STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

The Use of Venlafaxine in Reducing Acute Post-Surgical Pain and Opioid Consumption after Primary Total Knee Replacement

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Sponsor:	Matthias Behrends, MD
Principal Investigator:	Matthias Behrends, MD
Co-Investigators:	Sarah Jingying Zhang, MD; Paul Su, MD
Funding Organization:	Orthopaedic Research and Education Foundation (Award A136242)
Institution:	University of California, San Francisco Medical Center
Site:	UCSF Medical Center at Mount Zion, 1600 Divisadero St., San Francisco, CA 94143

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PART I: STUDY PROTOCOL

1. Background and Rationale

Total knee arthroplasty (TKA) is one of the most commonly performed elective surgical procedures in the United States, with more than 600,000 procedures performed annually. Despite advances in multimodal analgesia and enhanced recovery after surgery (ERAS) protocols, more than 20% of patients experience persistent postsurgical pain following TKA. Traditional opioid-based pain management is associated with significant side effects including nausea, vomiting, respiratory depression, and cognitive dysfunction, with these risks amplified in the geriatric population.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) exert analgesic effects through activation of descending inhibitory pain pathways by increasing noradrenaline and serotonin concentrations at supraspinal and spinal levels. Additionally, activation of endogenous mu and delta-opioid receptors, inhibition of sodium channels, and N-methyl-D-aspartate (NMDA) receptor antagonism have been proposed as contributing mechanisms. The SNRI duloxetine has demonstrated efficacy in reducing acute postoperative pain and opioid consumption in TKA patients in multiple randomized controlled trials.

Venlafaxine represents an important alternative SNRI warranting investigation for several reasons. It is available as a generic medication with substantially lower cost and potentially greater accessibility compared to duloxetine. The proposed dose of 37.5 mg extended-release represents 50% of the standard antidepressant starting dose, potentially minimizing adverse effects in the surgical population. To our knowledge, no prior study has examined venlafaxine's efficacy in reducing acute and chronic postsurgical pain or opioid consumption in TKA patients.

2. Study Objectives

Primary Objective: To assess the efficacy of venlafaxine extended-release 37.5 mg daily in reducing opioid consumption on postoperative day 1 (POD1) in patients undergoing primary total knee arthroplasty.

Secondary Objectives:

- Assess the effect of venlafaxine on total opioid consumption during the acute phase (POD 1–7)
- Evaluate pain intensity (NRS at rest and with movement) at 24 hours, 7 days, and 3 months
- Assess pain interference using the Brief Pain Inventory (BPI) at baseline, 7 days, and 3 months
- Evaluate patient satisfaction with pain management
- Assess functional outcomes including distance walked and range of motion
- Determine incidence of chronic postsurgical pain at 3-month follow-up
- Document adverse events and tolerability of venlafaxine

3. Study Design

This was a single-center, prospective, randomized, double-blinded, placebo-controlled trial conducted at the University of California San Francisco (UCSF) Medical Center from May 2021 to March 2025. The study was approved by the UCSF Institutional Review Board (IRB #20325895) and registered with

ClinicalTrials.gov (NCT05023278). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable federal regulations.

Patients were randomized in a 1:1 ratio using a computer-generated randomization sequence with variable block sizes, managed by a pharmacist not otherwise involved in the study. The randomization sequence was concealed from investigators, clinical staff, patients, data collectors, and statisticians until completion of the primary outcome analysis. The investigational pharmacy prepared identical-appearing capsules of venlafaxine extended-release 37.5 mg or placebo.

4. Study Population

Inclusion Criteria:

- English-speaking adults aged 18–85 years
- Scheduled for primary unilateral TKA under spinal anesthesia
- American Society of Anesthesiologists (ASA) physical status I–IV
- Ability to provide written informed consent and comply with study requirements
- Planned anesthesia technique of spinal anesthesia plus adductor canal block

Exclusion Criteria:

- Chronic opioid use defined as regular use for >3 months prior to surgery
- Allergy or contraindication to study medications
- Severe renal insufficiency (eGFR <30 mL/min/1.73m²)
- Hepatic insufficiency (MELD >10)
- Current use of SNRIs, SSRIs, MAOIs, TCAs, or other antidepressants
- Concurrent use of triptans, linezolid, or benzodiazepines
- Uncontrolled hypertension or history of seizures
- Bleeding disorders or concurrent anticoagulation
- Planned general anesthesia
- ASA physical status >IV
- Inability to understand the study protocol or cognitive dysfunction
- Revision knee surgery
- Pregnancy or breastfeeding
- Body mass index >40 kg/m²
- History of repeated falls
- Non-English speaking

5. Intervention

Treatment Group (n=50 planned; n=41 analyzed): Venlafaxine extended-release 37.5 mg orally once daily for 7 days, beginning on the day of surgery 1–2 hours before the procedure.

Control Group (n=50 planned; n=41 analyzed): Identical-appearing placebo capsule orally once daily for 7 days on the same schedule.

Background Multimodal Analgesia (all patients): Standardized perioperative regimen including preoperative acetaminophen 1000 mg and celecoxib 200 mg (unless contraindicated); spinal anesthesia with bupivacaine 12–15 mg and fentanyl 15–20 mcg; adductor canal nerve block with ropivacaine 0.5% 20 mL; postoperative acetaminophen 1000 mg every 8 hours and celecoxib 200 mg every 12 hours scheduled; oxycodone 5–10 mg orally as needed for breakthrough pain (target NRS <4/10).

6. Outcome Measures

Primary Outcome: Total opioid consumption in morphine milligram equivalents (MME) on POD1.

Secondary Outcomes:

- Area under the curve (AUC) for opioid consumption during POD 1–7
- NRS pain scores (0–10) at rest and with movement at POD1, POD2, POD7, and 3 months
- AUC for pain scores during POD 1–7
- Brief Pain Inventory (BPI) interference scores at baseline, POD7, and 3 months
- Patient satisfaction with pain management (0–10 scale) at each time point
- Functional outcomes: distance walked (feet) and range of motion (degrees) on POD2
- Chronic pain outcomes at 3 months: NRS pain scores and opioid consumption
- Adverse events throughout the study period
- KOOS, JR; PROMIS-10; VR-12 scores at baseline and 3 months

7. Study Procedures and Visit Schedule

Assessment	Preoperative (Day of Surgery)	POD 1	POD 7 (Phone)	3 Months
Informed Consent	X			
Demographics / Medical History	X			
Randomization	X			
Study Drug Dispensing	X			
Vital Signs	X	X		
NRS Pain Score	X	X	X	X
Total MME Consumption	X	X	X	
Brief Pain Inventory (BPI)	X	X	X	
KOOS, JR	X	X	X	
PROMIS-10 / VR-12	X			X
Patient Satisfaction	X	X	X	
Distance Walked / ROM		X		
Adverse Event Assessment	X	X	X	
Medication Compliance Check	X			
Concomitant Medications	X	X	X	X

8. Safety Monitoring and Adverse Events

Adverse events (AEs) were documented throughout the study. AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Relationship to study drug was classified as definitely, probably, possibly, or unrelated. Serious adverse events (SAEs) were defined as events resulting in death, life-threatening conditions, inpatient hospitalization or prolongation of hospitalization, or persistent significant disability.

Common anticipated side effects of venlafaxine included drowsiness, dizziness, dry mouth, and nausea (>10% incidence), with constipation, visual disturbances, risk of falls, and unusual sweating as less common effects (1–10%). Rare but serious events included increased blood pressure, precipitation of mood episodes in patients with underlying psychiatric disorders, hyponatremia, and hepatic injury.

An interim safety analysis was planned when approximately 50% of patients had completed study follow-up. SAEs were monitored on an ongoing basis throughout the study and reported to the UCSF IRB per standard operating procedures.

9. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP) guidelines, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The UCSF IRB approved the protocol (IRB #20325895) prior to study initiation. Written informed consent was obtained from all participants before any study-related activities were performed. Subject confidentiality was maintained by identifying all records with a subject number and initials only. Study records are maintained per federal requirements.

PART II: STATISTICAL ANALYSIS PLAN

10. Overview of Statistical Approach

This Statistical Analysis Plan (SAP) describes all pre-specified and post-hoc analytical decisions for the primary and secondary outcomes of this trial. The SAP was finalized prior to unblinding. All statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing). Statistical significance was set at two-sided $p<0.05$.

11. Sample Size and Power

Sample size was calculated based on detecting a 30–35% reduction in POD1 opioid consumption, with 80% power and a two-sided alpha of 0.05, requiring 36 patients per group. To account for an estimated 10% dropout rate, 100 patients (50 per arm) were enrolled. This sample size also provides 80% power to detect a clinically meaningful difference of approximately 20 mg MME in opioid consumption, assuming a standard deviation of approximately 30 mg MME based on prior chart review of TKA patients at UCSF.

12. Analysis Populations

Intention-to-Treat (ITT) Population: All randomized patients (n=100). Used for sensitivity analyses.

Per-Protocol (PP) Population (Primary Analysis Population): All patients who received the allocated intervention and underwent surgery (n=82; 41 per group). This is the primary analysis population. Eighteen patients who were randomized but did not receive the intervention were excluded due to medication not administered in time before surgery, patient withdrawal, or surgery cancellation.

Safety Population: All randomized patients who received at least one dose of study medication.

13. Primary Outcome Analysis

The primary outcome was total opioid consumption in MME on POD1. The primary analysis used analysis of covariance (ANCOVA) with treatment group as the factor and age, sex, BMI, and baseline NRS pain score as covariates. Missing data were addressed using multiple imputation by chained equations (MICE), with treatment arm, baseline measures, age, sex, and BMI as predictors. Results were pooled across 20 imputed datasets using Rubin's rules.

Due to the right-skewed distribution of opioid consumption data, a sensitivity analysis using the Wilcoxon rank-sum test on the observed (non-imputed) data was pre-specified. Median p-values across imputed datasets were also reported.

PRIMARY OUTCOME RESULT

POD1 MME: Venlafaxine mean 42.3 ± 28.1 mg vs. Placebo 53.4 ± 31.2 mg

Mean difference: –11.09 mg (95% CI –23.24 to 1.05), p=0.073

Median: 37.5 [IQR 20–55] vs. 45.0 [IQR 30–70], p=0.158 (Wilcoxon)

Primary endpoint not met (p>0.05)

14. Secondary Outcome Analyses

14.1 Opioid Consumption: Acute Phase (POD 1–7)

Mixed-effects linear regression models were used to analyze opioid consumption across the entire acute phase (POD 1–7). The model included treatment group, time (as a categorical variable: POD1, POD2, POD7), and their interaction as fixed effects, with patient-specific random intercepts to account for repeated measures within subjects. The average marginal effect (AME) of treatment across all days was estimated as the primary secondary endpoint. Day-specific differences and group-by-time interactions were also examined.

Note on 3-Month Opioid Data: Three-month opioid consumption data were excluded from the mixed-effects model due to sparse distribution (only 3 patients remained on opioids at 3 months), which violated model assumptions. These data are reported descriptively.

Time Point	Venlafaxine Mean (95% CI)	Placebo Mean (95% CI)	Difference (95% CI)	P Value
POD1 (AME)	23.60 mg	32.15 mg	–8.55 (–20.95 to 3.85)	0.173
POD7 (predicted)	18.65 mg	33.67 mg	–15.03 (–27.55 to –2.50)	0.019*
Overall AME (POD 1–7)	—	—	–11.42 (–21.97 to –0.87)	0.034*

* Statistically significant (p<0.05). MME = morphine milligram equivalents; AME = average marginal effect.

14.2 Pain Score Analysis

Mixed-effects models were used for pain score analysis at postoperative time points (POD1, POD2, POD7, 3 months). Preoperative baseline pain scores were reported descriptively in the baseline characteristics table to confirm group comparability, but were NOT included in the mixed-effects model for postoperative pain due to group differences in baseline values that would have introduced confounding. The model included treatment, time (categorical), and treatment-by-time interaction as fixed effects, with patient-specific random intercepts.

Time Point	Venlafaxine Mean ± SD	Placebo Mean ± SD	Difference (95% CI)	P Value
POD2	3.8 ± 2.1	4.8 ± 2.3	–1.01 (–1.86 to –0.16)	0.020*
POD7	2.9 ± 2.0	3.9 ± 2.2	–0.99 (–1.83 to –0.15)	0.022*
3 Months	1.0 ± 1.6	1.5 ± 2.2	–0.61 (–1.49 to 0.27)	0.176
Overall AME	—	—	–0.71 (–1.34 to –0.08)	0.028*

* Statistically significant (p<0.05). NRS = numerical rating scale (0–10).

14.3 Patient Satisfaction

Patient satisfaction with pain control was analyzed using mixed-effects models with the same structure described above. The average marginal difference across all postoperative time points was estimated, along with time-specific comparisons. Results demonstrated significantly higher satisfaction in the venlafaxine group (average marginal difference +10.5 points, 95% CI 2.8 to 18.1, p=0.007), with particularly notable differences at POD7 (74.6 vs. 61.0, p=0.010) and 3 months (89.6 vs. 74.1, p=0.006).

14.4 Functional Outcomes

Distance walked on POD2 and knee range of motion were compared between groups using independent samples t-tests. No statistically significant differences were observed (distance walked: 145 ± 62 vs. 138 ± 58 feet, p=0.61).

14.5 Brief Pain Inventory (BPI)

BPI interference scores were compared using mixed-effects models at POD7 and 3 months. Results are reported as median [IQR] with Mann-Whitney U tests for descriptive comparisons.

14.6 Multiple Comparisons Adjustment

Holm-Bonferroni correction was applied for multiple secondary comparisons within each outcome domain. No secondary outcomes remained statistically significant after adjustment, consistent with the exploratory nature of secondary analyses. The mixed-effects model results for average marginal effects represent the pre-specified primary secondary analysis approach.

15. Missing Data Handling

Missing data were addressed using multiple imputation by chained equations (MICE), implemented in R using the 'mice' package (version 3.15.0). Twenty imputed datasets were generated, including treatment arm, all baseline measures (age, sex, BMI, baseline NRS), and relevant covariates as predictors. Estimates from each imputed dataset were combined using Rubin's rules. For outcomes with minimal missing data (<5%), complete case analysis was also performed as a sensitivity check.

16. Sensitivity Analyses

The following pre-specified sensitivity analyses were conducted:

- Wilcoxon rank-sum test on observed (non-imputed) opioid data to account for skewness
- Complete case analysis for primary outcome excluding imputed values
- Adjusted analysis using ANCOVA with age, sex, BMI, and baseline pain as covariates
- Subgroup analysis by ASA physical status (I–II vs. III)
- Subgroup analysis by sex

17. Safety Analyses

Adverse events were summarized descriptively by treatment group. Event rates were compared using Fisher's exact test or chi-square test as appropriate. Adverse events were coded by type and categorized as definitely, probably, possibly, or unrelated to study drug. The overall AE incidence rate and serious adverse event rate were compared between groups with risk differences and 95% confidence intervals reported.

18. Protocol Deviations from Original SAP

The following analytical decisions represent deviations from or amendments to the original protocol statistical analysis plan, made based on the observed data structure prior to unblinding and after consultation with the study statistician:

Deviation	Reason	Impact
3-month opioid data excluded from primary analysis	Sparse data: only 3 patients on opioids at 3 months; insufficient for model convergence	Data reported descriptively; does not affect acute phase findings
Baseline pain scores excluded from change-score calculation	Group difference in baseline pain (6.2 vs. 5.8, $p = 0.02$) created confounding when baseline was subtracted from outcome	Baseline retained as covariate in all models
Mixed-effects models used in place of RM-ANCOVA for repeated measures	Multiple post-operative assessments required longitudinal modeling approach	More appropriate for data structure; average marginal effect pre-s
Multiple imputation (MICE) implemented	To address missing follow-up data per model assumptions	Reduces bias from missing at random data; pre-specified in final

Appendix A: Schedule of Study Visits

Procedure	Visit 1 (Day of Surgery)	Follow-Up 1 (POD 1)	Follow-Up 2 (POD 7 Phone)	Follow-Up 3 (3 Months)
Informed Consent / HIPAA	X			
Demographics / Medical Hx	X			
Physical Examination	X	X (abbreviated)		
Vital Signs	X	X		
Randomization & Drug Dispensing	X			
NRS Pain Score	X	X	X	X
Total MME Opioid Consumption	X	X	X (descriptive)	
Brief Pain Inventory (BPI)	X	X	X	
KOOS, JR	X	X	X	
PROMIS-10 / VR-12	X			X
Patient Satisfaction (0–10)	X	X	X	
Distance Walked / ROM		X		
Study Drug Compliance Check	X	X		
Adverse Event Assessment	X	X	X	
Concomitant Medications Review	X	X	X	X

END OF DOCUMENT — Study Protocol and Statistical Analysis Plan | NCT05023278 | Version 4 | March 5, 2025