Duloxetine and Subacute Pain after Knee Arthroplasty when Added to a Multimodal Analgesic Regimen

A Randomized, Placebo-controlled, Triple-blinded Trial

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ABSTRACT

Background: Duloxetine is effective for chronic musculoskeletal and neuropathic pain, but there are insufficient data to recommend the use of antidepressants for postoperative pain. The authors hypothesized that administration of duloxetine for 15 days would reduce pain with ambulation at 2 weeks after total knee arthroplasty.

Methods: In this triple-blinded, randomized, placebo-controlled trial, patients received either duloxetine or placebo for 15 days, starting from the day of surgery. Patients also received a comprehensive multimodal analgesic regimen including neuraxial anesthesia, epidural analgesia, an adductor canal block, meloxicam, and oxycodone/acetaminophen as needed. The primary outcome was the pain score (0 to 10 numeric rating scale) with ambulation on postoperative day 14.

Results: One hundred six patients were randomized and analyzed. On day 14, duloxetine had no effect on pain with ambulation; mean pain was 3.8 (SD, 2.3) for placebo *versus* 3.5 (SD, 2.1) for duloxetine (difference in means [95% CI], 0.4 [−0.5 to 1.2]; $P = 0.386$). Symptoms potentially attributable to duloxetine discontinuation at study drug completion (nausea, anxiety) occurred among nine patients (duloxetine) and five patients (placebo); this was not statistically significant ($P = 0.247$). Statistically significant secondary outcomes included opioid consumption (difference in mean milligram oral morphine equivalents [95% CI], 8.7 [3.3 to 14.1], $P = 0.002$ by generalized estimating equation) over the postoperative period and nausea on day 1 ($P = 0.040$). There was no difference in other side effects or in anxiety and depression scores.

Conclusions: When included as a part of a multimodal analgesic regimen for knee arthroplasty, duloxetine does not reduce subacute pain with ambulation. **(ANESTHESIOLOGY 2016; 125:561-72)**

PAIN after total knee arthroplasty (TKA) can be severe and persistent.[1,2] Acute pain (pain during postoperative days [PODs] 1 to 3) can be well managed with patient-controlled epidural analgesia (PCEA), adductor canal block, and multimodal analgesia (acetaminophen, meloxicam, and oral opioids).[3] High levels of pain are inherently undesirable and associated with persistent postsurgical pain.[4]

Despite improved in-hospital analgesia, excessive postdischarge pain after TKA remains a problem.[5] Mean pain scores at 2 weeks after TKA are 2.9 (SD, 2.2; rest) and 3.6 (SD, 2.0; with ambulation),[6] respectively, despite oxycodone/acetaminophen and meloxicam. Excessive pain can cause psychologic distress and impair participation in physical therapy. Pain that occurs in the time period between acute and chronic pain, such as pain at 2 weeks, can be termed *subacute* pain.[5] Chronic pain after TKA can be defined as persistent pain at 3 to 6 months.[7]

What We Already Know about This Topic

- Duloxetine is effective for treatment of chronic musculoskeletal and neuropathic pain, but whether it reduces pain after surgery is unclear

What This Article Tells Us That Is New

- In a triple-blinded, randomized control trial of duloxetine, 60 mg/day for 14 days begun on the day of total knee arthroplasty *versus* placebo in 106 patients, duloxetine failed to reduce pain with ambulation on postoperative day 14, the primary outcome

Current multimodal outpatient analgesia often uses opioids, acetaminophen, and nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs improve pain after TKA,[8] but do not eliminate the need for opioids. Even when given both

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NSAIDS and opioids, many TKA patients have increased subacute pain levels and opioid-related side effects. Perioperative pregabalin may improve analgesia.[9] Pregabalin has been found to reduce chronic pain after TKA,[7] but in recent studies, both gabapentin and pregabalin failed to reduce pain or opioid consumption.[6,10] Systemic steroids have analgesic effects, particularly at dexamethasone doses more than or equal to 0.2 mg/kg.[11] Dexamethasone, 10 mg intravenously, improved analgesia after TKA.[12] A recent review of antidepressant drugs for postsurgical pain concluded that it is too early to recommend routine use, but several positive trials suggest benefits that need evaluation with high-quality trials.[13]

Duloxetine, a serotonin and norepinephrine dual reuptake inhibitor (SNRI), is approved for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.[14] Pain relief from duloxetine is independent of duloxetine's effects on depression. Duloxetine has similar effects on pain for depressed and nondepressed patients. Onset of analgesia from duloxetine occurs earlier and at lower doses than are needed to treat depression.[15] Duloxetine reduced morphine usage in the first 48 h after TKA, in the context of general anesthesia and intravenous morphine analgesia, but did not reduce pain or side effects.[16] Duloxetine improved the quality of recovery and reduced opioid consumption for 24 h after abdominal hysterectomy.[17] Duloxetine efficacy for painful diabetic neuropathy was associated with inefficient conditioned pain modulation, suggesting that duloxetine may be more useful among patients displaying a pronociceptive pattern.[18]

Although limited data suggest efficacy for duloxetine in treating acute pain, its effects in subacute pain as a part of a structured multimodal perioperative analgesic regimen for TKA remain unknown. We hypothesized that administration of duloxetine, 60 mg daily for 15 days, starting on the day of surgery, would reduce pain severity with ambulation at 2 weeks after TKA. Secondary aims were to assess the effect on pain at rest, pain with flexion, opioid consumption, affect, neuropathic pain, and side effects (at 2 weeks postoperatively). Additionally, we assessed the effect on persistent pain and opioid consumption (at 3 months postoperatively).

Materials and Methods

This single-center trial was approved by the Hospital for Special Surgery Institutional Review Board and registered with clinicaltrials.gov (NCT02005601, December 4, 2013, by Dr. YaDeau [principal investigator]; https://clinicaltrials.gov/ct2/show/NCT02005601). The trial was conducted at Hospital for Special Surgery (New York, New York), a Weill Cornell Medical School (New York, New York)–affiliated teaching hospital that specializes in musculoskeletal disease. Written informed consent was obtained from all participants. The study presentation conforms to the Consolidated Standards of Reporting Trials reporting standards.[19]

Study Participants

Eligible patients were English speakers, age 25 to 75 yr, who were judged able to follow the protocol and who planned to have regional anesthesia and to be discharged either to home or to a participating rehabilitation center. Exclusion criteria included planned general anesthesia, allergy or intolerance to one of the study medications, major previous ipsilateral open knee surgery, American Society of Anesthesiologists physical status IV, hepatic failure, renal failure (estimated creatinine clearance less than 30 ml/min), contraindication to using dexamethasone in the peripheral nerve block, difficult to manage diabetes mellitus (including insulin dependence), chronic gabapentin or pregabalin use (regular use for longer than 3 months), and chronic opioid use (regular use for longer than 3 months). Patients were additionally excluded for concurrent use of duloxetine or other SNRIs, monoamine oxidase inhibitors, tricyclic antidepressants, triptans, lithium, buspirone, or St. John's Wort. Selective serotonin reuptake inhibitors were not grounds for exclusion.

Study Intervention

This triple-blinded, parallel arm trial was designed to examine the superiority of duloxetine. Group assignment was concealed from the patients, the treating physicians, and the statistician. A computer-generated randomization table was provided to the hospital pharmacy. Patients were randomized (1:1) to receive either duloxetine (60 mg orally daily for 15 days) or placebo. The hospital pharmacy prepared indistinguishable capsules containing either duloxetine or placebo, which were used for the study. A capsule (60 mg) was given approximately 30 min before transfer to the operating room. Patients received one capsule per day up to and including POD14. Open-labeled use of duloxetine for postoperative pain, which was not a standard at our institution, was not allowed.

The dose of duloxetine, 60 mg, was chosen after review of relevant publications. Ho *et al.*[16] showed that two doses of duloxetine, 60 mg, reduced morphine usage after TKA. Additionally, the Cochrane database review of duloxetine for painful neuropathy or chronic pain stated that the usual dose was 60 mg daily, as 20 mg was ineffective and 120 mg was no more effective than 60 mg.[15]

Anesthetic and Analgesic Protocol

Patients received a standardized anesthetic and multimodal analgesic protocol. This included a combined spinal epidural anesthetic (bupivacaine spinal, 10 to 12.5 mg); adductor canal block (ultrasound guided in mid-thigh, 15 ml bupivacaine, 0.25%, with 2 mg preservative-free dexamethasone); intravenous sedation with midazolam and propofol; intraoperative intravenous dexamethasone (4 mg); and intravenous ketorolac (a single intraoperative dose of 30 mg unless age

more than 70 yr or weight less than 60 kg, in which case 15 mg), PCEA (bupivacaine/hydromorphone until 5 PM on POD1), meloxicam (daily postoperative dose of 15 mg unless age more than 70 yr or weight less than 60 kg, in which case 7.5 mg), and oxycodone 5 mg/acetaminophen 325 mg. Patients were discharged with meloxicam (7.5 to 15 mg orally daily) and oxycodone/acetaminophen (5/325 mg; 1 to 2 orally every 4 h prn). Patients were provided with a journal to track opioid use and study drug intake.

Preoperative Phenotyping

Preoperative "phenotyping" included the pain severity, both overall and knee specific (0 to 10 numeric rating scale), fibromyalgia survey score (Michigan Body Map + the Fibromyalgia Symptom Severity Index),[20–22] physical and emotional function (Hospital Anxiety and Depression Scale [HADS]),[23] life satisfaction (0 to 10 Likert scale), neuropathic pain (painDETECT),[24] and preoperative analgesic use. Probable presence of an anxiety or mood disorder was defined as a HADS anxiety or depression subscale score, respectively, greater than or equal to 11.[23] Additional preoperative data collection included patient characteristics: age, sex, race, educational status, body mass index, and American Society of Anesthesiologists physical status.

Outcomes

The primary outcome was the self-reported pain severity with ambulation (0 to 10 numerical rating scale [NRS] score) on POD14. Following guidelines from the Initiative on Methods, Measurement, and Pain Assessment,[25] we assessed a number of other outcome domains. Secondary acute and subacute outcomes (first 14 days) included pain at rest, pain with knee flexion, opioid consumption (assessed on POD1, POD3, and POD14 and at 6 weeks and 3 months), pain severity at other time points (NRS assessed on POD1, POD3, and POD14 and at 6 weeks and 3 months and the PainOUT Patient Outcomes Questionnaire assessed on POD1, POD3, and POD14 and at 3 months),[26] postoperative anxiety and depression (HADS on POD14), side effects (PainOUT), blinding (assessed on POD14), and compliance with the study drug (assessed on POD14). Outcomes at 6 weeks included pain severity (NRS), opioid consumption, neuropathic pain (painDETECT), anxiety and depression (HADS), life satisfaction, and knee-specific outcomes (Knee Society Score).[27] Delayed (3-month) outcomes included analgesic use, PainOUT (including pain severity), and incidence of manipulations.

Duloxetine discontinuation syndrome has been defined as new-onset symptoms including dizziness, nausea, headache, fatigue, irritability, insomnia, and anxiety.[14] On POD 18 to 20, patients were asked about symptoms after cessation of study drug (the open-ended question was "Have you noticed any changes since you stopped taking the study drug?"). If "yes," the symptoms were noted and assessed for either increased pain and/or possible evidence of duloxetine discontinuation syndrome.

Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Hospital for Special Surgery.[28]

A previous trial found a mean ± SD NRS pain score with ambulation at 2 weeks post-TKA to be 3.6 ± 2.0 points in the placebo group.[6] These data are derived from patients who received an analgesic regimen similar to that used in the current study: spinal/epidural anesthesia, PCEA, peripheral nerve blockade (femoral), dexamethasone, meloxicam, and oxycodone/acetaminophen.[6] Assuming a common within-group SD of 2.0 points, we determined that a sample size of 48 patients per group would provide 80% power at a 2-sided α of 0.05 to detect a 1.2-point (33%) difference in mean NRS pain score between the duloxetine and placebo groups using a two-sample *t* test.[25,29] To account for attrition, we planned to enroll 53 patients per group for a total of 106 patients in the trial.

The duloxetine and placebo groups were compared for balance on demographics, pain and medical phenotype, preoperative medications, and surgical variables by calculating standardized differences. Standardized differences were calculated as the difference in means or mean rankings divided by the pooled SD for normally distributed or skewed continuous variables, respectively.[30] For categorical variables, standardized differences were calculated as the difference in proportions divided by the pooled SD. Imbalance was defined as a standardized difference with absolute value greater than 0.2.[31]

All results are presented on an intention-to-treat basis (unless otherwise noted). NRS pain with ambulation at 2 weeks post-TKA, the primary outcome, was compared between the duloxetine and placebo groups using a two-sample *t* test. Continuous and ordinal secondary outcomes measured at a single time point per patient were compared between groups using two-sample *t* tests or Wilcoxon rank sum tests, depending upon the distribution of the data. Absolute effect sizes are presented as differences in means or Wilcoxon–Mann–Whitney odds, respectively, with corresponding 95% CIs. Normality was assessed *via* Shapiro–Wilk tests and visual inspection of quantile–quantile plots and histograms. Categorical variables measured at a single time point per patient were compared between groups using chi-square or Fisher exact test, as appropriate, with effect sizes presented as both relative risk and risk difference with 95% CIs. The generalized estimating equation (GEE) method[32,33] with an autoregressive [AR(1)] correlation structure was used to compare secondary outcomes measured at multiple time points per patient. The GEE method accounts for the correlation between repeated measurements on the same patient, where the AR(1) correlation

structure assumes a greater degree of correlation among measurements recorded closer in time. Each GEE model was initially fit with a treatment by time interaction term. If no evidence of an interaction was found (*i.e.*, $P > 0.05$ for the treatment by time interaction term), the model was refit without an interaction term, and results were reported as overall postoperative difference in means or odds ratio with 95% CIs. If evidence of an interaction was found, treatment arms were compared at each time point separately, and the Holm–Bonferroni step-down procedure[34] was used to control the familywise error rate. Models of longitudinal NRS pain scores were adjusted for the corresponding baseline pain score based on an *a priori* decision to correct for any chance imbalance in baseline pain severity between groups. All statistical hypothesis tests were two sided, with $P < 0.05$ considered statistically significant. Statistical analyses were performed with SAS version 9.3 (SAS Institute, USA).

Results

Study Participants

After informed written consent was obtained, 106 patients with osteoarthritis scheduled for primary TKA with a participating surgeon were enrolled (November 2013 to May 2015). Patient flow through the study is depicted in figure 1. As indicated in figure 1, 569 of 675 screened patients did not enter the study. The most common reason was patients declining to enter (236/675 or 35%). Other common reasons were failure to conform to inclusion criteria (28%) or lack of research staff for follow-up (17%); these were typically cases occurring late in the day or before weekends without coverage. Among 189 patients who failed to meet inclusion criteria, 67 used prohibited antidepressants, 48 used prohibited analgesics, 32 had previous ipsilateral surgery, 22 had medical contraindications, 13 had social reasons, and 7 were previously enrolled in the study. Patient characteristics, preoperative use of analgesics by study participants, and surgical factors are shown in table 1.

Duloxetine Did Not Reduce Pain at Rest, with Ambulation, or with Flexion

NRS pain with ambulation on POD 14 (primary outcome) was 3.8 ± 2.3 (placebo; mean ± SD) *versus* 3.5 ± 2.1 (duloxetine; difference in means [95% CI], 0.4 [–0.5 to 1.2]; $P = 0.386$). NRS pain scores with ambulation, flexion, and at rest did not differ between groups over the postoperative period (POD 1 through 6 weeks postoperatively) after adjustment for corresponding baseline pain severity ($P = 0.293$, 0.110, and 0.978, respectively, by GEE; fig. 2).

Duloxetine Reduced Opioid Consumption and Nausea in the First 14 Days after Surgery

Total opioid use (fig. 3) was significantly reduced in the duloxetine group over the postoperative period (day of surgery through 3 months postoperatively; difference in means [95% CI], 8.7 [3.3 to 14.1]; $P = 0.002$ by GEE).

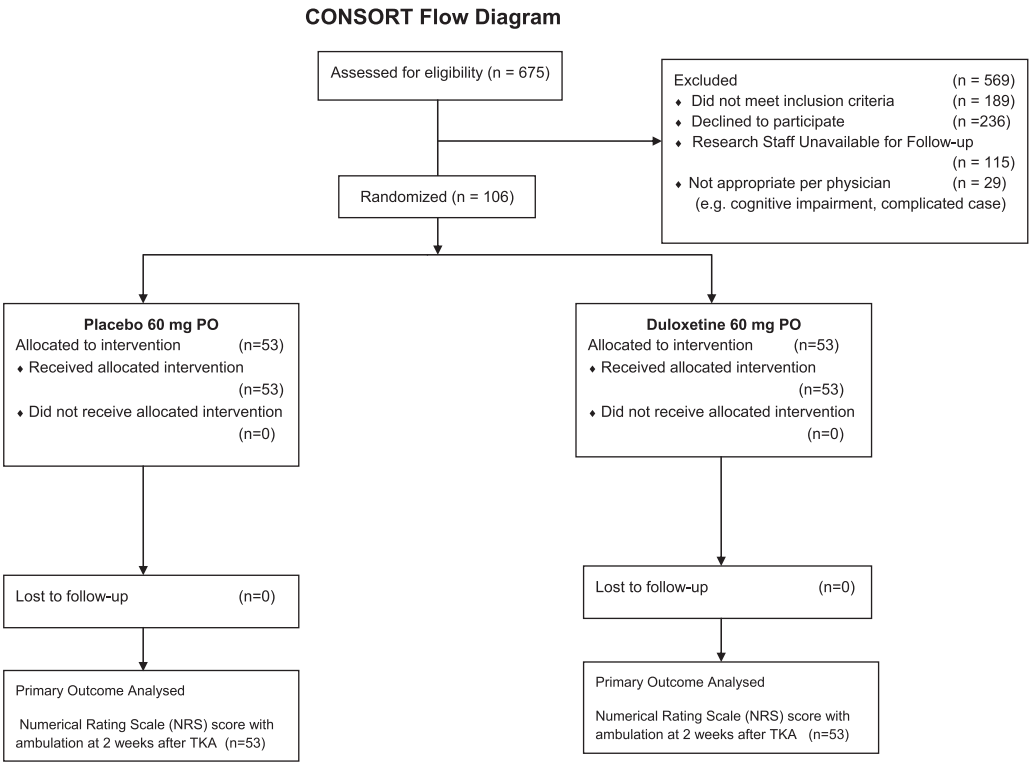

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow through the study. PO = by mouth; TKA = total knee arthroplasty.

Table 1. Demographics, Pain and Medical Phenotype, Preoperative Medications, and Surgical Variables

	Placebo	Duloxetine	Standardized Difference
Demographics			
Age (yr)	63 (57–67)	67 (61–71)	0.49
Gender, n (%)			−0.08
Male	27 (50.9)	25 (47.2)	—
Female	26 (49.1)	28 (52.8)	—
Race (% Caucasian)			—
Asian	0 (0)	1 (1.9)	0.20
Black/African American	4 (7.5)	2 (3.8)	−0.16
White	48 (90.6)	48 (90.6)	0
Some other race	0 (0)	1 (1.9)	0.20
Decline	1 (1.9)	1 (1.9)	0
Education level, n (%)			—
High school	5 (9.4)	5 (9.4)	0
Some college	7 (13.2)	9 (17)	0.11
Technical degree/associate's degree	2 (3.8)	5 (9.4)	0.23
Bachelor's degree	19 (35.8)	11 (20.8)	−0.34
Advanced/professional degree (MA, PhD, MD, *etc*.)	20 (37.7)	23 (43.4)	0.12
Pain and medical phenotype			
Knee pain severity at rest	2.9 ± 2.5; 2 (1–5)	3.6 ± 2.8; 3 (1–7)	0.26
Knee pain severity with flexion	5.5 ± 3.1; 6 (3–8)	5.8 ± 3.0; 6 (3–8)	0.09
Knee pain severity with ambulation	5.2 ± 2.6; 5 (4–8)	5.8 ± 2.5; 6 (4–8)	0.22
Average overall body pain	4.3 ± 2.4; 4 (2–6)	4.9 ± 2.5; 5 (3–7)	0.25
Worst overall body pain	6 (4–8)	8 (4–9)	0.35
Neuropathic pain (painDETECT)	7 (4–10)	8 (4–11)	0.11
Duration of pain in surgical knee (yr)	3 (2–8)	4 (2–7)	0.16
Fibromyalgia full score	5 (3–8)	6 (3–8)	0.14
Fibromyalgia symptom severity index	2 (1–4)	3 (1–4)	0.18
Depression (HADS)	3 (2–6)	3 (1–6)	0.04
Probable presence of depression (HADS ≥ 11), n (%)			0.20
Yes	0 (0)	1 (1.9)	—
No	53 (100)	52 (98.1)	—
Anxiety (HADS)	4 (2–6)	4 (2–6)	−0.01
Probable presence of anxiety (HADS ≥ 11), n (%)			−0.20
Yes	3 (5.7)	1 (1.9)	—
No	50 (94.3)	52 (98.1)	—
Life satisfaction	8 (7–10)	8 (6–9)	−0.12
Knee Society Total Score	98 (72–118)	102 (87–127)	0.26
Knee Society Knee Score	48 (39–58)	55 (48–65)	0.43
Knee Society Function Score	50 (30–70)	60 (30–70)	0.17
Body mass index	31 ± 5; 31 (27–35)	32 ± 7; 31 (27–36)	0.07
ASA physical status 1/2/3	3/44/6	3/37/13	0.29
Preoperative medications (%)			
Acetaminophen	20.8	24.5	0.09
NSAIDs	15.1	24.5	0.24
Opioids including tapentadol/tramadol	7.5	9.4	0.07
Antidepressants	3.8	1.9	−0.11
Count: No antidepressant	51	52	—
Count: Bupropion	1	1	—
Count: Escitalopram	1	0	—
Muscle relaxants	1.9	1.9	0
Gabapentinoids	0	0	0
Surgical variables			
Tourniquet time (min)	46 (40–52)	44 (34–52)	−0.21

Data are presented as mean ± SD and/or median (first to third quartiles) for continuous variables and frequency (%) for categorical variables. Imbalance is defined as a standardized difference with absolute value > 0.2.

ASA = American Society of Anesthesiologists; HADS = Hospital Anxiety and Depression Scale; NSAIDs = nonsteroidal antiinflammatory drugs.

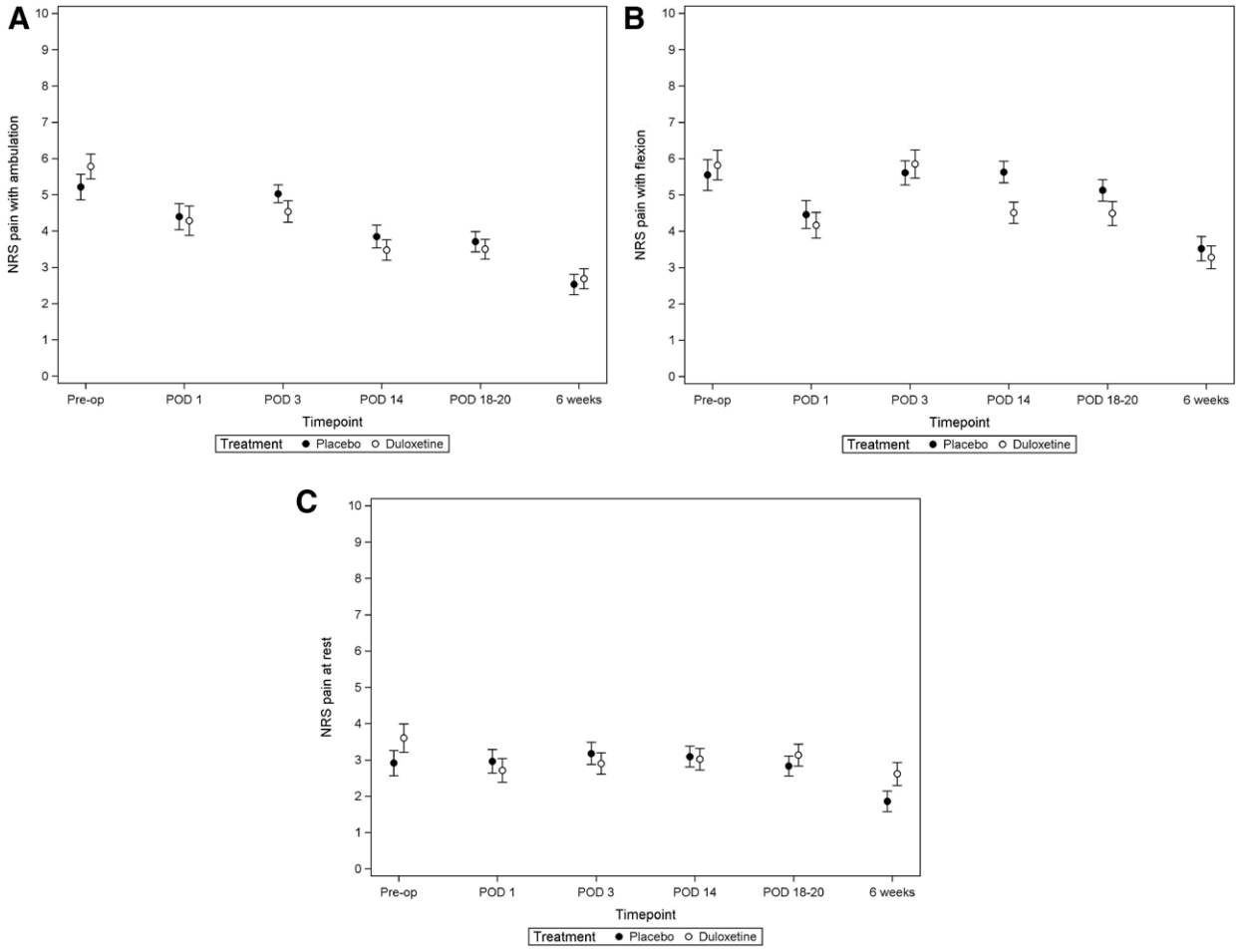

Fig. 2. Pain scores over time (numerical rating scale [NRS] for pain [0 to 10]), at rest, with flexion, and with ambulation. Mean NRS pain score with ambulation (*A*), with bending (*B*), and at rest (*C*) for each of the randomized groups over time. Data are plotted as mean ± SE. *Error bars* extend to 1 SEM. POD = postoperative day.

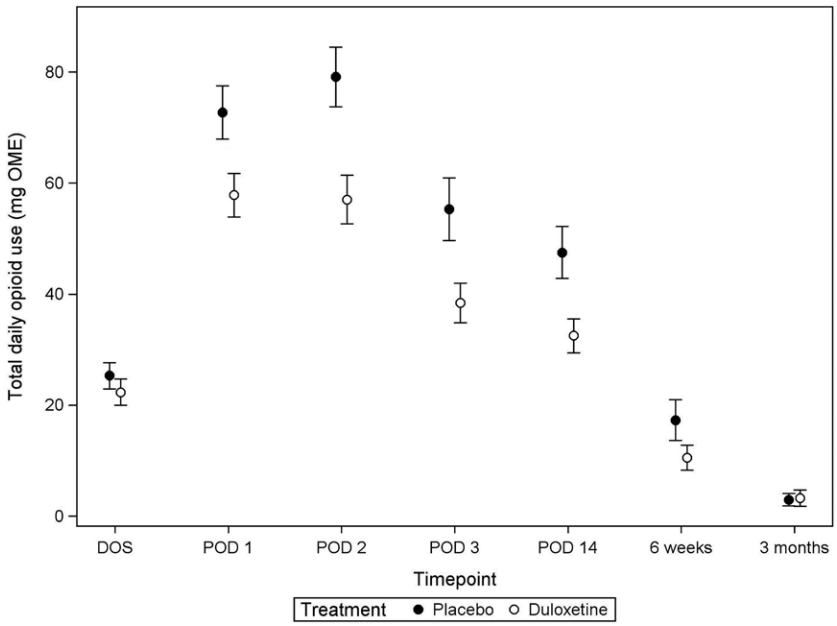

Fig. 3. Total daily opioid use. Mean oral morphine equivalents (OMEs) in milligram consumed by each of the randomized groups over time. Data are plotted as mean ± SD. *Error bars* extend to 1 SEM. DOS = day of surgery (postoperative); POD = postoperative day.

Table 2. Side Effects: Nausea, Drowsiness, Itching, and Dizziness Scores from PainOUT

	Placebo (n)	Placebo	Duloxetine (n)	Duloxetine	Difference in Means (95% CI)	*P* Value
Nausea severity						
POD1	53	2.3±3.4; 0 (0 to 5)	53	0.9±2.2; 0 (0 to 0)	1.4 (0.3 to 2.5)	0.040
POD3	53	1.8±2.8; 0 (0 to 2)	52	1.8±3.0; 0 (0 to 3)	0.1 (–1.0 to 1.2)	0.917
POD14	53	1.3±2.7; 0 (0 to 0)	53	0.5±1.3; 0 (0 to 0)	0.8 (0 to 1.6)	0.121
3 mo	49	0±0; 0 (0 to 0)	47	0.1±0.5; 0 (0 to 0)	–0.1 (–0.2 to 0)	0.210
Drowsiness severity						
POD1	53	3.3±3.2; 3 (0 to 6)	53	4.0±3.3; 4 (1 to 7)	–0.6 (–1.2 to 0)	0.067
POD3	53	3.4±2.9; 3 (0 to 5)	52	5.0±3.1; 5 (3 to 8)		
POD14	53	2.3±2.8; 2 (0 to 4)	53	1.9±2.4; 0 (0 to 4)		
3 mo	49	0.2±1.0; 0 (0 to 0)	47	0.6±1.8; 0 (0 to 0)		
Itching severity						
POD1	53	2.6±3.1; 1 (0 to 5)	53	2.4±3.1; 1 (0 to 4)	0.3 (–0.3 to 0.9)	0.323
POD3	53	2.2±2.4; 2 (0 to 4)	52	1.5±2.8; 0 (0 to 2)		
POD14	53	1.2±2.0; 0 (0 to 2)	53	0.9±2.2; 0 (0 to 0)		
3 mo	49	0.4±1.5; 0 (0 to 0)	47	0.4±1.3; 0 (0 to 0)		
Dizziness severity						
POD1	53	2.1±3.2; 0 (0 to 3)	53	1.8±2.3; 1 (0 to 3)	0 (–0.5 to 0.4)	0.963
POD3	53	0.8±1.5; 0 (0 to 1)	52	1.5±2.3; 0 (0 to 3)		
POD14	53	0.8±2.1; 0 (0 to 0)	53	0.4±1.2; 0 (0 to 0)		
3 mo	49	0.1±0.6; 0 (0 to 0)	47	0.2±0.8; 0 (0 to 0)		
Worst pain						
POD1	53	6.2±2.8; 7 (4 to 8)	53	5.9±2.7; 6 (4 to 8)	0 (–0.6 to 0.6)	0.938
POD3	53	6.9±2.0; 7 (5 to 8)	52	7.2±2.3; 8 (6 to 9)		
POD14	53	6.4±2.1; 6 (5 to 8)	53	5.9±2.4; 7 (4 to 8)		
3 mo	49	2.0±1.9; 2 (0 to 3)	47	2.3±2.3; 2 (0 to 3)		

Patients in the duloxetine group had significantly reduced nausea severity on POD1. Data are measured using Likert scales ranging from 0 (none) to 10 (severe) and presented as mean ± SD; median (first to third quartiles). PainOUT scores compared between duloxetine and placebo groups using regression based on the generalized estimating equation method, with effect sizes presented as differences in means. Each model was initially fit with a treatment by time interaction term. If no evidence of an interaction was found, the model was refit without an interaction term, and effect size reported as overall difference in means. If evidence of an interaction was found, treatment arms were compared at each time point separately and the Holm–Bonferroni step-down procedure was used to control the familywise error rate.

POD = postoperative day.

Nausea severity (table 2, measured by PainOUT) was substantially reduced in the duloxetine group on POD1. Severity of drowsiness, itching, or dizziness were not significantly different among groups.

Duloxetine Did Not Change Anxiety, Depression, and Chronic Pain

Changes in HADS anxiety and HADS depression scores were not significantly different among groups (table 3). Changes in chronic pain measures (painDETECT) were also not significantly different among groups.

Additional Outcomes

Length of stay and disposition at discharge did not differ among groups (table 4). Compliance at POD 14 did not differ among groups. Knee Society Score did not differ among groups. By 3 months, four patients received postoperative manipulations for knee stiffness among placebo group, *versus* one in the duloxetine group, but the difference was not statistically significant. At 3 months, pain scores and side effects (nausea, drowsiness, itching, dizziness) did not differ among groups. The majority of patients (54/106) answered "don't know" when blinding

Table 3. Changes in Anxiety, Depression, and Neuropathic Pain

	Placebo	Duloxetine	Wilcoxon–Mann–Whitney Odds (95% CI)	*P* Value
Change in HADS anxiety score (preoperative to POD14)	–2 (–3 to 0)	–2 (–4 to 0)	1.14 (0.73 to 1.81)	0.560
Change in HADS depression score (preoperative to POD14)	0 (–2 to 3)	–1 (–2 to 1)	1.42 (0.91 to 2.28)	0.128
Change in painDETECT (preoperative to 6 wk postoperative)	0 (–5 to 5)	–1 (–3 to 4)	0.99 (0.62 to 1.58)	0.953

Data are measured using Likert scales ranging from 0 (none) to 10 (severe) and presented as median (first to third quartiles). Duloxetine compared to placebo group using Wilcoxon rank sum tests with effect sizes reported as Wilcoxon–Mann–Whitney odds.

HADS = Hospital Anxiety and Depression Scale; POD = postoperative day.

Table 4. Other Outcomes

	Placebo	Duloxetine	Wilcoxon–Mann–Whitney Odds or Relative Risk (95% CI)	Risk Difference (95% CI)	*P* Value
Length of stay (h), median (Q1 to Q3)	76 (72 to 98)	76 (71 to 100)	0.85 (0.53 to 11.33)		0.466
Disposition at discharge, home/rehab (n)	37/16	40/13	1.23 (0.64 to 2.54)	5.7% (–11.2 to 22.1)	0.513
Manipulations after surgery, n (%)	4 (7.5)	1 (1.9)	4.00 (0.56 to 101.09)	5.7% (–3.6 to 16.1)	0.363
Compliance (POD 14), n (%)	45 (84.9)	40 (75.5)	0.62 (0.28 to 1.36)	9.4% (–5.9 to 24.4)	0.223
Change possibly related to study drug discontinuation (POD 18 to 20), n (%)	11 (20.8)	14 (26.4)	0.78 (0.36 to 1.60)	–6.3% (–23.3 to 11.2)	0.485
Pain increase with study drug discontinuation (POD 18 to 20), n (%)	6 (11.3)	6 (11.3)	1.00 (0.31 to 3.22)	0.0% (–13.9 to 13.9)	0.999
Possible discontinuation syndrome (POD 18 to 20), n (%)	5 (9.4)	9 (17.0)	0.56 (0.20 to 1.54)	–8.3% (–22.8 to 6.2)	0.247
Change in KSS function score (preoperative to 6 wk postoperative), median (Q1 to Q3)	20 (0 to 3)	17.5 (–5 to 30)	0.86 (0.41 to 1.72)		0.661
Change in KSS knee score (preoperative to 6 wk postoperative), median (Q1 to Q3)	29 (17 to 50)	25.5 (10.5 to 47.5)	1.26 (0.63 to 2.70)		0.512
Change in KSS total score (preoperative to 6 wk postoperative), median (Q1 to Q3)	50 (29 to 62)	32 (7 to 66)	1.32 (0.63 to 3.05)		0.441

Blinding	Guess: Duloxetine	Guess: Placebo	"Don't Know"	Bang Blinding Index (95% CI)	*P* Value
Actual treatment: duloxetine	17	12	24	0.09 (–0.07 to 0.26)	0.175
Actual treatment: placebo	6	17	30	0.21 (0.07 to 0.35)	0.008

Data are presented as median (first to third quartiles) for continuous variables and frequency (%) for discrete variables. Continuous outcomes compared between duloxetine and placebo group using two-sample *t* tests or Wilcoxon rank sum tests with effect sizes reported as difference in means or Wilcoxon–Mann–Whitney odds, respectively. Discrete outcomes compared using chi-square or Fisher exact test with effect sizes reported as both risk differences and risk ratios. The Bang Blinding index indicated that 9% more and 21% more patients in the duloxetine and placebo groups, respectively, correctly guessed their treatment assignment than would be expected by chance.

KSS = Knee Society Score; POD = postoperative day.

was assessed. Bang's Blinding Index indicated that for the duloxetine group, 9% more patients correctly guessed that they were assigned duloxetine than would be expected by chance. For the placebo group, 21% more patients correctly guessed that they were assigned placebo than would be expected by chance.

Symptoms possibly related to study drug discontinuation were reported in both groups, without statistical significant difference in rates. Pain increases upon discontinuation occurred at the same rate in both placebo and duloxetine groups. Possible duloxetine discontinuation syndrome occurred in five patients (placebo group) and 9 patients (duloxetine group); this difference was not statistically significant ($P = 0.247$).

Seven adverse events were reported to the institutional review board: three in the placebo group (atrial fibrillation; nausea, insomnia, and hypervigilance; and headache) and four in the duloxetine group (nausea, drowsiness, and fatigue; somnolence and dizziness; confusion and syndrome of inappropriate antidiuretic hormone secretion; and nausea, drowsiness, and hypervigilance). The patient with nausea, drowsiness, and hypervigilance was diagnosed with duloxetine discontinuation syndrome by an outside physician (who was unaware of group assignment) and was treated with a tapering course of duloxetine, which resolved the symptoms. The patient expressed a desire to resume duloxetine as it improved her mood and reduced pain. No other patients underwent weaning from study drug.

Discussion

Administration of duloxetine for 2 weeks after TKA did not improve pain with ambulation, the study primary outcome. Duloxetine did not appear to cause major side effects.

Most secondary outcomes were similar among groups. Duloxetine reduced opioid use (fig. 3) and reduced nausea (table 2). These improvements were statistically significant and clinically relevant in magnitude. Duloxetine is an antidepressant; preoperative affective distress was low (median HADS anxiety score of 4 in each group and median HADS depression score of 3 in each group). Median day 14 depression scores were 4 (interquartile range [IQR], 1 to 6) in the placebo group and 3 (IQR, 1 to 4) in the control group (not significant). The rate of manipulations for arthrofibrosis was not significantly different among groups (7.5% in placebo *vs.* 1.9% in duloxetine). Results from secondary outcomes can be considered hypothesis-generating findings for exploration in subsequent trials.

This study described the natural course of pain and analgesic use after TKA. Pain scores in general did not exceed preoperative levels, but patients required large opioid doses from POD1 to POD14. The indication for TKA is often

pain, but major reductions in pain were not noted until 6 weeks, despite liberal analgesic use. Study patients used little preoperative opioids and by 3 months returned to minimal use.

The primary endpoint was assessed on POD14 due to interest in subacute pain. In one study, about 45% of TKA patients had significant pain (Visual Analogue Scale, more than 40) at 1 month, which declined to about 12% of patients at 1 yr.[35] Another study documented pain scores (at approximately POD 10) of 3.7 (IQR, 2.9 to 4.7).[8] A recent randomized trial, utilizing a similar analgesic regimen, documented mean pain at rest of 2.9 (SD, 2.3); mean pain with flexion was 4.0 (SD, 2.3).[6] This moderate to severe subacute pain level is clinically important because postoperative pain correlates with the development of chronic pain.[4] The study intervention (placebo or duloxetine) continued until POD14, representing an additional reason to assess the effect on POD14.

Increased Interest in the Use of Antidepressants for Postoperative Pain

Current enthusiasm about the use of antidepressant drugs for postoperative pain[13] focuses on tricyclic antidepressants, selective serotonin reuptake inhibitors, and SNRIs. A review of antidepressant drugs for postoperative pain concluded that there is insufficient evidence to support clinical use.[13] Several studies demonstrated benefit, and it was suggested that additional procedure-specific trials were needed that assess movement-evoked pain. Four studies of SNRIs for postoperative pain were noted (three positive and one negative), but only one of these used duloxetine.[16] A study of TKA patients who received general anesthesia and intravenous morphine found that two doses of duloxetine reduced opioid use, without reduction in pain or side effects.[16] Differences between the current study and the Ho *et al.*'s study include longer duration of therapy (15 doses) and the concomitant use of multimodal analgesia (neuraxial anesthesia, nerve blockade, and NSAIDs). These factors may help explain divergent results.

Duloxetine improved the quality of recovery at 24 h after hysterectomy (including physical comfort, independence, emotional, and pain subcomponents).[17] Study differences include patient population and surgery type (gynecologic surgery, not orthopedic), time of assessment of primary outcomes (no difference was found in Quality of Recovery–40 instrument at 48 h after hysterectomy), and duration of therapy (2 doses *vs.* 15 doses).

Escitalopram, a selective serotonin reuptake inhibitor, did not alter pain at 24 h after TKA among high pain catastrophizing patients.[36] Secondary analyses found that escitalopram reduced pain on POD 2 to 6 without reduced opioid use or nausea. Study differences include primary outcome, patient population (catastrophizing patients *vs.* relatively unselected TKA patients), duration of therapy (6 days *vs.* 15 days), and drug studied (selective serotonin reuptake inhibitor *vs.* SNRI).[37]

Side effects and tolerability are important issues in analgesic trials. Among patients with depression, duloxetine increases nausea compared to placebo,[38] but the opposite effect was noted in this trial. Speculatively, the reduction in opioid use by duloxetine (observed on PODs 1 to 14) may outweigh potential emetogenic effects of duloxetine.

Antidepressants and Multimodal Analgesia

The structured multimodal analgesic regimen, including neuraxial anesthesia, postoperative peripheral nerve block, dexamethasone, and nonsteroidal analgesics, is a distinguishing factor of this trial. Many studies of nonopioid analgesics for postoperative pain do not include other commonly used analgesics or regional anesthesia, thereby limiting the understanding of how the findings apply to a broader multimodal regimen. It is important to note that different results may have been obtained if multimodal analgesia had not been used.

Strengths and Limitations

Study strengths include study design; duloxetine was prescribed for 15 days in a prospective, blinded, randomized trial, with assessment of numerous outcomes consistent with recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[25] A recent review called for additional studies on this topic,[13] and this trial is consistent with the outlined need for larger, procedure-specific trials assessing pain with movement. The study employed a robust multimodal analgesic regimen. Blinding was assessed; the majority of patients did not know their group assignment.

There were limitations. The study was performed at a single center, reducing generalizability. Generalizability is also affected by inclusion and exclusion criteria, as is commonly the case for efficacy trials. Patients with chronic opioid use were excluded to reduce heterogeneity in the study population. It is possible that excluding chronic pain patients removed from the study those patients most likely to benefit from duloxetine. Diabetic neuropathy patients with inefficient inhibitory pain control system may be more likely to benefit from duloxetine,[18] but testing that could have delineated such patients (conditioned pain modulation) was not performed in this study.

There was insufficient power for some secondary outcomes, such as changes in affect, rates of manipulation for stiffness, and long-term pain outcomes. Measurement of serum duloxetine was not performed, but might have been useful to verify compliance and determine whether therapeutic levels were achieved. Additionally, if oxycodone levels were also measured, inferences could have been made about whether the reduction in oxycodone use associated with duloxetine use reflects pharmacokinetic or pharmacodynamic interaction.

Patient compliance at POD14 (80% overall) was not complete, but was better than the recently reported 63% compliance in a similar pregabalin trial.[6] Compliance in clinical trials is often not reported.[39] Rates of study drug

discontinuation were not substantially influenced by group; rates were similar in patients receiving placebo (84.9% compliant) and duloxetine (75.5% compliant). This suggests that noncompliance was not due to duloxetine side effects. Patients were asked to take the study drug for 15 days, mostly as an outpatient. Many outpatients are not compliant with prescribed medication; for example, after an acute myocardial infarction, adherence rates for cardiovascular drugs are 66 to 76%.[40] Among patients eligible to participate, 69% declined. Analogous percentages for recent randomized TKA trials at this institution were 48,[6] 37,[3] and 25%.[41] We did not formally collect reasons for refusal, but anecdotally it seemed that many patients were reluctant to commit to a 2-week course of a drug that has received extensive advertising.

Duloxetine may increase the risk of bleeding.[14] Although duloxetine did not increase bleeding after coronary artery bypass graft surgery,[42] bleeding-related adverse event reports found placebo rate of 1.2 *versus* 1.8% for duloxetine.[43]

Future Opportunities

Subsequent duloxetine studies could focus on patients at an increased risk for adverse pain outcomes. This could include patients using chronic opioids, patients with inefficient inhibitory pain control systems, and pain catastrophizers.[18] Studies could also investigate in more detail the effects of duloxetine on development of chronic pain. Further exploration is needed of the secondary outcomes reported in this study (opioid use, nausea). There are insufficient data at this time to recommend duration of therapy for analgesic trials of perioperative duloxetine. It would be interesting to determine dose–response and optimal duration of therapy. Of note, antidepressant discontinuation syndrome is rare among patients receiving less than 6 to 8 weeks of treatment.[44] Large-scale studies are needed to determine rates of possible rare benefits (*e.g.*, does duloxetine reduce the rate of postoperative manipulation for knee stiffness?) and side effects (*e.g.*, does discontinuation syndrome occur at a clinically important frequency after administration for 15 days?).

Given the negative result for the primary outcome and the paucity of studies about perioperative analgesic use of duloxetine, it is premature to recommend the routine use of duloxetine for analgesia after TKA. Subsequent studies could use multiple hypothesis testing. For example, perioperative duloxetine would be beneficial if (1) duloxetine was noninferior on pain, opioid use, and side effects, or (2) duloxetine was superior on at least one of pain, opioid use, and side effects.

Conclusions

Duloxetine (60 mg daily for 15 days) did not improve pain with ambulation at POD14 after TKA in the context of multimodal analgesia. Some secondary results favored the use of duloxetine.

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Competing Interests

Dr. Brummett receives research funding from Neuros Medical Inc. (Willoughby Hills, Ohio) and is a consultant for Tonix Pharmaceuticals (New York, New York). Dr. Mayman is a consultant for Smith & Nephew (Memphis, Tennessee) and StrykerMako (Warsaw, Indiana) and has stock options in OrthAlign (Aliso Viejo, California). Dr. Padgett reports personal fees from StrykerMako. Dr. Alexiades receives research support from StrykerMako and is a consultant for Biomet, Inc. (Warsaw, Indiana). Dr. Westrich reports grants and personal fees from Stryker Orthopedics (Mahwah, New Jersey), Exactech (Gainesville, Florida), and DJO Global (Austin, Texas) and other relationships with the Eastern Orthopedic Association (Towson, Maryland) and Knee Society (Rosemont, Illinois), outside the submitted work. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Thuyvan Luu: luut@hss.edu. Raw data available from Thuyvan Luu: luut@hss.edu.

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