

Analgesic Effect of Perioperative Escitalopram in High Pain Catastrophizing Patients after Total Knee Arthroplasty

A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background: Sufficient pain treatment remains a challenge after total knee arthroplasty (TKA), especially in high pain catastrophizing patients. Serotonergic signaling may be involved in pain processing, but the effect of selective serotonin reuptake inhibitors on well-defined postoperative pain has not previously been investigated. The authors hypothesized that perioperative escitalopram would reduce pain after TKA in high pain catastrophizing patients.

Methods: A total of 120 pain catastrophizing patients (selected using the pain catastrophizing scale as preoperative screening tool) scheduled for TKA were randomized in a double-blind manner to either 10 mg escitalopram or placebo daily from preanesthesia to postoperative day 6 in addition to a standardized analgesic regime. The primary outcome was pain upon ambulation 24 h after surgery. Secondary outcomes were overall pain during well-defined mobilizations and at rest from 2 to 48 h and from days 2 to 6, morphine equivalents, anxiety, depression, and side effects.

Results: Pain upon ambulation (mean [95% CI]) 24 h after surgery in the escitalopram *versus* placebo group was 58 (53 to 64) *versus* 64 (58 to 69), the mean difference being -5 (-13 to 3), $P = 0.20$. Overall pain upon ambulation and at rest from days 2 to 6 was lower in the escitalopram *versus* placebo group, as was depression score at day 6 (all $P \leq 0.01$ in analyses uncorrected for multiple tests). Side effects were nonsignificant except for reduced tendency to sweat and prolonged sleep in the escitalopram group. No other between-group differences were observed.

Conclusions: Escitalopram did not reduce pain upon ambulation 24 h after TKA in high pain catastrophizing patients. Future studies on optimal timing, dose, and duration of selective serotonin reuptake inhibitor treatment might be warranted. (ANESTHESIOLOGY 2015; 122:884–94)

TOTAL knee arthroplasty (TKA) is a frequently performed surgical procedure undertaken mainly due to advanced osteoarthritis causing pain, functional impairment, and reduced quality of life.¹ Favorable long-term functional outcomes are reported with TKA,¹ but pain may be pronounced in the early and subacute postoperative phase,² and approximately 20% of patients may have persistent postsurgical pain.³

There is general agreement of a large interindividual variability in postoperative pain responses, and methods to preoperatively identify (predict) the high postoperative pain responders are suboptimal.^{4,5} However, pain coping strategies are putatively important, and it is well documented that high pain catastrophizing patients evaluated by the pain catastrophizing scale

What We Already Know about This Topic

- Individuals with high pain catastrophizing report more pain acutely after surgery, yet whether targeted therapy can reduce pain in this group has not been investigated

What This Article Tells Us That Is New

- In 120 patients with high pain catastrophizing scores before total knee arthroplasty, 1 week treatment with the serotonin selective reuptake inhibitor escitalopram did not differ from placebo in pain on ambulation 24 h after surgery

(PCS) have higher postoperative pain responses^{6–9} and thereby potentially benefit from targeted interventions.¹⁰

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Multimodal, nonopioid analgesic strategies have become the standard of care to reduce postoperative pain¹¹ and the surgical stress response and improve recovery on a procedure-specific basis.^{12,13} However, preoperative, targeted, patient-specific analgesia is so far rarely pursued, and there is still a need for optimization in TKA.¹⁴

Selective serotonin reuptake inhibitors (SSRIs) target serotonergic tonus in the central nervous system and are widely used for treating major depression and anxiety disorders. The serotonin reuptake site (serotonin transporter) is placed presynaptically on serotonergic nerve terminals and is the key regulator of synaptic serotonin levels in central nervous system.¹⁵ The primary action of SSRIs is to block and subsequently down-regulate serotonin transporters, which ostensibly increases serotonin levels.¹⁶ Presynaptic and postsynaptic markers of serotonergic signaling in brain regions relevant to affective cognition have been demonstrated to be coupled to tonic pain ratings in healthy volunteers.^{17,18} This suggests a role of serotonergic signaling in the modulation and/or the affective appreciation of pain. Notably, effects on basic subconscious processing of negative emotions, as evaluated by functional magnetic resonance imaging in an emotional face paradigm, are possibly established with short-term (7 days) SSRI treatment in healthy controls, at risk, or depressed patients,^{19–21} or even after single-dose treatment in healthy volunteers^{22,23} as suggested by some but not all studies.^{24,25} If these acute SSRI effects translate to a negative stimulus as pain, we propose that a reduced reactivity to pain and in the processing of postoperative pain by SSRI may be advantageous, particularly, in high pain catastrophizing patients, who might be more susceptible to negative emotionality when faced with frustration. However, to our knowledge, serotonin signaling and SSRI have not previously been investigated as a target/drug in the postoperative pain management of these patients.

Therefore, we performed a randomized, double-blind, placebo-controlled study in high pain catastrophizing patients undergoing TKA, using the PCS as a preoperative screening tool, to investigate the analgesic effect of oral escitalopram 10 mg daily for 7 days initiated on the day of surgery. We hypothesized that escitalopram would reduce postoperative pain relative to placebo, the primary outcome being pain upon ambulation (walking 5 m) 24 h after surgery.

Materials and Methods

Study Design and Patients

The study was approved by the Danish Medicines Agency, the regional ethics committee, and the Danish Data Protection Agency and was registered at EudraCT (2011-002034-38) and www.ClinicalTrials.gov (NCT01430520, July 9, 2011, by principal investigator T.H.L.). It was conducted

* Among these, monoamine oxidase inhibitors, dopamine agonists, triptanes, tryptophanes, linezolid, and herbal medicine containing pericon.

in accordance with the Good Clinical Practice principles and was monitored by the Danish Good Clinical Practice Monitoring Units. Oral and written informed consent was obtained from all patients before participation in this three-center, randomized, double-blind, parallel-arm, placebo-controlled, superiority study.

Patients aged 18 yr or older who were scheduled to undergo elective, unilateral, primary TKA were recruited and assessed for eligibility (by surgeons/project nurses) between September 9, 2011 and March 25, 2013 (last patient operated on April 16, 2013) at the departments of Orthopedic Surgery at Copenhagen University Hospital, Gentofte, Denmark; Aarhus University Hospital, Holstebro, Denmark; and South of Denmark University Hospital, Vejle, Denmark. Patients with a PCS score²⁶ of 21 or greater were eligible for inclusion. Exclusion criteria were nonethnic Danes, age more than 80 yr, treatment for anxiety or depression (including SSRI, last 6 months) and/or history of bipolar affective disorder or other psychiatric diseases, drugs causing a potential risk for serotonergic syndrome in combination with escitalopram (within 6 months),* use of systemic glucocorticoids (within 6 month), use of opioids of any kind (within 4 weeks), history of alcohol or drug abuse and of malignant disease, fertile women, history of epilepsy, treatment with anticoagulants, body mass index greater than 40 kg/m², diseases affecting central or peripheral nerve function, history of dementia or other cognitive dysfunction, gastrointestinal bleeding or hepatic or renal insufficiency, and allergies to escitalopram.

Randomization and Blinding

All randomization and blinding procedures and study drug preparations were handled by a state-registered and certificated pharmacy, The Capital Regional Pharmacy, not otherwise involved in the trial. A computer-generated 1:1 random allocation sequence (X and Z) was generated in blocks of 12 without the use of stratification variables, using Randomization.com.

The study drug, escitalopram 10 mg (Ciprallex; Lundbeck Pharma A/S, Taastrup, Denmark) and placebo, was prepared as small capsules, identical in appearance. The capsules were packed in 120 small boxes supplied with a unique number (1 to 120) corresponding to the randomization list. Each box contained seven capsules to be administered once daily for 7 days, starting preoperatively on the day of surgery. The study drug boxes were delivered to each of the three centers together with the case report forms with randomization numbers ready printed. At inclusion, after providing informed consent, patients were given a unique consecutive study number (1 to 120) corresponding to the same case report form and study drug box (randomization) number.

All trial participants, care providers, investigators, and outcome assessors (data collectors) were blinded to allocation. After termination of the study, the typing of data was carried out by double-control. Subsequently, the blinded randomization list (allocation to group X vs. Z) was dispatched

by The Capital Regional Pharmacy to the principal investigator enabling blinded “group X versus Z” analyses. This list was unblinded with respect to intervention type and released by The Capital Regional Pharmacy only after all statistical analyses had been carried out; thus, all analyses were carried out blinded.

Preoperative Screening and Selection of “High Pain Catastrophizing” Patients

Patients were preoperatively screened using the PCS.²⁶ The PCS is a 13-item survey, where patients rate their thoughts and feelings about pain on a 5-point scale ranging from “not at all” to “all the time.” Thus, the total score ranges from 0 to 52, 0 indicating no “pain catastrophizing” and 52 indicating worst “pain catastrophizing.”²⁶ The PCS questionnaire was mailed to all patients scheduled for TKA in the study period. It was completed by patients at home before a scheduled hospital visit for general clinical examination (and potential study inclusion), which preceded admission for TKA.

In a pilot study preceding this trial, 171 patients completed the PCS before TKA on participating centers. Median PCS score was found to be 15 (range 0 to 48), and 54 out of 171 (32 %) had a score 21 or greater. We decided to include the 30 to 40% of our TKA population with highest PCS score in the present trial. Thus, a PCS score of 21 or greater was chosen for patients to be arbitrary classified as high pain catastrophizing patients and placed them eligible for inclusion.

Outcome Measures and Assessments

The primary outcome was pain upon ambulation (walking 5 m with a walking aid) 24 h after surgery, as pain on movement exerts the most direct adverse impact on postsurgical functional recovery.²⁷

Secondary pain outcomes were overall pain upon ambulation (walking 5 m) from 4 to 48 h, upon passive 60° knee flexion from 2 to 48 h, upon passive 45° hip flexion with straight leg from 2 to 48 h, at rest (supine) from 2 to 48 h, and upon ambulation and at rest from days 2 to 6 after surgery. Pain was assessed preoperatively and at 2 (except upon walking), 4, 6, 24, 28, 32, and 48 h after surgery by a trained project nurse, and in the morning (when getting up) and evening (before going to bed) from days 2 to 6 in a pain diary questionnaire (starting on the evening on day 2). The 100-mm visual analog scale (VAS) was used (0 = no pain and 100 = worst pain imaginable; subjective rating by patients). At every time point throughout the study, a VAS score of 100 upon ambulation was registered if patients were unable to walk due to pain from the operated knee.

Other secondary outcomes were use of intravenous sufentanil in the postanesthesia care unit (PACU), use of oral morphine equivalents from 0 to 48 h and from days 2 to 6 after surgery, and anxiety and depression scores at day 6 (self-report questionnaires). Anxiety and depression symptoms were assessed preoperatively and at day 6 with the Hospital

Anxiety and Depression Scale.²⁸ The Hospital Anxiety and Depression Scale ranges from 0 to 21; 0 to 7 indicates no symptoms of anxiety/depression, 8 to 10 indicates possible symptoms of anxiety/depression, and 11 to 21 indicates severe symptoms of anxiety or depression.²⁸ Sufentanil and morphine equivalents from 0 to 48 h were registered by a project nurse and from days 2 to 6 morning and evening in the pain diary by patients.

The explanation for overall analyses of secondary pain outcomes (for the first 48 h and days 2 to 6) was to increase sensitivity by including all assessments for each outcome. The two time frames were analyzed separately according to the protocol due to the different ways of data recording—by investigator (project nurse) and in pain diary, respectively (in and out of hospital). The same two time frames were used for morphine equivalents also.

To score potential side effects to treatment, participants were interviewed in the morning on day 2 (face to face) and day 7 (telephone interview) by a trained project nurse. Side effects were scored according to a comprehensive Danish rating scale for psychotropic drugs, the UKU rating scale,²⁹ slightly modified to adhere to the perioperative patient setting. Each side effect item was rated on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Furthermore, global severity (impact of existing side effects on daily life) was rated by both patient and project nurse.²⁹

Finally, all undesirable reactions (judged to be caused by the study drug) and events (judged not to be caused by the study drug) were evaluated and registered by a senior physician. We used the following definitions: adverse reactions, serious adverse reactions, adverse events, serious adverse events, and suspected unexpected serious adverse reactions. In this context serious was defining an event/reaction causing death, prolonged hospitalization, readmission, disablement, or being life threatening.

Anesthesia, Surgery, Analgesia, and Study Drug Intervention According to Protocol

Included patients were scheduled for surgery as number 1 or 2 each day. Surgery was performed under lumbar spinal anesthesia with hyperbaric bupivacaine 0.5% and optional supplemental propofol (1 to 5 mg kg⁻¹ h⁻¹). TKA was performed using a standard medial parapatellar approach and a femoral tourniquet (100 mmHg above systolic blood pressure) and without application of surgical drains. Local infiltration analgesia was performed intraoperatively with 150 ml ropivacaine 0.2% with epinephrine (10 µg/ml).³⁰ By the end of surgery, an elastic bandage was applied.

A basic analgesic regime was used consisting of oral slow release acetaminophen and celecoxib. One-two hours preoperatively, acetaminophen 2 g and celecoxib 400 mg were administered; thereafter, acetaminophen 2 g and celecoxib 200 mg were administered regularly at 8:00 AM and 10:00 PM up to and including postoperative day 6. Rescue analgesics (administered on demand as required if VAS >50 mm at rest)

consisted of intravenous sufentanil 5 µg in the PACU and subsequently of oral morphine 10 mg at the ward. In the very few cases other opioids (ketobemidone, oxycodone, and intravenous morphine) were used due to resistant pain, these were converted into per oral morphine equivalents.

The study drug, oral escitalopram *versus* placebo, was administered daily for 7 days, starting preoperatively before the patient was taken to the operating theatre and continued until postoperative day 6. It was administered together with the basic analgesic regime preoperatively and thereafter each morning at 8:00 AM. An escitalopram dose of 10 mg/day was chosen analogous to the recommended initial dose in the treatment of major depression.^{16,31}

In hospital, the study drug and basic and rescue analgesics were administered by project nurses and were self-administered by patients after discharge. To secure compliance and completion of the pain diary, patients were regularly contacted by phone by project nurses after discharge.

Patients followed a well-defined, fast-track rehabilitation regime and were discharged to their homes according to routine functional discharge criteria.³²

Statistical Analysis

Estimated sample size for the primary outcome was calculated based on the results from a previous pain study in TKA with a similar perioperative approach as used in this study. Here, pain upon ambulation the first day after surgery was found to have a mean of 54 mm on the VAS with an SD of 25 mm.² A total sample of 120 patients (60 in each group) would allow the detection of a clinically relevant 30% difference in VAS in the escitalopram group compared with the placebo group, at a two-sided 5% significance level, with a power of 90%, and allow for 20% dropouts ($54 \text{ mm} \times 0.3 = 16.2 \text{ mm}$, minimal relevant difference).

The analytical framework was superiority. Continuous outcome variables were assessed for normality of distribution by inspection of Q-Q-plots and histograms of frequencies and with Kolmogorov–Smirnov test. The fit was accepted for the primary outcome; hence, between-group difference was evaluated by the unpaired *t* tests, and the data were presented as mean with 95% CIs and a mean difference with 95% CI between groups.

Each of the secondary pain outcomes with repeated measures was analyzed using a linear mixed-effects model for repeated measures. As fixed effects, we included group (intervention, escitalopram *vs.* placebo), time, and the interaction between these. Insignificant effects ($P \geq 0.05$) were removed one at a time from the model (starting with the interaction) until all included effects were significant at a 5% level. An unstructured covariance structure was used to model the correlation between the assessments across time. Each of the secondary pain outcomes was assessed for (multivariate) normality of distribution. The fit was accepted for pain upon ambulation from 4 to 48 h and pain upon passive knee flexion from 2 to 48 h, whereas the fit was doubtful

for pain upon passive hip flexion with straight leg from 2 to 48 h, pain at rest from 2 to 48 h, and pain upon ambulation and at rest from days 2 to 6 after surgery. A best fit was achieved with square root transformation (evaluated with Box-Cox transformation),³³ and this transformation was used in the analyses. The pain data are graphically presented as mean with 95% CI for every time point investigated. Furthermore, these data are presented as mean with 95% CI for each pain outcome and a mean difference with 95% CI between groups, together with an overall between-group difference (intervention effect) for each outcome.

For the other secondary outcomes (sufentanil in PACU, morphine equivalents 0 to 48 h and days 2 to 6 and Hospital Anxiety and Depression Scale anxiety score and Hospital Anxiety and Depression Scale depression score at day 6), normality of distribution was not accepted. Hence, between-group differences were evaluated by the nonparametric Mann–Whitney rank sum test, and the data were presented as median with interquartile range and range and a mean difference with 95% CI between groups.

To minimize the risk of random errors by repeated testing (mass significance), between-group differences for secondary outcomes evaluated on more time frames (pain from 2 to 48 h and from days 2 to 6; and morphine equivalents from 0 to 48 h and from days 2 to 6) were Bonferroni corrected, if significant, with a factor 2 for the two different time frames investigated.

For side effects, between-group differences in scores were evaluated by the Mann–Whitney rank sum test and frequencies by the chi-square test. These were presented without correction for multiple comparisons to reveal any tendencies.

Data analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC) and SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL). *P* value less than 0.05 was generally considered statistically significant, but for side effects, *P* value less than 0.1 were stressed also.

Results

A total of 1,110 patients were assessed for eligibility; of these, 120 patients were randomized and 114 were included in the modified intention-to-treat analysis of the primary outcome (fig. 1). Two patients were excluded because they withdrew their informed consent after randomization. For four patients, data were missing, as they were not mobilized at 24 h postoperatively. As to the secondary outcomes, data were rarely missing (in case left missing), and between 112 and 118 patients were included in the modified intention-to-treat analysis of these outcomes.

Baseline patient characteristics and preoperative data, including preoperative PCS score and pain, were similar in the two groups (table 1). Likewise, perioperative data were similar (table 2). Apart from presented in table 2, four patients (two in each group) received a saphenous nerve block due to intolerable pain (escitalopram group: 1 patient

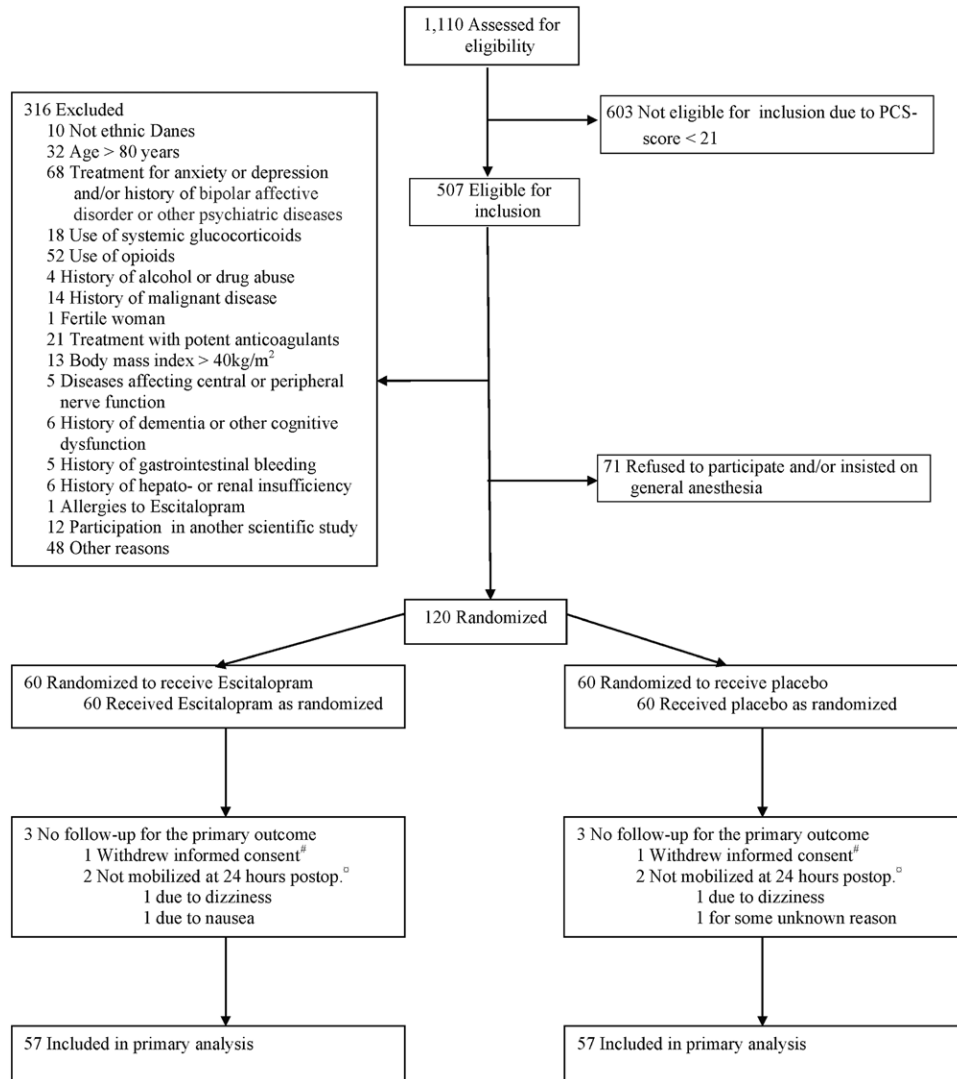


Fig. 1. Flow of patients through the phases of the trial. #No baseline or outcome data described for these patient. ◊No primary outcome data described for these patients (but baseline and secondary outcome data described). PCS = pain catastrophizing scale.

single shot after 28 h, 1 patient twice after 48 h; placebo group: 1 patient single shot in the PACU, 1 patient twice during the first 24 h).

No statistically significant between-group difference was observed for the primary outcome, pain upon ambulation (walking 5 m) 24 h after surgery (table 3 and fig. 2).

As to the secondary pain outcomes (also presented in table 3 and fig. 2), no between-group differences (intervention effects) were observed in overall pain upon ambulation from 4 to 48 h, overall pain upon passive knee flexion from 2 to 48 h, overall pain upon passive hip flexion with straight leg from 2 to 48 h and overall pain at rest from 2 to 48 h after surgery. Conversely, overall pain upon ambulation and overall pain at rest from day 2 to 6 after surgery were lower in the escitalopram *versus* placebo group (Bonferroni corrected with a factor 2 for the two different time frames investigated, first 48 h and days 2 to 6, but not otherwise corrected for multiple tests). Pain was changed over time for

all the secondary pain outcomes ($P < 0.001$), but no interactions between intervention and time were present ($P > 0.27$).

Other secondary outcomes are also presented in table 3. No between-group differences were observed in the use of sufentanil in PACU, morphine equivalents from 0 to 48 h and from days 2 to 6 after surgery, and in the anxiety score at day 6. However, depression score at day 6 was lower in the escitalopram *versus* placebo group (uncorrected for multiple tests).

Side effects are presented in table 4. The two groups reported largely similar side effect symptoms at days 2 and 7 postoperatively. However, at the uncorrected level, the escitalopram group reported reduced tendency to sweat at day 2 and slept longer than usual at night at day 7. When comparing total side effect scores across items and global severity scores by patient and project nurse, no differences were observed between groups. However, the frequency of patients reporting some nonspecific side effects, with a cutoff

Table 1. Baseline Patient Characteristics and Preoperative Data

Variables	Escitalopram (n = 59)	Placebo (n = 59)
Age, yr	68 (43–78)	67 (36–80)
Sex, male/female	29/30	31/28
BMI, kg/m ²	29.2 (4.3)	29.1 (3.9)
ASA physical status, I/II/III	15/40/4	15/39/5
Smoking, yes/no	8/51	12/47
PCS (0–52)	32 (21–52)	34 (21–52)
Pain, visual analog scale (0–100)		
Upon ambulation	43 (0–100)	49 (0–89)
Upon passive knee flexion	28 (0–81)	26 (0–84)
Upon passive hip flexion	25 (0–76)	14 (0–74)
At rest	16 (0–78)	15 (0–56)
Daily analgesic use, yes/no		
Acetaminophen	18/41	24/35
NSAID	18/41	17/42
HADS (0–21)		
Anxiety	4 (0–14)	3 (0–12)
Depression	1 (0–8)	1 (0–10)

Data are expressed as median (range), mean (SD), or count where appropriate. ASA = American Society of Anesthesiologists; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; NSAID = nonsteroidal antiinflammatory drugs; PCS = pain catastrophizing scale.

of UKU score 5 or greater, was higher in the escitalopram *versus* placebo group at day 7.

No suspected unexpected serious adverse reactions, serious adverse reactions, or adverse reactions (adverse reactions being judged to be caused by the study drug) were observed.

Discussion

In this trial of oral escitalopram 10 mg administered daily for 7 days initiated preoperatively on the day of surgery in high pain catastrophizing patients and continued for 6 days postoperatively, pain upon ambulation 24 h after TKA was not reduced relative to placebo. In an exploratory analysis of secondary outcomes, overall pain upon ambulation, upon passive hip and knee flexion, and at rest was not reduced at the first 48 h. However, at later time points, the escitalopram group experienced less overall pain upon ambulation and at rest from days 2 to 6 after surgery. No reduction in use of rescue opioid and anxiety symptom score was observed, but depressive symptom score was reduced.

The potential delayed onset of postoperative pain relief with escitalopram observed in this study suggests that the brain responses to treatment may take days to establish. Some studies have suggested that at least 2 weeks are required for escitalopram to be effective in anxiety disorders,³⁴ whereas other studies suggest that short-term SSRI treatment (7 days) in healthy controls, at risk, or depressed patients^{19–21} or even a single dose in healthy volunteers^{22,23} may have positive effects on processing of negative emotions, that is, dampens the reactivity to negative threat-related and fear-related stimuli as probed with an emotional face paradigm using functional magnetic resonance imaging.

Table 2. Perioperative Data and Compliance

Variables	Escitalopram	Placebo
Hospital, Gentofte/Holstebro/Vejle	15/20/24	19/24/16
Spinal anesthesia*	57	56
General anesthesia†	2	3
Use of local infiltration analgesia	58	58
Duration of femoral tourniquet, min	62 (5–127)	62 (10–115)
Duration of surgery, min	66 (50–146)	65 (23–126)
Bleeding intraoperatively, ml	50 (0–450)	50 (0–400)
Use of compression bandage	59	59
PACU stay, min	96 (30–340)	100 (30–240)
LOS, postoperative nights	2 (2–6)	2 (2–5)
Study drug compliance‡		
Day 0 (preoperatively)	59	59
Day 1	59	59
Day 2	59	59
Day 3	58§	59
Day 4	58§	59
Day 5	58§	59
Day 6	58§	59
Basic analgesia compliance		
Day 0 (preoperatively)	58#	59
Day 0 (evening)	59	58**
Day 1 (morning)	59	58**
Day 1 (evening)	59	58
Day 2 (morning)	59	58
Day 2 (evening)	59	58
Day 3 (morning)	58	57
Day 3 (evening)	59	56
Day 4 (morning)	59	58
Day 4 (evening)	56	57
Day 5 (morning)	58	58
Day 5 (evening)	59	58
Day 6 (morning)	59	58
Day 6 (evening)	59	58

Data are expressed as count or median (range) where appropriate.

* With bupivacaine 7.5–15 mg (±sedation with propofol); † Total intravenous or gas anesthesia due to insufficiency of the spinal anesthesia; ‡ Escitalopram or placebo; § In one patient, study medication was stopped by the investigator due to increased azotemia; || Acetaminophen and celecoxib; # One patient received ibuprofen 400 mg (instead of celecoxib) and gabapentin 600 mg; ** One patient received todolac 200 mg (instead of celecoxib) and gabapentin 600 mg.

LOS = length of stay; PACU = postanesthesia care unit.

Notably, recent molecular neuroimaging studies point toward opposing effects between acute and prolonged treatment (weeks).^{35–37} Although two studies point toward a reduction in central serotonergic tone with acute SSRI treatment in humans,^{36,37} another recent study suggests that when administered for 3 weeks in clinical dosages, SSRI elevated central serotonin levels relative to placebo.³⁵ These opposing brain responses to acute *versus* prolonged SSRI treatment may relate to the time it takes for autoinhibitory serotonin 1A receptors to desensitize.³¹

There is a large body of evidence from animal studies that serotonin signaling is involved in pain processing, but human data are limited. However, presynaptic and postsynaptic markers of serotonergic signaling in brain regions relevant to affective cognition have been demonstrated to

Table 3. Postoperative Pain and Other Outcome Data

Outcomes	Escitalopram	Placebo	Mean Difference (95% CI)	P Value
Primary outcome	(n = 57)	(n = 57)		
Pain upon ambulation, 24 h	58 (53–64)	64 (58–69)	–5 (–13 to 3)	0.20
Secondary pain outcomes	(n = 56–59)	(n = 56–59)		
Ambulation, 4–48 h	50 (46–55)	53 (49–58)	–3 (–9 to 3)	0.37
Passive knee flexion, 2–48 h	49 (45–53)	50 (46–54)	–1 (–6 to 5)	0.73
Passive hip flexion, 2–48 h	35 (31–39)	31 (27–35)	4 (–2 to 10)	0.18
At rest, 2–48 h	27 (24–31)	29 (26–32)	–2 (–6 to 3)	0.25
Ambulation, days 2–6	28 (24–33)	35 (31–39)	–7 (–13 to –1)	0.02*
At rest, days 2–6	18 (15–22)	23 (20–27)	–5 (–9 to –1)	0.02*
Other secondary outcomes	(n = 56–59)	(n = 56–59)		
Sufentanil in PACU, µg	0 (0–5) (0–110)	0 (0–5) (0–45)	2 (–4 to 7)	0.91
Morphine equivalents, 0–48 h, mg	100 (60–174) (10–274)	112 (80–157) (30–439)	–15 (–40 to 10)	0.27
Morphine equivalents, days 2–6, mg	80 (30–200) (0–810)	130 (63–190) (0–605)	–11 (–63 to 40)	0.20
HADS, anxiety, day 6	2 (1–4) (0–11)	4 (1–6) (0–17)	–1.0 (–2.2 to 0.2)	0.14
HADS, depression, day 6	1 (0–2) (0–11)	2 (1–5) (0–12)	–1.1 (–2.1 to –0.2)	0.008†

Primary and secondary pain outcome data are expressed as mean with 95% CI, along with mean difference with 95% CI between groups. For the primary outcome, between-group difference was evaluated by the unpaired *t* tests; for each of the secondary pain outcomes with repeated measures, between-group difference was evaluated by linear mixed-effects model for repeated measures. Other secondary outcome data are expressed as median with interquartile range and range, along with mean difference with 95% CI between groups. For each of the other secondary outcomes, between-group difference was evaluated by the Mann–Whitney rank sum test.

* Bonferroni corrected with a factor 2 for the two different time frames investigated (first 48 h and days 2–6) but not otherwise corrected for multiple tests;

† Uncorrected for multiple tests.

HADS = Hospital Anxiety and Depression Scale; PACU = postanesthesia care unit.

be coupled to tonic pain ratings in healthy volunteers,^{17,18} suggesting a role of serotonergic signaling in the modulation and/or the affective appreciation of pain. Apart from central and cognitive elements, serotonin may exert both pronociceptive and antinociceptive actions at the level of the spinal cord dorsal horn, mediated through descending pathways in the dorsolateral funiculus originating in the rostroventromedial medulla.³⁸

In a recent review evaluating trials of antidepressants for acute and chronic postsurgical pain, it was concluded that the evidence to support clinical use is currently insufficient.³⁹ However, the positive trials suggest a therapeutic potential, calling for future higher-quality trials.³⁹ Randomized clinical trials on the effect of SSRI in specific are severely limited; to our knowledge, only one study has been carried out in “major” surgery. Chocron *et al.*⁴⁰ investigated the effect of daily escitalopram (10 mg) from 2 to 3 weeks before to 6 month after coronary artery bypass grafting. No effect on a combined primary endpoint including mortality and morbidity events was observed, but mental health and quality of life aspects were improved (secondary endpoints).⁴⁰ Also, pain score was better in a preoperative depressed subgroup.⁴⁰ However, pain was evaluated with the SF-36 1, 3, and 6 month after surgery. Thus, our study is the first approach to investigate the potential effect of SSRI on well-defined, acute postoperative pain and the first intervention study on postoperative pain in a preoperative selected high-pain responder population, that is, high pain catastrophizing patients. Despite, the primary efficacy analysis was negative, and our study may have clinical interest with the novel approach targeting an intervention to a psychosocial risk factor for acute postoperative pain.

The positive exploratory analyses of secondary pain outcomes naturally preclude any conclusions but may serve as a basis for designing and conducting of future clinical trials.

SSRIs have well-documented antidepressive- and anxiety-relieving properties. However, in this study, patients preoperatively treated for anxiety or depression were excluded not to compromise the strictly standardized analgesic regime (acetaminophen, celecoxib, and escitalopram/placebo). This explains why median depressive symptom score and anxiety symptom score were low in both the escitalopram and the placebo group (categorized, 0 to 7 indicates no anxiety/depression)²⁸ with only depression but not anxiety reaching a level of significance between groups at day 7. As regards anxiety, an inherent risk of a type 2 error obviously exists.

Side effects to escitalopram treatment when used in the traditional setting for treatment of major depression and anxiety disorders primarily include drowsiness, dizziness, insomnia, nausea, loss of appetite, diarrhea, weight changes, and decreased libido. With our 7 days treatment at low clinical dosages, we did not detect any such specific side effects. Although no apparent side effects were observed, other studies have suggested an increased risk of perioperative bleeding and other postoperative morbidities by SSRIs,^{41–43} calling for more procedure-specific studies.

Escitalopram in our study appeared to have a combined effect by lowering pain scores (from days 2 to 6) and prolonging sleep (at day 7). Obviously, the finding of prolonged sleep should be interpreted with caution, as the median score of “sleeping longer than usual” was 0 in both groups, and the multiple comparisons of side effects were reported at an uncorrected level to reveal any tendency, with a risk of

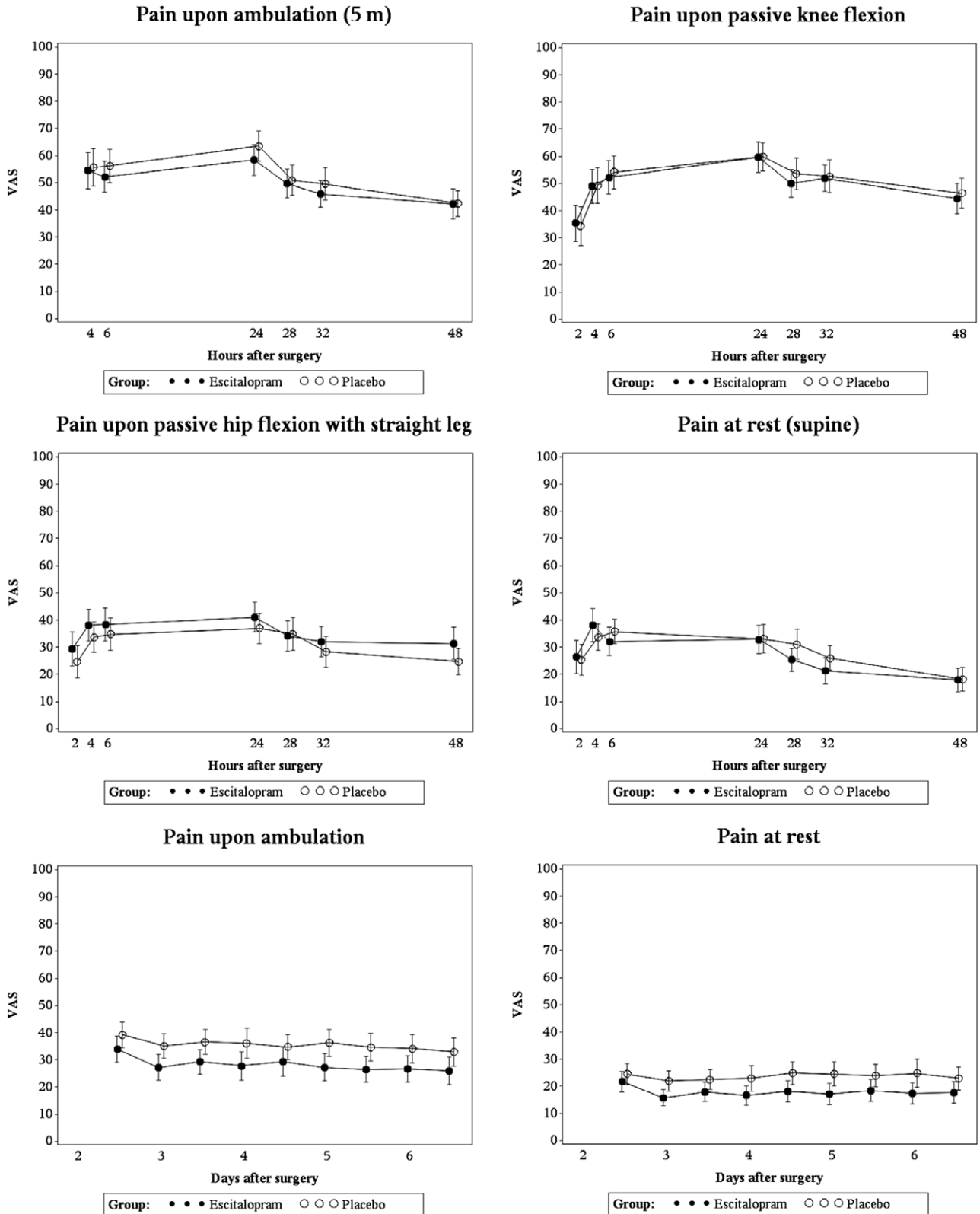


Fig. 2. Postoperative pain. The graphs show mean pain with 95% CI for every time point for the escitalopram and the placebo groups. The day of surgery corresponds to day 0. Thus, 48h after surgery corresponds to the morning on day 2. Thereafter, pain was assessed in the evening and in the morning until day 6. Morning recordings are appearing right above a given day, evening recordings between that day and the next (day 2½ represents the evening of day 2, etc.). VAS = visual analog scale.

Table 4. Side Effects

Side Effect	Day 2			Day 7		
	Escitalopram (n = 59)	Placebo (n = 59)	P Value	Escitalopram (n = 59)	Placebo (n = 59)	P Value
	Median Score (Sum Score)	Median Score (Sum Score)		Median Score (Sum Score)	Median Score (Sum Score)	
1.2 Difficulties concentrating	0 (41)	1 (55)	NS (0.08)*	0.5 (43)	1 (34)	NS (0.63)
1.3 Exhaustion	0 (27)	0 (33)	NS (0.18)	0 (16)	0 (9)	NS (0.28)
1.4 Memory problems	0 (3)	0 (5)	NS (0.74)	0 (2)	0 (4)	NS (0.87)
1.5 Depressed mood	0 (3)	0 (8)	NS (0.25)	0 (5)	0 (6)	NS (0.74)
1.6 Tension	0 (10)	0 (6)	NS (0.38)	0 (10)	0 (11)	NS (0.77)
1.7 Sleeping longer than usual	0 (15)	0 (7)	NS (0.35)	0 (16)	0 (5)	0.02**
1.8 Sleeping less than usual	0 (14)	0 (13)	NS (0.81)	0 (8)	0 (16)	NS (0.13)
1.9 Vivid dreams	0 (5)	0 (4)	NS (0.99)	0 (6)	0 (9)	NS (0.39)
1.10 Emotional indifference	0 (3)	0 (10)	NS (0.18)	0 (3)	0 (6)	NS (0.43)
2.5 Tremor	0 (5)	0 (0)	NS (0.12)	0 (6)	0 (2)	NS (0.35)
2.8 Paresthesia	0 (1)	0 (4)	NS (0.55)	0 (1)	0 (3)	NS (0.62)
3.2 Dryness of mouth	1 (61)	1 (59)	NS (0.97)	0 (32)	1 (32)	NS (0.75)
3.4 Nausea	0 (26)	0 (29)	NS (0.69)	0 (7)	0 (9)	NS (0.71)
3.5 Diarrhea or obstipation	0 (10)	0 (15)	NS (0.32)	0 (12)	0 (5)	NS (0.35)
3.11 Sweating	0 (4)	0 (13)	0.03**	0 (13)	0 (16)	NS (0.54)
4.17 Headache	0 (0)	0 (3)	NS (0.24)	0 (1)	0 (5)	NS (0.21)
Total score	3 (228)	4 (264)	NS (0.19)	2 (180)	3 (175)	NS (0.93)
Global severity (patient)	0 (24)	0 (27)	NS (0.79)	0 (23)	0 (27)	NS (0.50)
Global severity (project nurse)	0 (19)	0 (23)	NS (0.54)	0 (17)	0 (16)	NS (0.93)
Frequency of patients reporting some side effects (score ≥ 5)	18 (30.5%)	15 (25.4%)	NS (0.54)	26 (44.0%)	12 (20.3%)	0.006***

Each side effect item was rated on a 4-point numeric rating scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Between-group differences in scores were evaluated by the Mann-Whitney rank sum test and frequencies by the chi-square test. *P* values are given without correction for multiple comparisons to reveal any tendencies.

P* < 0.10, *P* < 0.05, ****P* < 0.01.

NS = not statistically significant.

a type 1 error. However, it is an interesting finding because improved sleep may have antinociceptive effects,⁴⁴ and oppositely, sleep deprivation may lead to hyperalgesia, pain, and depression.^{45,46} Furthermore, pain may obviously contribute to impaired sleep.⁴⁷ In this context, the sleep architecture after major joint arthroplasty is severely disturbed,^{48,49} which is associated with pain and decreased motor activity.⁴⁸

The standardized perioperative procedures, including analgesia, the few protocol violations (table 2), and the low frequency of missing data might have strengthened our results by increasing internal validity. However, the study population was highly selected, which was intended not to compromise our intervention and not to increase the risk of side effects. However, obviously, the exclusion and refusal number limits the external validity in the cohort intended to be studied, and the results might not be extrapolated to a broader surgical population with no pain catastrophizing. Furthermore, exploratory analyses were conducted for several predefined secondary outcomes. Thus, the risk of type 1 errors should be taken into account when interpreting the findings. We acknowledge that a stricter correction for multiple tests could have been used. However, when having several correlated outcomes as in our case, it is well known that a Bonferroni correction taking all tests

into account is highly conservative.^{50,51} Consequently, we adjusted for the two overall tests conducted for each outcome. Finally, the clinical relevance of the exploratory finding of a small reduction in pain after 48 h, from days 2 to 6 postoperatively, might be questionable. However, these preliminary findings raise the intriguing question that if initiating the SSRI intervention earlier, it may exert an effect immediately after surgery, where pain is more pronounced. Consequently, we consider future postoperative pain studies with earlier initiation of treatment targeting serotonergic tonus to be relevant. If positive, our data also suggest future studies to evaluate the optimal (prolonged) duration of SSRI treatment because moderate to severe pain during mobilization, having impact on functional recovery,²⁷ has been reported to be a significant problem even 30 days after TKA.² Also, if positive, the target patient population should be defined with potential extrapolation to patients with no pain catastrophizing.

In summary, pain upon ambulation 24 h after TKA in preoperative high pain catastrophizing patients was not reduced by escitalopram for 7 days initiated preoperatively on the day of surgery relative to placebo. However, the results of exploratory secondary analyses of pain upon ambulation and at rest from day 2 to 6 call for future studies on effect, optimal

timing of initiation, dose, and duration of SSRI treatment, and detailed assessment on potential side effects.

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Competing Interests

The authors declare no competing interests.

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