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SYSTEMATIC REVIEW

Perioperative Ketamine and Esketamine for Postoperative Mood Symptoms After Orthopaedic Surgery: A Systematic Review of Randomized Controlled Trials

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Abstract

Objectives: Perioperative anxiety and depression are common following major orthopaedic surgery and may adversely affect postoperative recovery. Ketamine and esketamine have rapid psychotropic effects; however, their effectiveness in reducing postoperative mood symptoms in orthopaedic patients remains uncertain. We systematically reviewed randomized evidence on the effects of these agents on postoperative anxiety, depression, and adverse events.

Methods: PubMed, Embase, and the Cochrane Library were searched for randomized controlled trials enrolling adults undergoing major orthopaedic procedures. Eligible studies compared ketamine or esketamine administered preoperatively, intraoperatively, or postoperatively with placebo or no ketamine-class agent. The primary outcomes were postoperative anxiety and depression assessed using validated scales. Secondary outcomes included drug-related adverse events.

Results: Nine randomized controlled trials were included, with follow-up durations ranging from 24 hours to 12 months. Five trials assessed postoperative anxiety using validated scales; four reported significantly lower anxiety scores with ketamine or esketamine at early postoperative time points, whereas one trial using a single preoperative dose of ketamine found no significant anxiolytic effect. Overall, perioperative ketamine or esketamine may be associated with lower early postoperative anxiety and depressive symptom scores in selected orthopaedic populations. Regarding safety, ketamine or esketamine did not appear to increase the incidence of common adverse events.

Conclusion: Perioperative ketamine or esketamine appears to reduce early postoperative anxiety and depressive symptoms in orthopaedic patients without increasing postoperative nausea, vomiting, or dizziness. Further standardized trials are needed before firm conclusions can be drawn.

Level of evidence: II

Keywords: Anxiety, Depression, Ketamine, Orthopaedic, Perioperative

Introduction

Perioperative anxiety and depression are common concerns among surgical patients and can influence recovery trajectories, contributing to dissatisfaction and post-traumatic stress disorder (PTSD).[1-3] Recent evidence suggests that improved postoperative mood, reflected by lower levels of anxiety and depression, is associated with fewer complications, including pain and delirium, enhanced recovery, better functional outcomes, and shorter hospital stays. These concerns are particularly relevant after major orthopaedic procedures, including total hip and knee arthroplasty.[4-6]

Various strategies have been proposed to reduce postoperative anxiety and depression, including nonpharmacological approaches and pharmacological treatments.[7-9] Ketamine and esketamine are well known for their anaesthetic and analgesic effects, as well as for their

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rapid antidepressant properties.[10-12] Mechanistic and clinical studies suggest that the rapid effects of ketamine involve NMDA receptor blockade and downstream changes in glutamatergic signalling and synaptic plasticity, which may translate into improvements in mood symptoms.[13,14] In addition, recent studies have reported that ketamine and esketamine may reduce opioid-related postoperative adverse effects, including nausea, vomiting, and dizziness. However, the evidence supporting their perioperative use for improving postoperative mood-related outcomes remains inconclusive.[15,16] Verdonk et al. reported that a single preoperative ketamine bolus did not reduce postoperative anxiety.[17]

Uncertainty remains regarding the efficacy of perioperative ketamine or esketamine in orthopaedic settings. Therefore, we conducted a systematic review to evaluate the effectiveness of these agents in reducing postoperative anxiety and depression in patients undergoing orthopaedic procedures. In addition, we assessed their impact on common adverse events associated with analgesic medications.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The protocol was registered prospectively in PROSPERO before study screening under the registration number CRD420261293013.

Search strategy

A systematic search was performed in PubMed, Embase, and the Cochrane Library from database inception to 2 January 2026. No date restrictions were applied. Full-text studies published in English were eligible for inclusion. A comprehensive search strategy was developed using main keywords combined with Boolean operators: ("ketamine" OR "esketamine" OR "N-methyl-D-aspartate" OR "NMDA") AND ("orthop*" OR "arthroplast*" OR "fracture*" OR "arthroscop*" OR "fixation") AND ("anxiety" OR "depression" OR "mood" OR "HADS" OR "HAMA" OR "HAMD" OR "PHQ-9" OR "SAS" OR "SDS"). The PubMed MeSH terms included "Ketamine"[MeSH], "Orthopaedic Procedures"[MeSH], "Anxiety"[MeSH], and "Depression"[MeSH].

Eligibility Criteria

The eligibility criteria were defined according to the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework. The population (P) comprised adult patients undergoing major orthopaedic procedures, including arthroplasty, fracture fixation, hip fracture surgery, and amputation. Paediatric studies were excluded. The intervention (I) was the administration of ketamine or esketamine before, during, or after major orthopaedic procedures. The comparator (C) included placebo, usual care, or no ketamine-class agent. The primary outcome (O) of interest was postoperative mood, assessed using validated clinician-rated or patient-reported instruments, including the Hospital Anxiety and Depression Scale (HADS), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Patient Health Questionnaire-9 (PHQ-9), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS). Postoperative anxiety and depression were defined as anxiety or depressive symptoms assessed after surgery. Trials were eligible whether anxiety or depression was reported as a primary or secondary outcome, provided that postoperative mood outcomes were assessed using a validated scale. Postoperative assessment time points were categorized a priori as early postoperative recovery and longer-term follow-up. Early postoperative outcomes were defined as assessments conducted from postoperative day 1 to day 7, whereas longer-term outcomes were defined as assessments conducted more than 1 week after surgery. Because the included trials assessed outcomes at different time points and using different instruments, findings were not statistically pooled; instead, results were reported according to outcome and timing categories. Drug-related adverse events were reported as secondary outcomes, including dizziness, nausea and vomiting, delirium, psychiatric symptoms, pruritus, confusion, and sleep disturbance. For study design (S), only randomized controlled trials (RCTs) were included. Reviews, book chapters, letters, case reports, case series, non-randomized studies, and studies not published in English were excluded.

Study Selection

Two authors (MF and MF), blinded to each other's assessments, independently conducted the study selection process. First, titles and abstracts were screened using Rayyan, an online tool designed to facilitate screening in systematic reviews, to identify potentially relevant studies.[19] After duplicates were manually removed, full-text articles were reviewed to assess eligibility against the predefined criteria. Disagreements between the two authors were resolved through consultation with a third author (NN).

Data extraction and data synthesis

Data extraction was performed using Google Sheets. To ensure accuracy, two authors (FM and MF) independently extracted the data. Any discrepancies were resolved through discussion, and the extraction sheet was completed using predefined domains: study characteristics, patient demographics, methods, and results. The following data were extracted from each study: first author, year of publication, country, number of patients, sex distribution, mean age, intervention drug and group allocation, procedure type, analgesic dose, duration of administration, anxiety or depression assessment tool, anxiety or depression assessment time point, overall results, and adverse events. Any remaining disagreements were resolved by another author (NN), resulting in a final master sheet. For multi-arm randomized trials, all randomized arms were recorded in the study characteristics table. For outcome synthesis, only comparisons between ketamine or esketamine and non-ketamine treatments were considered. If a third treatment arm was unrelated to the main comparison, it was included in the study characteristics table but was not analyzed in the main outcome synthesis. The included trials examined various orthopaedic populations, including patients undergoing arthroplasty, fracture fixation, hip fracture

surgery, and amputation. Therefore, the findings should not be considered directly interchangeable across different procedure types. Because of clinical and methodological heterogeneity in procedure type, ketamine or esketamine formulation, dose, route of administration, timing, comparator intervention, outcome measurement instruments, and follow-up duration, a meta-analysis was not conducted. Instead, the results were synthesized narratively.

Quality assessment

Two authors (FM and MF) independently assessed the risk of bias in the included randomized controlled trials using the RoB 2 tool.[20] We assessed each article based on five domains of the Risk of Bias 2 tool guidelines. Each domain was evaluated as "Low risk," "Some concerns," or "High risk". A study was classified as "Low risk" if all domains were rated low risk; as "Some concerns" if at least one domain raised some concerns, with no high-risk domains; and as "High risk" if one domain was rated as high risk [Table 1].

Table1. Details of Quality Assessment

RoB 2:	D1	D2	D3	D4	D5	Overall
Zhao, et al., 2026	Low	Some concerns	Some concerns	Low	Low	Some concerns
Min, et al., 2023	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Verdonk, et al., 2024	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Qu, et al., 2025	Some concerns	High	Low	High	Low	High
Wilson, et al., 2008	Low	Some concerns	High	Low	Some concerns	High
Kudoh, et al., 2002	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Jiang, et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns
Liu, et al., 2025	Low	Low	Low	Low	Low	Low
Cai, et al., 2024	Low	Low	Some concerns	Low	Low	Some concerns

RoB 2: Risk of Bias 2, D1: Randomization, D2: Deviations, D3: Missing data, D4: Outcome measurement, D5: Selective reporting

Results

Study selection

The final search identified 246 records: 54 from PubMed, 90 from Embase, and 102 from the Cochrane Library. After 56 duplicates were removed, 190 records were screened by title and abstract, of which 173 were excluded. Of the 17 reports sought for retrieval, three could not be retrieved, leaving 14 reports for full-text assessment. Five studies were excluded for the following reasons: two had ineligible interventions, and three had ineligible study designs. Ultimately, nine randomized controlled trials met the eligibility criteria and were included in the review [Figure 1].

Risk of bias assessment

One trial was judged to have a low overall risk of bias, six trials raised some concerns, and two trials were judged to have a high risk of bias. The risk-of-bias assessments are presented in [Table 1].

Study and patient characteristics

Nine randomized controlled trials were included in this systematic review,[5,17,21-27] which articles were mostly published in China, with one each in Japan,[25] France,[17] and the UK,[24] between 2002 and 2026. Follow-up periods ranged from 24 hours to 12 months after surgery. Six RCTs were two-arm trials, and three were three-arm trials. Overall, 1,241 randomized participants were included across all study arms. Because several studies included more than two treatment arms, participants were not aggregated into a single overall total for the intervention and control groups. For outcome synthesis, we focused on comparisons that directly addressed the review question: ketamine or esketamine versus non-ketamine comparator arms. When a third group was not relevant to the main comparison, it was included in the study characteristics but excluded from the main outcome synthesis. Among the eight trials reporting sex distribution, 628 participants were women and 518 were men. One RCT did not report the number of male and female participants separately.[25] Seven studies used general anesthesia, and two studies used spinal anesthesia[5,24] for patients undergoing orthopaedic procedures. Interventions differ in drug type and dose across studies, both in the control and treatment groups. Based on the predefined timing categories, five studies administered the intervention postoperatively,[5,21-23,27] two preoperatively,[17,25] one both preoperatively and intraoperatively,[26], and one preoperatively, intraoperatively, and postoperatively.[24] Four studies assessed depression states,[5,25-27] and five studies reported both anxiety and depression levels compared to baseline [Table 2] .[17,21-24]

Anxiety rating scales and outcomes

Among these nine included studies, five used various scales to assess postoperative anxiety [17,21-24], including the HADS and the SAS anxiety rating scores, with the HADS being the most commonly used assessment tool.[17,21-24]

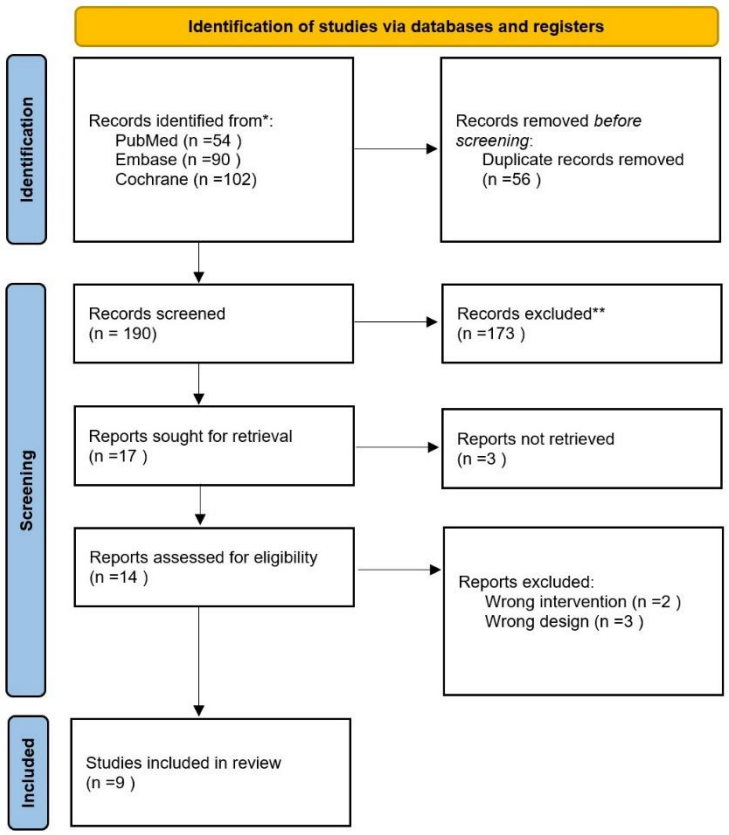

Figure 1. PRISMA flow diagram

Table 2. Study Characteristics and Demographic Data

First Author, year	Country	Study design	Study arms	Procedure type	Type of anesthesia	Total randomized patients	Sex (F/M)	Age (Mean ± SD)	Follow-up duration
Zhao, et al.,[18] 2026	China	RCT	2	THA / TKA	General	112 (57/55)	79/33	65.5 ± 3.2	7 days
Min, et al.,[19] 2023	China	RCT	2	THA	General	132 (67/65)	70/62	73.9 ± 6.3	1 month
Verdonk, et al.,[14] 2024	France	RCT	2	Major orthopedic surgery	General	292 (149/143)	180/112	72.3 ± 7.2	3 months
Qu, et al.,[20] 2025	China	RCT	3	THA	General	133 (44/45/44)	67/66	59.8 ± 15	7 days
Wilson, et al.,[21] 2008	UK	RCT	2	Amputation	Spinal/Epidural	47 (21/26)	12/35	71.0 ± 9.0	12 months
Kudoh, et al.,[22] 2002	Japan	RCT	3	Fracture fixation	General	95 (35/35/25)	NR	78.5 ± 8.1	4 days
Jiang, et al.,[23] 2016	China	RCT	2	Fracture fixation	General	120 (60/60)	53/67	42.4 ± 0.6	5 days
Liu, et al.,[24] 2025	China	RCT	3	Fracture fixation	General	225 (75/75/75)	116/109	46.5 ± 8.3	7 days
Cai, et al.,[4] 2024	China	RCT	2	Hip fracture	Spinal + Block	85 (42/43)	51/34	75.2 ± 6.8	1 month

SD: standard deviation, THA: Total Hip Arthroplasty, TKA: Total Knee Arthroplasty, NR: Not Reported, RCT: Randomized Controlled Trial, UK: United Kingdom, F :Female, M:Male

Three studies have reported lower early anxiety scores within the first postoperative week. Zhao *et al*.[21] evaluated the use of esketamine and sufentanil postoperatively, compared with sufentanil alone. The result showed lower HADS scores on postoperative days one, two, and three. Min *et al*.[22] and Qu *et al*.[23] compared the postoperative use of esketamine with sufentanil. According to Min, lower HADS scores were reported on three days and one week after the operation. Qu *et al*. administered lower SAS scores one week after the operation. For longer-term findings, Min observed no differences at one month. Verdonk *et al*. [17] compared single-dose preoperative ketamine with normal saline and found no significant differences in HADS scores at seven and 90 days postoperatively. Wilson *et al*.[24] evaluated a combined preoperative, intraoperative, and postoperative epidural ketamine regimen in lower-limb amputation, reported lower HADS anxiety scores at longer follow-up for 6 weeks after the operation. However, this trial differed significantly from arthroplasty and fracture-fixation studies in procedure type, route of administration, and follow-up duration [Table 3].

Table 3. Anxiety outcomes and analgesic drugs protocol

Author, year	Assessment tool	Assessment time	Period of intake			Analgesic drugs		Overall results
			Pre op	op	Post op	Treatment group	Control group	
Zhao, et al 2026	HADS	POD 1, 2, 3, 7			*	PCIA: esketamine 0.72 mg/kg + sufentanil 2 μg/kg, diluted with NS to 100 mL; background 2 mL/h; bolus 1 mL; lockout 15 min.	PCIA: sufentanil 2 μg/kg, diluted with NS to 100 mL; background 2 mL/h; bolus 1 mL; lockout 15 min.	Significantly Lower anxiety scores on POD 1 (*P Value*:0.019), 2 (*P value*: 0.039), and 3 (*P value*: 0.022)
Min, et al 2023	HADS	POD 3, 7, 30			*	PCIA: esketamine 2.5 mg/kg, diluted with NS to 100 mL; background 2 mL/h; PCA bolus 3 mL; lockout 15 min.	PCIA: sufentanil 2.5 μg/kg, diluted with NS to 100 mL; background 2 mL/h; PCA bolus 3 mL; lockout 15 min.	Significantly Lower anxiety scores on POD 3 and 7 (*P value* < 0.05); no difference on POD 30
Verdonk, et al 2024	HADS	POD 7, 90	*			Single Dose Ketamine 0.5 mg/kg IV bolus before incision	Placebo (0.9% sodium chloride) IV bolus; same timing/volume.	No significant difference in anxiety scores at any time point
Qu, et al 2025	SAS	POD 7			*	PCIA: esketamine 1.5 mg/kg + flurbiprofen axetil 250 mg, diluted with NS to 150 mL; loading 4 mL; background 3 mL/h; bolus 2 mL; lockout 15 min.	PCIA: sufentanil 2.0 μg/kg + flurbiprofen axetil 250 mg, diluted with NS to 150 mL; loading 4 mL; background 3 mL/h; bolus 2 mL; lockout 15 min.	Significantly Lower anxiety scores on POD 7 (*P value* < 0.05)
Wilson, et al 2008	HADS	6 weeks, 3 & 12mo	*	*	*	Bupivacaine 0.5% (1 mg/kg) + preservative-free racemic ketamine 0.5 mg/kg; infusion bupivacaine 0.125% + ketamine 3.3 mg/kg/L (15 mL/h intra-op, then 10–20 mL/h post-op for 48–72 h). Top-up boluses 10–15 mL	Bupivacaine 0.5% (1 mg/kg) + saline (equivalent volume); infusion bupivacaine 0.125% + saline at the same rates/duration (15 mL/h intra-op; 10–20 mL/h post-op for 48–72 h). Top-up boluses 10–15 mL	Significantly lower anxiety scores on all time points (*P value* < 0.001)

HADS: Hospital Anxiety and Depression Scale, SAS: Self-Rating Anxiety Scale, POD: Post-operative day, PCIA: Patient-controlled intravenous analgesia, PCA: patient-controlled analgesia, IV: intravenous, NS: Normal saline, Mo: month

Depression rating scales and outcomes

All studies evaluated postoperative depression levels using various scales, including the HADS, HAMD, GDS-15, SDS, and PHQ-9, but the effect was inconsistent across follow-up assessments.

Early postoperative benefits were reported in seven studies assessing outcomes within postoperative days (PODs) 1–7. Kudoh et al.[25] evaluated a single preoperative dose of ketamine and reported lower Hamilton Depression Rating Scale (HAM-D) scores on postoperative day 1. Zhao et al.[21] evaluated postoperative esketamine combined with sufentanil and reported lower Hospital Anxiety and Depression Scale (HADS) scores on PODs 1, 2, and 3. Jiang et al.[26] compared preoperative and intraoperative ketamine with placebo and reported lower Patient Health Questionnaire-9 (PHQ-9) scores in the ketamine group on

PODs 1 and 5. Liu et al.[27] compared postoperative low- and high-dose esketamine with saline and observed lower HAM-D scores on PODs 1 and 3, with no significant difference on POD 7. Cai et al.[5] assessed postoperative esketamine versus placebo and reported lower Geriatric Depression Scale-15 (GDS-15) scores on PODs 2 and 7. Min et al.[22] reported lower HADS scores on POD 3 and at 1 week after surgery. Qu et al.[23] compared postoperative esketamine with sufentanil and reported lower Self-Rating Depression Scale (SDS) scores at 1 week after surgery. Verdonk et al.[17] assessed preoperative ketamine versus normal saline and reported no difference in depressive symptoms on POD 7. Longer-term findings were mixed. Cai et al.[5] and Min et al.[22] reported no significant difference at 1 month. Verdonk et al.[17] reported lower depressive symptoms in the ketamine group at 3 months. Wilson et al.v reported lower HADS depression scores after amputation at 6 weeks and 12 months. Overall, the evidence suggests a possible early postoperative benefit, although the durability and generalizability of this effect remain uncertain [Table 4].

Table 4. Depression Outcomes and Analgesic Drugs Protocol

Author	Assessment tool	Assessment time	Period of intake			Analgesic drugs		Overall results
			Pre op	op	Post op	Treatment group	Control group	
Zhao, et al 2026	HADS	POD 1, 2, 3, 7			*	PCIA: esketamine 0.72 mg/kg + sufentanil 2 μg/kg, diluted with NS to 100 mL; background 2 mL/h; bolus 1 mL; lockout 15 min.	PCIA: sufentanil 2 μg/kg, diluted with NS to 100 mL; background 2 mL/h; bolus 1 mL; lockout 15 min.	Significantly Lower depression scores on POD 1 (*P value*: 0.013), 2 (*P value:* 0.003), and 3 (*P value*: 0.035)
Min, et al 2023	HADS	POD 3, 7, 30			*	PCIA: esketamine 2.5 mg/kg, diluted with NS to 100 mL; background 2 mL/h; PCA bolus 3 mL; lockout 15 min.	PCIA: sufentanil 2.5 μg/kg, diluted with NS to 100 mL; background 2 mL/h; PCA bolus 3 mL; lockout 15 min.	Significantly Lower depression scores on POD 3 and 7 (*P value* < 0.05); no difference on POD 30
Verdonk, et al 2024	HADS	POD 7, 90	*			Single Dose Ketamine 0.5 mg/kg IV bolus before incision	Placebo (0.9% sodium chloride) IV bolus; same timing/volume.	Significantly Lower depression scores on POD 90 (*P value*: 0.023); no difference on POD 7
Qu, et al 2025	SDS	POD 7			*	PCIA: esketamine 1.5 mg/kg + flurbiprofen axetil 250 mg, diluted with NS to 150 mL; loading 4 mL; background 3 mL/h; bolus 2 mL; lockout 15 min.	PCIA: sufentanil 2.0 μg/kg + flurbiprofen axetil 250 mg, diluted with NS to 150 mL; loading 4 mL; background 3 mL/h; bolus 2 mL; lockout 15 min.	Significantly Lower depression scores on POD 7 (*P value* < 0.05)
Wilson, et al 2008	HADS	6 weeks, 3 & 12mo	*	*	*	Bupivacaine 0.5% (1 mg/kg) + preservative-free racemic ketamine 0.5 mg/kg; infusion bupivacaine 0.125% + ketamine 3.3 mg/kg/L (15 mL/h intra-op, then 10–20 mL/h post-op for 48–72 h). Top-up boluses 10–15 mL	Bupivacaine 0.5% (1 mg/kg) + saline (equivalent volume); infusion bupivacaine 0.125% + saline at the same rates/duration (15 mL/h intra-op; 10–20 mL/h post-op for 48–72 h). Top-up boluses 10–15 mL	Significantly Lower depression scores on all time points (*P value*: 0.003)
Kudoh, et al 2002	HAMD	POD 1, 3	*			Ketamine 1.0 mg/kg IV + propofol 1.5 mg/kg + fentanyl 2 μg/kg.	propofol 1.5 mg/kg + fentanyl 2 μg/kg	Significantly Lower depression scores on POD 1 (*P value* < 0.05)
Jiang, et al 2016	PHQ-9	POD 1, 5	*	*		Ketamine: 0.5 mg/kg, then 0.25 mg/kg/h IV infusion for 30 min (ketamine diluted to 10 mg/mL; total 20 mL).	Saline: 0.05 mL/kg IV, then 0.025 mL/kg/h IV infusion for 30 min (total 20 mL 0.9% saline).	Significantly Lower depression scores on POD 1 (*P value*: 0.042), POD 5 (*P value*: 0.03)

Table 4. Continued

Liu, et al 2025	HAMD	POD 1, 3, 7	*	PCIA: sufentanil 2 μg/kg + tropisetron 10 mg, diluted with saline to 100 mL; basal rate 1.5 mL/h; PCA bolus 2 mL; lockout 20 min. esketamine infusion for 24 h via separate pump: Group L 0.5 mg/kg in NS to 48 mL at 2 mL/h; Group H 0.75 mg/kg in NS to 48 mL at 2 mL/h.	PCIA: sufentanil 2 μg/kg + tropisetron 10 mg, diluted with saline to 100 mL; basal rate 1.5 mL/h; PCA bolus 2 mL; lockout 20 min. 24-h saline infusion (48 mL at 2 mL/h) via separate pump.	Significantly Lower depression scores on POD 1 and 3 (*P value* < 0.05)
Cai, et al 2024	GDS-15	POD 2, 7, 30	*	PCIA: esketamine 0.5 mg/kg + sufentanil 2 μg/kg + tropansetron 5 mg, diluted with saline to 100 mL; background 1.5 mL/h; bolus 1.5 mL; lockout 15 min.	PCIA: sufentanil 2 μg/kg + tropansetron 5 mg, diluted with saline to 100 mL; background 1.5 mL/h; bolus 1.5 mL; lockout 15 min.	Significantly Lower depression scores on POD 2 (*P value:* 0.007), 7 (*P value:* 0.035); no difference on POD 30

HADS: Hospital Anxiety and Depression Scale, SDS: Self-Rating depression Scale, HAMD: Hamilton Depression Rating Scale, PHQ-9: Patient Health Questionnaire-9, GDS-15: Geriatric Depression Scale-15, POD: Post-operative day, PCIA: Patient-controlled intravenous analgesia, PCA: patient-controlled analgesia, IV: intravenous, NS: Normal saline, Mo: month.

Adverse effects

Adverse-event reporting varied substantially across the included trials and was incomplete in several studies. The most frequently reported events were nausea and vomiting and dizziness. Seven studies assessed nausea and vomiting,[5,21-24,26,27] and five assessed dizziness.[5,21-23,27] Overall, ketamine or esketamine was not associated with a consistent increase in commonly reported adverse events. Min et al.[22] reported lower rates of dizziness and nausea and vomiting, and Liu et al.[27] reported lower rates of nausea and vomiting.

No notable differences were reported in postoperative delirium or sleep disturbance. Other adverse events, including psychiatric symptoms, pruritus, and confusion, were inconsistently reported across studies. The current evidence does not indicate any definitive safety concerns associated with perioperative ketamine or esketamine. However, tolerability should be interpreted cautiously because adverse-event definitions, assessment methods, and reporting practices varied substantially across studies [Table 5].

Table 5. Adverse Events

Author	dizziness	nausea/vomiting	Psychiatric symptoms	Pruritus	delirium	Insomnia/nightmare	Confusion
Zhao, et al 2026	Esketamine: 3% Sufentanil: 7% (*P value*: 0.29)	Esketamine: 15% Sufentanil: 7% (*P value*: 0.25)	Esketamine: 0 Sufentanil: 1% (*P value*: 0.50)	Esketamine: 1% Sufentanil: 0 (*P value*: 1)	Esketamine: 8.8% Sufentanil: 14.5% (*P value*: 0.34)	NR	NR
Min, et al 2023	Esketamine: 12% Sufentanil: 28% (*P value*: 0.023)	Esketamine: 15% Sufentanil: 40% (*P value* < 0.001)	Esketamine: 11% Sufentanil: 6% (*P value*: 0.372)	Esketamine: 7% Sufentanil: 12% (*P value*: 0.350)	NR	NR	NR
Verdonk, et al 2024	NR	NR	Ketamine: 2.68% Placebo: 3.5% (*P value*:0.76)	NR	Ketamine: 4.14% Placebo: 6.34% (*P value*:0.698)	NR	NR
Qu, et al 2025	Esketamine: 6.8% Sufentanil: 24.4% (*P value:* NR)	Esketamine: 13.6% Sufentanil: 35.6% (*P value:* NR)	Esketamine: 0 Sufentanil: 0 (*P value*: NR)	NR	NR	Esketamine: 0 Sufentanil: 0 (*P value*: NR)	NR
Wilson, et al 2008	NR	Ketamine: 19% Placebo: 11% (*P value:* 0.684)	NR	NR	NR	NR	Ketamine: 9% Placebo: 0 (*P value:* 0.194)

Table 5. Continued

Kudoh, et al 2002	NR	NR	NR	NR	NR	NR	Depressed + Ketamine Group: 14% Depressed + No Ketamine Group: 23% Ketamine Group: 0 (*P value:* NR)
Jiang, et al 2016	NR	ketamine: 20% Placebo: 22% (*P value:* 0.822)	NR	NR	NR	ketamine: 13% Placebo: 13% (*P value:* 1)	NR
Liu, et al 2025	*Low dose* Esketamine: 13.3%, *High dose* Esketamine: 13.3% Placebo:9.3% (*P value* < 0.05)	*Low dose* Esketamine: 4.0% *High dose* Esketamine: 4.0% Placebo: 13.3% (*P value* < 0.05)	NR	NR	*Low dose* Esketamine: 0 *High dose* Esketamine: 0 Placebo: 0 (*P value*: NR)	*Low dose* Esketamine: 2.7% *High dose* Esketamine: 2.7 % Placebo: 0% (*P value* < 0.05)	NR
Cai, et al 2024	Esketamine: 11.9% Control: 7.0% (*P value:*0.684)	Esketamine: 14.3% Control: 16.3% (*P value:* 0.799)	Esketamine: 4.8% Control: 7.0% (*P value:* 0.664)	Esketamine:14.3% Control: 11.9% (*P value:* 0.715)	NR	Esketamine: 14.3% Control: 11.9 (*P value*: 0.715)	NR

NR: Not Reported, P-value: probability value.

Discussion

This systematic review examined the effectiveness of ketamine and esketamine in reducing postoperative anxiety and depressive symptoms in adult and older patients undergoing orthopaedic procedures. Perioperative ketamine or esketamine may be associated with lower postoperative mood-symptom scores in selected orthopaedic populations, particularly during early postoperative recovery. However, the certainty of this finding is limited by substantial heterogeneity in procedure type, baseline patient characteristics, intervention formulation, dose, route of administration, comparator, outcome scale, and follow-up duration. The evidence for anxiety was more limited than that for depressive symptoms, as anxiety was assessed in only five of the nine included trials.

Ketamine and esketamine were administered using various regimens across the included studies. Our findings suggest that continuous postoperative administration may be more effective than a single perioperative dose in reducing mood symptoms, particularly during the early postoperative period. In contrast, the available evidence indicates that a single preoperative dose may not be sufficient to reduce postoperative anxiety.[17]

Previous studies have evaluated the efficacy of ketamine and esketamine for depressive symptoms across various surgical settings, including elective caesarean delivery and breast cancer surgery. Li et al.[28] published a systematic review on the effects of ketamine and esketamine in preventing postpartum depression after caesarean delivery. They reported that the incidence of postpartum depression was significantly lower in the ketamine or esketamine groups than in the control groups at 1 and 4 weeks postoperatively. Sun et al.[29] conducted a systematic review evaluating the efficacy and safety of perioperative ketamine and esketamine for postoperative pain and depression after breast cancer surgery. They reported that ketamine and esketamine were associated with improvements in postoperative depressive symptoms. In a randomized controlled trial, intravenous esketamine reduced postoperative sleep disturbance, anxiety, and depression in older patients undergoing laparoscopic abdominal surgery.[30] Lower depression and anxiety scores were reported on postoperative days 1 and 3. Another randomized controlled trial reported that a subanaesthetic dose of S-ketamine reduced postoperative pain and anxiety in patients undergoing breast and thyroid surgery; lower anxiety scores were observed on postoperative days 1, 2, and 3.[31] Overall, our findings are consistent with previous evidence suggesting a potential beneficial effect of ketamine and esketamine on postoperative anxiety and depressive symptoms across surgical populations.

Ketamine may also reduce postoperative pain. Mediation through pain relief or improved rehabilitation is plausible but remains unproven. Wang et al.[32] conducted a systematic review on the role of ketamine in pain management after caesarean section and reported that ketamine reduced postpartum pain. Khashan et al.[33] conducted a randomized controlled trial examining the effects of pre-emptive intra-articular morphine and ketamine on pain after arthroscopic rotator cuff repair and reported pain reduction at 2 weeks postoperatively.

These findings suggest that ketamine or esketamine may be considered as part of multimodal perioperative strategies in selected orthopaedic patients. However, standardized dosing protocols and longer follow-up are needed before firm recommendations can be incorporated into enhanced

recovery after surgery (ERAS) pathways. Such an approach may improve patient adherence to early rehabilitation and support better overall recovery outcomes.

Strengths and Limitations

This review provides valuable insight into the current evidence on the management of postoperative anxiety and depression. To our knowledge, this is the first systematic review to evaluate the effects of NMDA receptor antagonists on postoperative anxiety and depressive symptoms, with a specific focus on orthopaedic procedures. This review has several limitations. First, there was substantial heterogeneity in surgical procedures, ranging from total joint arthroplasty to amputation, as well as in anaesthetic techniques, including general and spinal anaesthesia. Second, few studies assessed the efficacy or safety of ketamine and esketamine during longer-term postoperative follow-up. In addition, variation in dosing regimens and timing of administration made it difficult to determine the optimal equipotent dose and timing.

Conclusion

Current randomized evidence suggests that perioperative ketamine and esketamine may reduce early postoperative mood symptoms in orthopaedic patients, with a more consistent signal for depressive symptoms than for anxiety. However, heterogeneity in surgical procedures, dosing regimens, timing of administration, and follow-up duration limits the certainty of the evidence. No consistent increase in reported adverse events was observed, although safety reporting was incomplete. Future research should focus on standardized dosing protocols and longer follow-up periods.

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