admission (d)	2.89 (0.95)^	2.99 (0.89)^	3.14 (0.983)^	0.127	0.496	0.1266	0.496
PACU opioid consumption (OMEs)	18.3 (22.8)	21.2 (25.4)^	38.3 (59.9)^	0.0092	0.995	0.023	0.015
Total postoperative opioid consumption (OMEs)	175 (129)^	221 (188)^	381 (515)^	<0.00001	0.30	<0.00001	0.00007

Patients in the High group had a significantly longer inpatient course when compared with patients in the Low group. Postoperative opioid consumption was higher in patients in the higher tertiles for the fibromyalgia scale. Data presented as mean (SD). Skewed data marked by ^ as determined by the Agostino test at 5% significance level. Medians and interquartile ranges for skewed variables are presented in the table in Supplemental Digital Content 2, http://links.lww.com/ALN/A983. Statistics and *P* values are regression model-based with fibromyalgia tertile group as a categorical covariate, and pain at surgical site and overall pain as continuous covariates. Model is linear regression. First *P* value represents the overall regression result, and the individual between-group comparisons are noted in the *P* values to follow, adjusted for multicomparisons (Holm method).

OME = oral morphine equivalents; PACU = postanesthesia care unit.

Table 3. Multivariate Analysis of Total Postoperative Opioid Consumption (Linear Regression, Best Model)

	Estimate (Regression Coefficient)	SE	Test Statistic	*P* Value
Intercept	5.75	0.21	27.07	<0.00001
Age (yr)	–0.025	0.0027	–9.16	<0.00001
Preoperative opioid use (OMEs)	0.004	0.0007	5.55	<0.00001
Preoperative overall body pain	0.051	0.016	3.27	0.0012
Anesthesia—GA + block (*vs*. GA)	–0.049	0.14	–0.34	0.74
Anesthesia—GA + neuraxial (*vs*. GA)	–0.27	0.088	–3.02	0.0026
Anesthesia— neuraxial (*vs*. GA)	–0.36	0.066	–5.43	<0.00001
TKA (*vs*. THA)	0.36	0.062	5.79	<0.00001
Length of postoperative stay (d)	0.19	0.033	5.71	<0.00001
Fibromyalgia survey score	0.022	0.0073	3.06	0.0024

Total postoperative opioid consumption was converted into OMEs (measured in mg) and log transformed to improve normality. The covariates in table 1 along with the length of stay (table 2) were analyzed to assess predictors of opioid consumption. After the backward search for best model, age, preoperative opioid use, overall body pain, and fibromyalgia survey score were the only phenotypic variables associated with opioid consumption. The full model before the backward variable selection is presented in the table in Supplemental Digital Content 3, http://links.lww.com/ALN/A984.

GA = general anesthesia; OME = oral morphine equivalents (mg); SE = standard error; THA = total hip arthroplasty; TKA = total knee arthroplasty.

Discussion

In this prospective, observational, cohort study of patients undergoing TKA and THA, the ACR survey criteria for fibromyalgia demonstrated robust prediction of preoperative phenotypic differences (table 1) and postoperative opioid consumption (tables 2–4). The survey is a simple, self-report measure of painful body areas (assessed by a check-box body map) and comorbid symptoms.[25] Whereas previously defined cutpoints for categorizing patients as being fibromyalgia positive or negative have been described,[25] the current analysis was based on the distribution of the measure within the cohort for descriptive analyses (table 1) and as a continuous measure for the multivariate analyses (tables 3 and 4). Only 8.6% of patients in the cohort met the cutpoint used to diagnose "categorical" fibromyalgia.[25] Yet across the entire continuum of "fibromyalgia-ness" there was a 9 mg increase in oral opioid equivalents administered during the hospital stay for every 1 point in this 0–31 scale. Similar findings have been noted when using this measure in other rheumatic disorders such as rheumatoid arthritis or systemic lupus erythematosus; across the entire continuum the measure is associated with higher pain and disability.[13,15]

Given the increasingly understood neurophysiological changes in patients with fibromyalgia and other centralized pain states,[6–8,32] some have proposed that this is a good surrogate for "centralized pain" or the degree of "centralization."[6–8,15] Fibromyalgia is a disorder defined by widespread body pain and comorbid symptomatology (*e.g.*, fatigue, trouble thinking, trouble remembering).[6,8,12,33] Whether categorical diagnosis of fibromyalgia is important or not is debatable. Instead, the degree of centralization or centralized pain as measured by a self-report questionnaire or

Table 4. Multivariate Analysis of Total Postoperative Opioid Consumption (Linear Regression) after Excluding Patients Taking Opioids Preoperatively

	Estimate (Regression Coefficient)	SE	Test Statistic	*P* Value
Intercept	5.62	0.25	22.90	<0.00001
Age (yr)	−0.023	0.0032	−6.99	<0.00001
Race—Black (*vs*. White)	−0.26	0.19	−1.42	0.16
Race—Other (*vs*. White)	−0.52	0.19	−2.81	0.0051
Overall body pain	0.063	0.017	3.61	0.00035
Anesthesia—GA + block (*vs*. GA)	−0.065	0.17	−0.38	0.70
Anesthesia—GA + neuraxial (*vs*. GA)	−0.21	0.10	−2.12	0.035
Anesthesia— neuraxial (*vs*. GA)	−0.36	0.074	−4.92	<0.00001
TKA (*vs*. THA)	0.42	0.070	5.96	<0.00001
Length of postoperative stay (d)	0.15	0.036	4.16	0.00004
Fibromyalgia survey score	0.018	0.0092	1.98	0.048

The model presented in table 3 was conducted after excluding patients taking opioids preoperatively. It is a result of a backward search for the best model, starting with a model including all variables in tables 1 and 2. After controlling for other covariates, fibromyalgia survey score was still predictive of opioid consumption. The full model before best model selection is presented in the table in Supplemental Digital Content 4, http://links.lww.com/ALN/A985.

GA = general anesthesia; SE = standard error; THA = total hip arthroplasty; TKA = total knee arthroplasty.

quantitative sensory testing is likely more important in differentiating cohorts and tailoring care. Depression, anxiety, and low positive affect are more common in patients with fibromyalgia; however, psychological variables alone do not fully explain the array of symptoms described with fibromyalgia. The correlations between psychological disorders and centralized pain states are likely due to overlapping neurophysiology.[32] Whereas psychological measures have been reported as being predictive of acute pain,[5] the current analysis did not find associations between postoperative opioid consumption and depressive or anxiety symptoms, catastrophizing, or low positive affect when controlling for other covariates.

Use of Opioids in Patients with a Fibromyalgia Phenotype

The primary outcome in the current study was postoperative opioid consumption. Although opioid consumption is widely used to assess acute pain, it is a surrogate for pain and does not directly address the patient report. Thus in the case of individuals with higher fibromyalgia survey scores, increased demand could represent higher pain as well as the failure of opioids to provide the desired relief. Baraniuk *et al.*[10] demonstrated that fibromyalgia patients have higher levels of endogenous opioids in the cerebrospinal fluid when compared with healthy patients, and Harris *et al.*[11] found that fibromyalgia patients have lower μ-opioid receptor binding potential in the brain using positron emission tomography. These studies may explain the anecdotal impression that exogenous opioids are less effective in patients with fibromyalgia.[32] Despite the lack of supportive efficacy data or guidelines recommending their use (except for tramadol in medically refractory cases),[34] it is estimated that 24–32% of patients with a diagnosis of fibromyalgia are prescribed opioids.[35,36] There were a higher proportion of patients in the Moderate and High tertiles taking opioids and average daily dosing was also higher (table 1). As was expected, preoperative opioid use was directly associated with postoperative opioid consumption along with higher scores on the ACR survey criteria for fibromyalgia (table 3). Importantly, the fibromyalgia survey score was still independently predictive of postoperative opioid consumption even when eliminating opioid tolerant patients from the analysis, with an increase of more than 7 mg OME for every 1-point increase on the survey (0.018 increase in the log-scale model; table 4). Future studies are needed to better understand the interactions between preoperative pain, postoperative pain reports, and opioid consumption in patients scoring higher on this measure.

Preoperative Phenotyping

Although "personalized analgesia" was described more than 12 years ago by the late Mitchell Max,[37] most analgesics and perioperative algorithms are applied broadly based on the surgery performed.‡‡ Although the creation of surgery-specific algorithms is important and is supported by the current study, the individual patient variance has been largely ignored. Most centers either use nonopioid or adjunctive analgesics in everyone, or no one. Further research is certainly needed to determine whether any of the factors identified in this or other studies can be used to "triage" patients and treat only some with these other regimens, because opioids (+/− neuraxial anesthesia) work well for many. If large numbers of questions or time- and cost-intensive measures are necessary to perform such "phenotyping" this will not likely be adopted in clinical practice, but the entire self-report battery we administered takes only approximately 15–20 min for a patient to complete, and the ACR survey criteria we found predictive of outcomes is short.

‡‡ Available at: www.postoppain.org. Accessed February 18, 2013.

Additional Predictors of Postoperative Opioid Consumption

There were additional phenotypic and clinical care variables that were predictive of postoperative opioid consumption that merit brief discussion, including age, preoperative opioid use, TKA (*vs.* THA), overall body pain, and the primary anesthetic type (GA associated with higher opioid usage). Many of these factors have been previously described.[4] These data, along with recent studies regarding perioperative morbidity and mortality by Memtsoudis *et al.*[38] and Neuman *et al.*,[39] make a compelling case for the widespread use of neuraxial anesthesia for TKA and THA as is common at some institutions. Our department is working with the orthopedic surgeons to implement a more uniform clinical care track for lower-extremity arthroplasty patients based on the current study and other recent data.[38,39] Although our data suggest that neuraxial anesthesia was associated with significantly less perioperative opioid consumption, individuals in the current cohort who had neuraxial anesthesia still had this significant effect of the fibromyalgia-like state or centralized pain.

Limitations

The varied techniques for primary anesthetic add to the heterogeneity of an already heterogeneous cohort and may affect the ability to detect some of the individual patient variance. Although neuraxial anesthesia is now widely described as the best primary anesthetic technique for TKA and THA, community-based data indicate that almost 75% of patients still receive GA alone.[38] In addition, the use of adjunctive agents, such as nonsteroidal antiinflammatory drugs, acetaminophen, and gabapentinoids, varies in clinical practice. Because these nonopioid techniques are variably used at our institution based in part upon patient characteristics, these analgesics could not be examined in this analysis. Future studies will be needed to determine the impact of these agents in the context of higher fibromyalgia survey scores. Mechanistically, it could be argued that patients with higher fibromyalgia survey scores would be more likely to respond to drugs such as gabapentinoids or serotonin-norepinephrine reuptake inhibitors. The cohort presented is from a single, large, tertiary-care institution, and the results may therefore not be generalizable to other populations.

Conclusion

In a cohort of patients undergoing TKA and THA, patients scoring higher on the ACR survey criteria for fibromyalgia demonstrated distinct preoperative phenotypic differences. In addition to other previously described predictors of acute pain in arthroplasty patients, higher scores on the fibromyalgia survey were significantly and independently predictive of postoperative opioid consumption. This self-report measure may provide a brief means of predicting postoperative pain and analgesic requirements, and be a future tool for identifying patients who might derive more benefit from nonopioid perioperative analgesic regimens. Future studies are needed to determine the neurobiological correlates of this measure and whether individualized or personalized analgesia for patients scoring higher on the fibromyalgia survey can improve postoperative pain.

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