SYSTEMATIC REVIEW

Selective Serotonin Reuptake Inhibitor Use and Total Joint Arthroplasty Outcomes: A Systematic Review and Meta-Analysis with Emphasis on Transfusion Risk

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Abstract

Objectives: This systematic review and meta-analysis aimed to evaluate the association between selective serotonin reuptake inhibitor (SSRI) use and complications and outcomes after total joint arthroplasty (TJA).

Methods: We systematically searched four databases for studies comparing outcomes between SSRI users and non-users undergoing TJA. Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies and the ROB-2 tool for randomized controlled trials (RCTs). Meta-analyses were performed using a random-effects model, with subgroup and sensitivity analyses used to explore between-study heterogeneity.

Results: Eight reports involving 162,329 study-level patient observations were included. SSRI use was associated with a significantly higher risk of transfusion (OR: 1.50, 95% CI: 1.22–1.85, $p < 0.0001$). Narrative findings also suggested longer hospital stays and higher readmission rates among SSRI users. However, the evidence was insufficient to draw firm conclusions regarding functional outcomes, quality of life, pain, periprosthetic joint infection (PJI), or revision surgery.

Conclusion: Clinicians should balance the quantitatively demonstrated increase in transfusion risk among SSRI users against the potential mental health consequences of abrupt SSRI discontinuation, including withdrawal symptoms or relapse of depression. The evidence remains insufficient to draw firm conclusions regarding functional outcomes, quality of life, pain, PJI, or revision surgery.

Level of evidence: III

Keywords: Depression, Length of stay, SSRI, Systematic review and meta-analysis, Total hip arthroplasty, Total knee arthroplasty, Transfusion

Introduction

The number of total joint arthroplasty (TJA) procedures continues to increase.[1] TJA is among the most effective treatments for relieving pain and improving clinical outcomes in patients with joint disease[2]; however, postoperative complications and dissatisfaction remain important concerns.[3,4] Patient comorbidities and mental health status may influence both satisfaction and complication rates.[5]

Depression is increasingly prevalent among patients undergoing TJA for osteoarthritis or rheumatoid arthritis, partly because the chronic pain associated with these conditions places patients at greater risk of mood disorders.[6,7,8] Approximately 25% of patients undergoing TJA are estimated to have major depressive disorder or anxiety, a prevalence that is higher than that observed in the general population.[9,10] Depression may adversely affect TJA outcomes by increasing complication rates, readmissions, and mortality and by increasing the use of healthcare resources.[11-13]

Accordingly, effective recognition and treatment of

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depression may represent an important strategy for improving outcomes and reducing complications after TJA. Pharmacologic therapy is one of the principal approaches to managing depression in this clinical setting.[14] A previous meta-analysis found that duloxetine was associated with less postoperative pain and better functional outcomes in patients undergoing TJA.[15]

Selective serotonin reuptake inhibitors (SSRIs) are among the medications most widely prescribed for patients with depression.[16] These agents increase serotonin availability through blockade of serotonin transporters.[17] The resulting increase in serotonin may reduce pain perception[18]; however, it may also increase the risk of bleeding.[19] Previous studies have reported that patients taking SSRIs had greater perioperative transfusion requirements.[20,21] Findings regarding functional outcomes and pain after TJA have been less consistent, with studies reporting both significant and non-significant effects of SSRI use.[22,23]

A systematic synthesis of the available evidence is therefore needed to clarify the effects of SSRIs on outcomes and complications after TJA procedures. To our knowledge, no previous systematic review has specifically examined this clinical question. Accordingly, this systematic review and meta-analysis aimed to compile and synthesize evidence regarding SSRI use in patients undergoing TJA and to evaluate its association with a broad range of postoperative outcomes and complications.

Materials and Methods

This systematic review and meta-analysis was conducted in accordance with Cochrane Collaboration guidance and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO) on 16 January 2025 under registration number CRD42025632939. No major deviations from the registered protocol occurred. Minor post-hoc decisions were made, and no unregistered outcome analyses were conducted.

Search Strategy and Screening

Four electronic databases (Scopus, PubMed, Web of Science, and Embase) were searched from inception through May 2026. The search strategy was developed collaboratively by two authors (A.M.A. and F.S.). To maximize sensitivity and comprehensiveness, the search combined controlled vocabulary (MeSH/Emtree) with free-text terms in the title and abstract fields for two concepts: (1) TJA (including 'arthroplasty, replacement, knee', 'arthroplasty, replacement, hip', OR 'total joint arthroplasty'); and (2) SSRIs (including drug class names and individual drug names). The complete search strategy is provided in [Supplementary file 1]. Records were imported into Rayyan (https://www.rayyan.ai).[24] After duplicate removal, two reviewers (A.M.A. and F.S.) independently screened the records using the predefined eligibility criteria. Disagreements were resolved through consultation with a third reviewer (A.M.A.).

Eligibility Criteria and Study Selection

This review was conducted using the PICOS framework:

Population (P): Patients undergoing primary or revision TJA, including TKA and THA, with no restrictions based on age, sex, or geographic location.

Exposure/Intervention (I): Preoperative or perioperative use of any SSRI, including but not limited to escitalopram, citalopram, fluoxetine, sertraline, paroxetine, and fluvoxamine. No restrictions were imposed on dose, duration, or indication for SSRI prescription.

Comparison (C): Patients undergoing TJA who did not receive SSRI therapy during the perioperative period. Non-SSRI users could include patients receiving no antidepressant therapy or antidepressants from other classes, provided that these groups were reported separately.

Outcomes (O): The primary outcome was the requirement for perioperative blood transfusion. Secondary outcomes included length of hospital stay, readmission, revision surgery, PJI, functional outcomes (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] and EuroQol 5-Dimension 5-Level questionnaire [EQ-5D-5L]), quality of life, and postoperative pain scores. Outcomes were defined as reported in the included studies.

Study design (S): RCTs and prospective or retrospective cohort studies comparing SSRI users with non-users were eligible. Case reports, case series, conference abstracts, expert opinions, and review articles were excluded.

Only English-language studies were eligible. No restriction was applied based on publication year. Gray literature (e.g., preprints, theses, and institutional repositories) was not searched because of concerns regarding peer-review status and data verifiability.

Data Extraction and Quality Assessment

The full texts of all eligible studies were reviewed, and data were extracted into a standardized Excel spreadsheet. Extracted variables included general study information, participant demographic characteristics, postoperative outcomes and complications, and relevant comorbidities. A second author (F.S.) independently rechecked the extracted data to improve accuracy and reduce extraction errors. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies.[25] The NOS contains eight items organized across three domains: selection, comparability, and outcome assessment. For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (ROB-2) tool[26] was used to evaluate methodological quality. This tool assesses five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result.

Statistical Analysis

For each outcome, pooled odds ratios (ORs) were calculated using a random-effects model based on the DerSimonian-Laird method. When a study reported both crude and adjusted effect estimates, the adjusted estimate, accounting for factors such as age, sex, and comorbidities, was preferentially used in the primary meta-analysis to reduce confounding. Crude estimates were used only when adjusted estimates were unavailable. For the primary outcome of transfusion, studies reporting mixed TJA populations in

which THA and TKA were combined were included in the primary analysis. When a sufficient number of studies reported results separately for THA, TKA, or combined THA/TKA populations, subgroup analyses were performed to compare the corresponding effect sizes. Differences between subgroups were evaluated using a chi-squared test. Heterogeneity was quantified using the I^2 statistic and interpreted according to Cochrane Handbook guidance as follows: 0-40%, potentially unimportant; 30-60%, moderate; 50-90%, substantial; and 75-100%, considerable. For outcomes with I^2 > 30%, prespecified sensitivity analyses included (1) a leave-one-out analysis to identify influential studies and (2) a separate analysis excluding a single outlier when removal of that study reduced I^2 to <30%. Publication bias was assessed using Egger's linear regression test. A P value <0.05 was considered statistically significant. All statistical analyses were performed in R version 4.3.2 using the meta package.

Results

Study Selection

After duplicate records had been removed, the initial literature search identified 183 unique records. Of these, 164 were excluded during title and abstract screening, leaving 19 articles for full-text assessment. Eleven of the 19 full-text articles were subsequently excluded for the following reasons: wrong population (no separate SSRI group or no TJA; n=6), wrong exposure (SSRI use not reported separately from other antidepressants; n=3), incomplete outcome data (n=1), and review article (n=1). A detailed list of the excluded full-text studies and the corresponding reasons for exclusion is provided in [Supplementary file S2]. After full-text review, eight studies[20-23, 27-30] met the eligibility criteria for inclusion in the systematic review, and six of these studies provided data suitable for meta-analysis. Figure 1 presents the complete study selection and screening process [Figure 1].

Baseline Characteristics

The eight included reports collectively comprised 162,329 study-level observations of patients undergoing TJA. Based on the demographic data available across the included studies, the mean age of the study population was 67.27±10.64 years, and 66.7% of participants were female. Of the total population, 49,384 patients (30.4%) had a history of SSRI use before TJA. In terms of procedure type, 41,535 patients (25.6%) underwent TKA, whereas 120,794 (74.4%) underwent THA. Although the exact minimum and maximum ages were not consistently reported, the mean age across studies was approximately 67 years, which is consistent with an older arthroplasty population. Follow-up duration ranged from seven days to an average of six years. Regarding study design, one study was a randomized clinical trial, [23] two were prospective cohort studies, [27,28] four were retrospective cohort studies [20,22,29,30] and one was a case-control study . [21] The included studies were conducted in the USA, Denmark, Canada, and China. Table 1 provides a comprehensive summary of the characteristics of the included studies [Table 1].

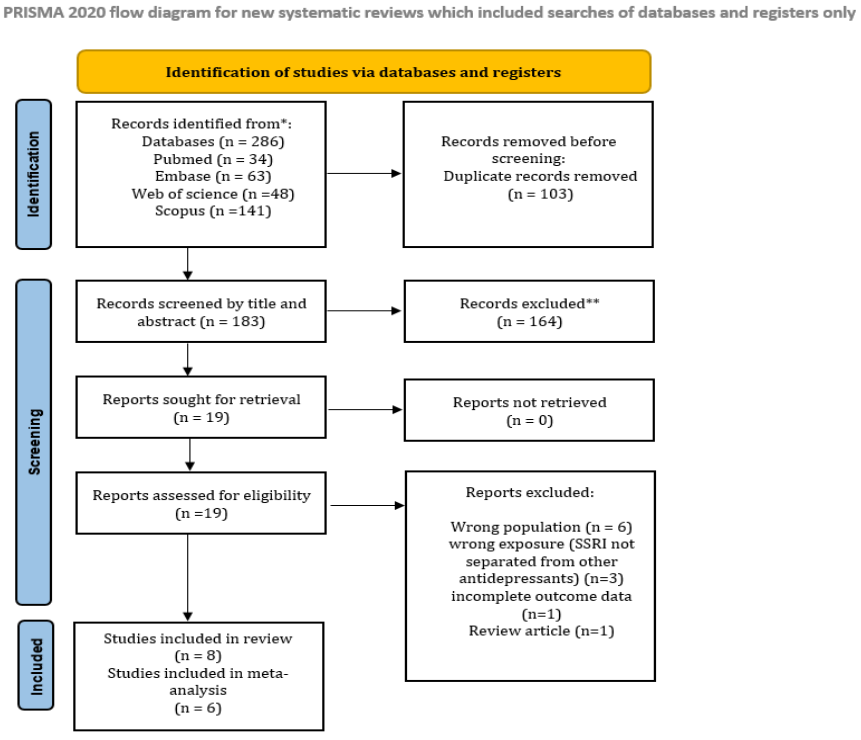

Figure 1. PRISMA flow diagram of the study selection process

Table 1. Baseline characteristics of included studies

Author (Year)	Country	Study type	Female (%)	Age (year)	Follow-up period	Type of Surgery	THA	TKA	Population size	SSRI group	SSRI duration	No SSRI group
Hoveidaei (2024)	USA	Case-control	63,091 (75.2%)	67.3 (mean)	10 days	Hip arthroplasty (pinning, ORIF, hemiarthroplasty, THA) - Only THA included	83,898	0	83,898	40,485	within one month before their surgery	43,413
Yao (2018)	USA	Retrospective cohort	10,975 (65%)	66 (mean)	6 years (mean)	Primary and revision THAs and TKAs	9,666	10,446	20,112	2,186	during the period of time between hospital admission and discharge	17,926
Belay (2019)	USA	Retrospective cohort	5,839 (58%)	SSRI: 65 No-SSRI: 66.1 (median)	during hospitalization	Primary THA or TKA	4,485	5,584	10,069	1,900	at the time of surgery	8,169
Murray (2021)	Canada	Retrospective cohort	16,481 (58.1%)	66.26 (mean)	1 year	Primary THA or TKA	10,953	17,433	28,386	2,303	regular SSRI use preoperatively	26,083
Gylvin (2017)	Denmark	Prospective cohort	4,815 (57.3%)	67.62 (mean)	during hospitalization	primary unilateral THA or TKA	4,423	3,979	8,402	569	6 months before and 3 months after surgery	7,833
Jørgensen (2015)	Denmark	Prospective cohort	4,815 (57.3%)	SSRI: 68 No-SSRI: 69 (median)	90 days	THA or TKA	4,423	3,979	8,402	1,001	6 months before and 3 months after surgery	7,401
Lunn (2015)	Denmark	Randomized clinical trial	58 (50.9%)	SSRI: 68 No-SSRI: 67 (median)	7 days	elective, unilateral, primary TKA	0	114	114	57	from pre-anesthesia to postoperative day 6	57

Table 1. Continued

Lethbridge(2025)	Canada	Retrospective cohort	71.2%	80.1 (mean)	189 days	Hip fracture arthroplasty	2946	0	2946	883	Filled SSRI prescription in the 180-day period prior to surgery	2063

SSRI = Selective serotonin reuptake inhibitor; THA = total hip arthroplasty; TKA = total knee arthroplasty; ORIF = open reduction and internal fixation; PJI = periprosthetic joint infection

Quality Assessment

Newcastle-Ottawa Scale scores for cohort studies were reported across three domains: Selection (0–4 stars), Comparability (0–2 stars), and Outcome (0–3 stars). All cohort studies scored ≥7 out of 9, indicating high methodological quality [Table 2]. For case-control studies, the Newcastle-Ottawa Scale domains were Selection (0–4 stars), Comparability (0–2 stars), and Exposure (0–3 stars). The included case-control study[29] scored 8 out of 9 and was considered high quality [Table 3]. The RCT conducted by Lunn et al. showed a low risk of bias across all ROB-2 domains [Table 4].[23]

Table 2. Quality assessment of cohort studies included in this systematic review and meta-analysis

	Selection				Comparability	Outcome			Overall
	Q1	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*	*Q7*	*Q8*	
Yao, 2018	*	*	*	-	**	*	*	*	8
Belay, 2019	*	*	*	*	**	*	*	*	9
Bourget-Murray, 2022	*	*	*	*	**	*	-	*	8
Gylvin, 2017	*	*	*	*	*	*	*	*	8
C. Jørgensen, 2015	*	*	*	*	*	*	*	*	8
Lethbridge, 2025	*	*	*	*	**	*	*	*	9

Each row represents the study, and each column corresponds to a bias category and questions:
Selection (Maximum: 4 stars)
Q1. Representativeness of the exposed cohort (e.g., truly representative of average in community)
Q2. Selection of the non-exposed cohort (e.g., drawn from the same community as the exposed cohort)
Q3. Ascertainment of exposure (e.g., secure record or structured interview)
Q4. Demonstration that outcome of interest was not present at start of study
Comparability (Maximum: 2 stars)
Q5. Comparability of cohorts based on design or analysis (e.g., study controls for SES/age/race/gender, etc.)
Outcome (Maximum: 3 stars)
Q6. Assessment of outcome (e.g., independent blind assessment or record linkage)
Q7. Was follow-up long enough for outcomes to occur?
Q8. Adequacy of follow-up of cohorts (e.g., complete follow-up or less than 20% lost)

Table 3. Quality assessment of case-control study included in this systematic review and meta-analysis

	Selection				Comparability	Exposure			Overall
	Q1	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*	*Q7*	*Q8*	
Hoveidaei, 2024	*	*	*	*	**	*	*	-	8

Each row represents the study, and each column corresponds to a bias category and questions:
Selection (Maximum: 4 stars)
Q1. Is the case definition adequate? (e.g., with independent validation)
Q2. Representativeness of the cases (e.g., consecutive or obviously representative series)
Q3. Selection of Controls (e.g., community controls)
Q4. Definition of Controls (e.g., no history of the target disease)
Comparability (Maximum: 2 stars)
Q5. Comparability of cases and controls based on design or analysis (e.g., study controls for the most important factor/additional factors)
Exposure (Maximum: 3 stars)
Q6. Ascertainment of exposure (e.g., secure record or structured interview)
Q7. Same method of ascertainment for cases and controls
Q8. Non-response rate (e.g., same rate for both groups)

Table 4. Risk of bias assessment for included randomized controlled trial using the Cochrane Risk of Bias 2.0 tool.

	D1	D2	D3	D5	D5	Overall
Lunn, 2015						

Each row represents a study, and each column corresponds to a bias domain:
D1 – Bias arising from the randomization process; D2 – Bias due to deviations from intended interventions;D3 – Bias due to missing outcome data;D4 – Bias in measurement of the outcome;D5 – Bias in the selection of the reported result.
Judgements are categorized as low risk (green) or some concerns (yellow). The final column indicates the overall risk of bias per study.

Association Between SSRI Use and Outcomes Following TJA

Transfusion

The meta-analysis included 133,701 TJA cases and showed that patients with a history of SSRI use had significantly higher transfusion requirements than non-users (OR: 1.50, 95%CI: 1.22-1.85, P-value: < 0.0001, I^2: 91.0%). In the subgroup analyses, the significantly higher transfusion rate among SSRI users was observed in both the THA subgroup (OR: 1.47, 95%CI: 1.10-1.96, I^2: 91.4%) and the TKA subgroup (OR: 1.31, 95%CI: 1.08-1.59, I^2: 0.0%). The formal comparison between these procedure-based subgroups also indicated a significant difference (P-value: 0.0009) [Figure 2].

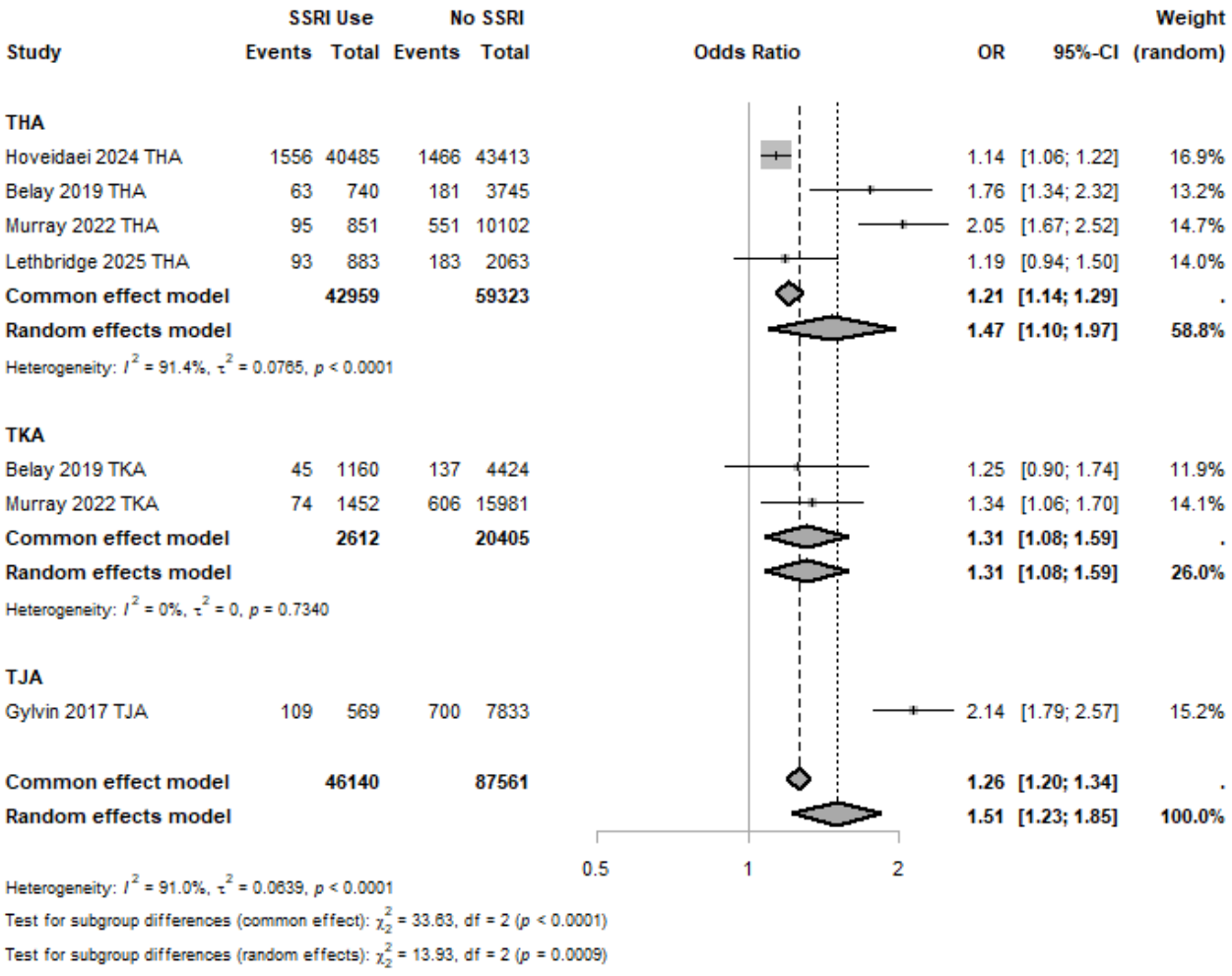

Figure 2. Meta-analysis Forest plot of odds ratios (95% CI) on the odds ratio of blood transfusion

Leave-one-out sensitivity analysis showed that the association between SSRI use and higher transfusion requirements remained consistent when each study was removed in turn [Figure 3]. Egger's test produced a bias intercept of 3.5686 (SE = 2.0261), *P-value* = 0.1385, indicating no statistically significant asymmetry. Publication bias was therefore unlikely to have materially influenced the meta-analysis [Figure 4].

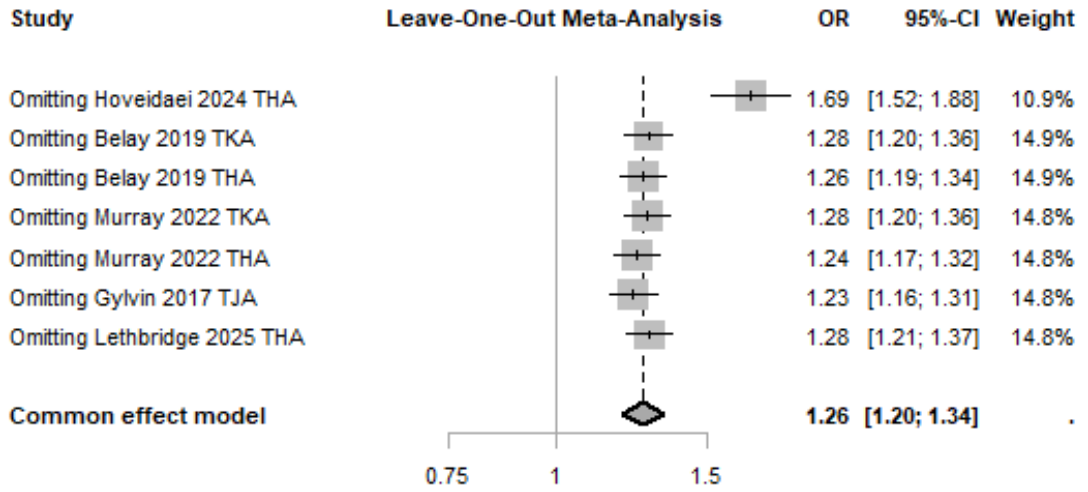

Figure 3. Sensitivity analysis (Leave one out meta-analysis) of odds ratios (OR) with 95% CIs

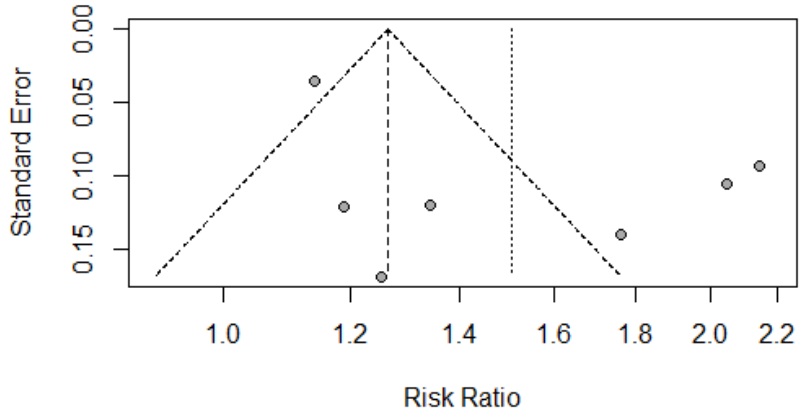

Figure 4. Egger's test and Begg's funnel plot for publication bias in blood transfusion

Length of Stay

All included observational studies reported longer LOS among SSRI users,[20, 22, 28] whereas the study by Lunn et al.[23] reported a median LOS of 2 (2–6) days in the escitalopram group and 2 (2–5) days in the placebo group [Table 5].

Readmission, Revision Surgery, and Periprosthetic Joint Infection (PJI)

Among the included studies, only two evaluated readmission,[22,28] and both reported significantly higher readmission rates among SSRI users. Revision surgery was assessed in two studies,[29,30] whereas PJI was evaluated in only one study [29]. With respect to revision surgery, Lethbridge et al. [30] reported no statistically significant unadjusted association between preoperative SSRI use and revision surgery (OR 1.57, p = 0.122); however, after adjustment, SSRI use was associated with significantly higher

odds of revision (adjusted OR 2.33, 95% CI 1.35–4.04, p = 0.002).” The current version of Table 5 correctly reports the findings of this study [Table 5].

Functional, Quality-of-Life, and Pain-Related Outcomes

Functional and quality-of-life outcomes were evaluated in only one study.[21] At 12-month follow-up, SSRI users had significantly lower EQ-5D-5L scores in both TKA and THA populations. WOMAC scores were comparable between the two groups in the TKA population but were lower among SSRI users in the THA population.

Pain was evaluated only in an RCT of 114 participants by Lunn et al.[23] During postoperative days 2-6, pain scores during ambulation (28 vs. 35) and at rest (18 vs. 23) were significantly lower in the escitalopram group than in the placebo group; however, the difference was not significant during the first 24 postoperative hours [Table 5].

Table 5 provides a comprehensive comparison of post-TJA complications between SSRI users and non-users across the included studies.

Table 5. Summary of the included studies' findings

Study	Outcome							
	Length of stay	Blood transfusion	Revision	Readmission	PJI	Functional outcomes	Quality of life	Pain
Hoveidaei (2024)		In THA cases, the blood transfusion rate was significantly higher in the SSRI group (OR: 1.144 (1.064—1.230)						
Yao (2018)			Among the population suffering from depression, a significantly lower risk of revision surgery was observed in patients using SSRI compared to patients who did not use SSRI (HR: 0.77, p-value: 0.001)		Among the population suffering from depression, there was no significant difference between these two groups of patients in terms of revision for aseptic loosening and PJI			
			Considering the non-depression population, there was no significant difference between SSRI users and the non-SSRI group in terms of revision or revision for aseptic loosening		Considering the non-depression population, The risk of PJI was significantly higher (HR: 4.96, p-value: 0.013) in SSRI users.			
Belay (2019)	A significantly more extended LOS was observed in the SSRI group (2.4 vs 2.3 days, p-value <0.001)	In THA cases, the blood transfusion rate was significantly higher in the SSRI group (8.5% vs. 4.8%)						
		In TKA cases, the blood transfusion rate was comparable (3.9% vs. 3.1%)						

Table 5. Continued

Murray (2021)	In TKA patients, a significantly more extended LOS was observed in the SSRI group (3.98 vs 3.62 days, p-value <0.001)	In THA cases, the blood transfusion rate was significantly higher in the SSRI group (11.1% vs. 5.4%)		demonstrated a significantly higher adjusted rate of 30-day readmission in SSRI users compared to the non-SSRI group among both the TKA (OR:1.71) and THA (OR:1.44) population.		After adjustment for baseline characteristics, including preoperative scores, reported a lower 3-month postoperative WOMAC score in SSRI users among both TKA (effect of SSRI use: -17.86) and THA populations (effect of SSRI use: -22.29).	The adjusted 3-month postoperative quality of life, measured by EQ-5D-5J, was comparable between SSRI and non-SSRI subgroups in both TKA and THA populations.	
	In THA patients, a significantly more extended LOS was observed in the SSRI group (4.36 vs 3.67 days, p-value <0.001)	In THA cases, the blood transfusion rate was significantly higher in the SSRI group (5.1% vs. 3.8%)				Regarding 12-month outcomes a significantly lower WOMAC score in the SSRI group was only observed in the THA population (effect of SSRI use: -4.36), and the 12-month WOMAC score in SSRI and non-SSRI users was comparable in the TKA population (effect of SSRI use: -1.92)	Regarding 12-month outcomes, while in both TKA and THA populations, there was a significantly lower EQ-5D-5L score in SSRI users (effect of SSRI use: -0.03 and -0.05, in TKA and THA populations, respectively)	
Gylvin (2017)		In TJA cases, the blood transfusion rate was significantly higher in the SSRI group (19.2% vs. 8.9%)						
Jørgensen (2015)	SSRI consumption was associated with a significantly higher risk of LOS> 4 days in patients who underwent TJA.			SSRI consumption was associated with a significantly higher risk of 30-day (OR: 1.97) and 90-day (OR: 1.77) readmission in patients undergoing TJA.				

Table 5. Continued

Lunn (2015)	LOS was comparable between the Escitalopram (2 (2–6)) and placebo (2 (2–5)) group							unveiled that SSRI use does not significantly decrease the pain (measured by VAS) upon ambulation in the 24-hour postoperative period (58 in the escitalopram group vs. 64 in the placebo group).
								During days 2-6, the pain upon ambulation (28 vs. 35) and at rest (18 vs. 23) was significantly lower in escitalopram compared to the placebo group.
Lethbridge (2025)		SSRI: 93/883 (10.5%) No SSRI: 183/2063 (8.9%) ; both unadjusted and adjusted ORs were not statistically significant.	SSRI: 20/883 (2.3%); no SSRI: 30/2063 (1.5%) (unadjusted OR 1.57, p = 0.122; adjusted OR 2.33, 95% CI 1.35–4.04, p = 0.002)					

Discussion

Depression is increasingly recognized as an important comorbidity among patients undergoing total joint arthroplasty (TJA), with prevalence reportedly increasing over time. Recent studies have highlighted not only the adverse effects of untreated depression on postoperative outcomes but also serious mental health crises, including reports of suicide after arthroplasty in vulnerable populations.[31,32] These findings underscore the importance of understanding both the effects of depression and the pharmacologic agents used to manage it on arthroplasty outcomes. To our knowledge, this is the first meta-analysis specifically evaluating bleeding risk associated with SSRI use in TJA. In the context of the global shift toward outpatient and same-day discharge arthroplasty,[33] perioperative bleeding and transfusion requirements are increasingly important because they may delay recovery and discharge. These findings have practical implications for arthroplasty surgeons, who must consider psychiatric comorbidity, bleeding risk, and recovery expectations when planning surgical care.

The perioperative use of SSRIs in patients undergoing surgical procedures, particularly TJA, remains a subject of debate because these medications may have complex and potentially competing effects on postoperative outcomes. Evidence from the studies included in this review provides

important insight into these associations and identifies both potential risks and possible benefits of continuing SSRI therapy during the perioperative period. These findings are discussed in greater detail in the following sections.

The most frequently examined concern in the literature was the effect of SSRIs on perioperative bleeding. Our meta-analysis showed that SSRI use was associated with significantly higher perioperative transfusion requirements (OR: 1.50, 95%CI: 1.22-1.85, *P-value*: < 0.0001, I^2: 91.0%). This association may be explained by the pharmacologic mechanism of SSRIs, which inhibit serotonin transporters on platelet membranes. By reducing intraplatelet serotonin, this mechanism impairs platelet aggregation and hemostasis and may thereby increase perioperative blood loss.[19] These findings are consistent with previous clinical studies that have reported an association between SSRI use and increased perioperative bleeding risk. For example, Movig *et al.*[34] found that orthopedic surgical patients receiving serotonergic antidepressants were more likely to require blood transfusion than non-users. Similarly, Auerbach *et al.*[35] reported that perioperative SSRI use was associated with an increased risk of postoperative bleeding complications. In addition, a retrospective cohort study focused on patients undergoing total hip arthroplasty (THA) found that SSRI users experienced a mean increase in intraoperative blood loss of 95 mL (95% CI: 9–181 mL) compared with non-users, although this difference did not result in a statistically significant increase in transfusion risk.[36] An important limitation of the included evidence is that most studies did not report critical variables such as preoperative hemoglobin levels or the volume of intraoperative blood loss; Belay *et al.*[20] was the exception. Future analyses that adjust transfusion outcomes for these variables may provide a more complete understanding of the observed associations.

A slight increase in length of stay was reported among SSRI users by Belay *et al.*[20] (median = 2.4 vs. 2.3, *P-value*<0.001) and Murray *et al.*[22] (TKA: OR = 0.38 (0.23-0.54), p<.001; THA: OR = 0.65 (0.41-0.88), *P-value* <0.001). This modest difference may be related to a higher frequency of perioperative complications, including bleeding and the consequent need for additional monitoring or treatment. However, a retrospective analysis of more than 530,000 patients treated at 375 U.S. hospitals found that perioperative SSRI use was associated with increased odds of in-hospital mortality, bleeding, and 30-day readmission but was not significantly associated with prolonged length of stay.[35] A separate investigation of patients undergoing elective non-cardiac surgery similarly found no significant difference in postoperative length of stay between preoperative antidepressant users and non-users, suggesting that antidepressant use may not necessarily prolong hospitalization in all surgical settings.[37] Differences among these findings may reflect variation in the type of surgery, patient comorbidities, and perioperative care pathways.

Regarding readmission, a prospective cohort study by Jørgensen *et al.*[28] found higher risks of both 30-day (OR: 1.97, 95% CI: 1.38–2.82, *P-value* <0.001) and 90-day (OR:1.77, 95% CI: 1.29–2.43, *P-value* <0.001) readmission among SSRI users than among non-users.

Murray *et al.*[21] reported that although the mean changes in WOMAC and EQ-5D-5L scores were comparable between the SSRI and non-SSRI groups, patients using SSRIs nevertheless had poorer absolute functional outcomes at 12 months after surgery. This finding was reflected in lower postoperative WOMAC scores (TKA: MD -4.7, *P-value* <0.001; THA: MD -5.6, p<0.001) and lower EQ-5D-5L quality-of-life scores (TKA: MD -0.05, *P-value* <0.001; THA: MD -0.07, *P-value* <0.001) compared with non-users. In a related analysis, Powell *et al.*[38] reported that patients prescribed SSRIs had lower preoperative WOMAC and EQ-5D-5L scores than patients who were not using SSRIs. Both groups experienced substantial improvement during the 12 months after arthroplasty; however, the magnitude of improvement was less pronounced among SSRI users. Interpretation of these findings requires caution because the association between SSRI use and postoperative recovery may be confounded by the underlying depression for which these medications are prescribed. Depression itself has been associated with poorer surgical outcomes. For example, Kohring *et al.*[39] found that untreated depression was associated with poorer postoperative outcomes, including higher complication rates and longer hospital stays.

Yao *et al.*[29] reported a fivefold hazard of PJI among non-depressed SSRI users compared with non-users, whereas no association was observed in the depressed population. However, direct evidence linking SSRI use to increased PJI risk remains very limited.

Conversely, the included literature also identified potentially beneficial outcomes associated with SSRI use in patients undergoing TJA. The reduced risk of revision among depressed SSRI users reported by Yao *et al.*,[29] emphasizes the potential importance of recognizing and treating depression in patients undergoing arthroplasty. This interpretation is supported by Schwartz *et al.*,[40] who reported 1.7-fold higher odds of revision among untreated depressed patients undergoing THA than among patients whose depression was treated. Furthermore, Lunn *et al.*[23] reported an association between perioperative escitalopram use and improved pain relief. These potential benefits should therefore be considered alongside the possible bleeding and transfusion risks of SSRI therapy.

A review by Oprea *et al.*[41] highlighted the lack of consensus regarding the preoperative management of psychiatric medications, including SSRIs, and the resulting variation in care. The authors recommended individualized decisions that balance the risks of discontinuation, including withdrawal symptoms and relapse, against the potential for increased bleeding. The competing effects of SSRIs underscore the complexity of managing patients undergoing TJA. Clinicians should therefore assess the risks and benefits of perioperative SSRI use individually, considering both the psychological and physiological implications of these medications.

More broadly, orthopedic literature emphasizes the importance of patient-specific risk assessment, accurate

characterization of musculoskeletal pathology, and individualized perioperative strategies to optimize clinical outcomes. [42,43,44,45]

Strengths and Limitations

This is the first comprehensive meta-analysis to evaluate he multifaceted effects of SSRI use in TJA populations. By pooling data from diverse geographic and clinical settings, the study provides insight into the perioperative risks and potential benefits associated with SSRI use. However, several limitations should be acknowledged.

First, the observational design of most included studies limits causal inference and introduces biases inherent to this type of evidence. Second, the high heterogeneity observed in some analyses, despite subgroup and sensitivity analyses, suggests residual confounding related to factors such as SSRI dose, treatment duration, and patient comorbidities. Further subgroup analyses were not feasible because of the limited number of studies. Finally, the lack of detailed data on individual SSRI agents and depression severity prevented a thorough assessment of dose-response relationships.

Future prospective studies and randomized controlled trials are needed to clarify the mechanisms underlying these associations and identify subpopulations at greatest risk. Integrating pharmacologic and psychological interventions into perioperative care pathways may also help optimize outcomes for patients who require SSRIs.

Conclusion

Among patients undergoing TJA, SSRI use was associated with increased perioperative transfusion requirements and longer hospital stays. Limited evidence also suggested possible associations with higher PJI risk among non-depressed patients and poorer functional recovery, while potential benefits were observed for pain modulation and revision risk among depressed patients. These findings highlight the need for individualized perioperative risk stratification and interdisciplinary management.

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Supplementary file

Table S1. Search strategy for databases

Pubmed	("Selective Serotonin Reuptake Inhibitors"[Mesh] OR "SSRI*"[Title/Abstract] OR "Selective Serotonin Reuptake Inhibitor*"[Title/Abstract] OR "Serotonin Uptake Inhibitor*"[Title/Abstract] OR "Serotonin Uptake Inhibitor*"[Title/Abstract] OR "Serotonin Reuptake Inhibitor*"[Title/Abstract] OR "5-HT Uptake Inhibitor*"[Title/Abstract] OR "5-Hydroxytryptamine Uptake Inhibitor*"[Title/Abstract] OR "5-HT Uptake Inhibitor*"[Title/Abstract] OR "5-Hydroxytryptamine Uptake Inhibitor*"[Title/Abstract] OR "Serotonin Reuptake Inhibitor*"[Title/Abstract] OR fluoxetine[Title/Abstract] OR sertraline[Title/Abstract] OR paroxetine[Title/Abstract] OR citalopram[Title/Abstract] OR escitalopram[Title/Abstract]) AND ("Arthroplasty, Replacement, Hip"[Mesh] OR "Arthroplasty, Replacement, Knee"[Mesh] OR "TJA"[Title/Abstract] OR "TKA"[Title/Abstract] OR "THA"[Title/Abstract] OR "TKR"[Title/Abstract] OR "knee arthroplast*"[Title/Abstract] OR "knee replacement"[Title/Abstract] OR "hip arthroplast*"[Title/Abstract] OR "hip replacement"[Title/Abstract] OR "Hip prosthesis implantation"[Title/Abstract] OR "Joint replacement"[Title/Abstract] OR "joint arthroplast*"[Title/Abstract] OR "total knee arthroplast*"[Title/Abstract] OR "total hip arthroplast*"[Title/Abstract])	34
Embase	('ssri*':ti,ab,kw OR 'selective serotonin reuptake inhibitor*':ti,ab,kw OR 'serotonin uptake inhibitor*':ti,ab,kw OR '5-ht uptake inhibitor*':ti,ab,kw OR '5-hydroxytryptamine uptake inhibitor*':ti,ab,kw OR 'serotonin reuptake inhibitor*':ti,ab,kw OR 'fluoxetine':ti,ab,kw OR 'sertraline':ti,ab,kw OR 'paroxetine':ti,ab,kw OR 'citalopram':ti,ab,kw OR 'escitalopram':ti,ab,kw) AND ('tja':ti,ab,kw OR 'tka':ti,ab,kw OR 'tha':ti,ab,kw OR 'tkr':ti,ab,kw OR 'knee arthroplast*':ti,ab,kw OR 'knee replacement':ti,ab,kw OR 'hip arthroplast*':ti,ab,kw OR 'hip replacement':ti,ab,kw OR 'hip prosthesis implantation':ti,ab,kw OR 'joint replacement':ti,ab,kw OR 'joint arthroplast*':ti,ab,kw OR 'total knee arthroplast*':ti,ab,kw OR 'total hip arthroplast*':ti,ab,kw)	63

Web of science	(TS=("SSRI*" OR "Selective Serotonin Reuptake Inhibitor*" OR "Serotonin Uptake Inhibitor*" OR "Serotonin Uptake Inhibitor*" OR "Serotonin Reuptake Inhibitor*" OR "5-HT Uptake Inhibitor*" OR "5-Hydroxytryptamine Uptake Inhibitor*" OR "5-HT Uptake Inhibitor*" OR "5-Hydroxytryptamine Uptake Inhibitor*" OR "Serotonin Reuptake Inhibitor*" OR fluoxetine OR sertraline OR paroxetine OR citalopram OR escitalopram)) AND TS=("TJA" OR "TKA" OR "THA" OR "TKR" OR "knee arthroplasty" OR "knee arthroplasties" OR "knee replacement" OR "Hip arthroplasty" OR "hip arthroplasties" OR "hip replacement" OR "Hip prosthesis implantation" OR "Joint replacement" OR "joint arthroplasty" OR "total knee arthroplasty" OR "total hip arthroplasty")	48
Scopus	(TITLE-ABS-KEY ("SSRI*" OR "Selective Serotonin Reuptake Inhibitor*" OR "Serotonin Uptake Inhibitor*" OR "Serotonin Uptake Inhibitor*" OR "Serotonin Reuptake Inhibitor*" OR "5-HT Uptake Inhibitor*" OR "5-Hydroxytryptamine Uptake Inhibitor*" OR "5-HT Uptake Inhibitor*" OR "5-Hydroxytryptamine Uptake Inhibitor*" OR "Serotonin Reuptake Inhibitor*" OR fluoxetine OR sertraline OR paroxetine OR citalopram OR escitalopram) AND TITLE-ABS-KEY ("TJA" OR "TKA" OR "THA" OR "TKR" OR "knee arthroplast*" OR "knee replacement" OR "Hip arthroplast*" OR "hip replacement" OR "Hip prosthesis implantation" OR "Joint replacement" OR "joint arthroplast*" OR "total knee arthroplast*" OR "total hip arthroplast*"))	141

Table S2. Reasons of the exclusion of studies in full-text review process

Author, year	Study title	Reason of exclusion
Lin D, 2022 [1]	Fluoxetine for reducing postoperative cognitive dysfunction in elderly patients after total knee replacement: study protocol for a single-centre, double-blind, randomised, parallel-group, superiority, placebo-controlled trial	Incomplete outcome data
Grammatikopoulos D, 2025 [2]	Use of serotonergic antidepressants and perioperative complications in patients undergoing lower limb arthroplasty: Systematic review and meta-analysis of comparative studies	Review article
Kornvig S, 2024 [3]	Psychopharmacological treatment in patients planned for hip or knee replacement	Wrong exposure
Bian T. 2023 [4]	Predisposing factors for allogeneic blood transfusion in patients with ankylosing spondylitis undergoing primary unilateral total hip arthroplasty: a retrospective study	Wrong exposure
Ho KY, 2010 [5]	Duloxetine reduces morphine requirements after knee replacement surgery	Wrong exposure
Schutte HJ, 2014 [6]	SSRIs increase risk of blood transfusion in patients admitted for hip surgery	Wrong population
van Haelst IM, 2010 [7]	Use of serotonergic antidepressants and bleeding risk in orthopedic patients	Wrong population
van Haelst IM, 2012 [8]	Selective serotonin reuptake inhibitors and intraoperative blood pressure	Wrong population
Tavakoli HR, 2012 [9]	Serotonin reuptake inhibitors and bleeding risks in major orthopedic procedures	Wrong population
Thakkar P. 2024 [10]	Hip arthroscopy failure rates: a healthcare database analysis in the United States	Wrong population
Miner AM, 2025 [11]	Fluoxetine and Paroxetine Exhibit a Protective Effect Against Total Joint Arthroplasty in Patients With Osteoarthritis	Wrong population

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