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REVIEW: Melatonin for the Management of Acute Postoperative Pain and Prevention of Persistent Postsurgical Pain: Mechanisms and Clinical Evidence

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ABSTRACT

Melatonin has attracted interest as a perioperative adjunct because of its potential antinociceptive, anxiolytic, sleep-regulating, and anti-inflammatory effects. Acute analgesia and prevention of persistent postsurgical pain represent distinct therapeutic objectives. To critically examine the mechanisms and clinical evidence supporting perioperative melatonin, emphasizing the distinction between early symptom relief and durable prevention.

A focused narrative synthesis was conducted using targeted retrieval of PubMed records, accessible publisher reports, and relevant reference lists. Experimental investigations, selected randomized clinical trials, and systematic reviews were examined. Evidence was organized by mechanism, surgical setting, regimen, and follow-up duration. No new meta-analysis or formal certainty assessment was performed.

Experimental evidence supports biological plausibility, while clinical findings vary across procedures. Evidence syntheses suggest possible early pain reduction, but heterogeneity, methodological limitations, and uncertain opioid-sparing effects restrict confidence. A 2022 randomized lumbar disc surgery trial reported lower postoperative pain after preoperative oral melatonin, without establishing a clear dose-response relationship or long-term prevention. Neutral clinical studies and recovery-related trade-offs qualify favorable findings. Limited longer-term observations do not establish a reproducible preventive effect on clinically defined persistent postsurgical pain.

Melatonin remains a candidate adjunct for acute postoperative analgesia. The evidence evaluated does not support routine administration specifically to prevent persistent postsurgical pain. Procedure-specific trials should assess pain, rescue analgesia, function, and safety, with prespecified follow-up beyond three months for preventive claims.

Introduction

Acute postoperative analgesia and prevention of persistent pain are related but distinct goals. The ICD-11 framework defines chronic postsurgical pain as pain that develops or increases after surgery and persists beyond healing for at least three months (1). Improvement during the first postoperative day therefore cannot establish prevention of this condition. The distinction is especially important when surgery is undertaken to relieve pre-existing pain.

Nerve injury and the association between acute pain severity and later persistent pain have informed preventive research (2). However, association does not establish that every intervention reducing early symptoms will change long-term outcomes. Prevention

must be tested directly, with baseline symptoms and alternative causes of pain appropriately considered.

Melatonin is of interest because its potential effects extend beyond nociception to anxiety and sleep. Perioperative studies have assessed several dimensions of recovery (3). This breadth creates an interpretive challenge: lower pain scores may reflect direct antinociception, altered anxiety, changes in sleep, or interacting effects. Moreover, a favorable pooled result does not necessarily indicate a clinically important benefit across operations (4). This review examines mechanistic evidence, representative trials, and broader syntheses, including the 2022 lumbar disc surgery study involving Sobhani.

Material and Methods

This focused narrative review used targeted web-based retrieval on September 10, 2026, with combinations of melatonin, postoperative pain, perioperative analgesia, randomized trial, lumbar disc surgery, and persistent postsurgical pain. PubMed records, accessible publisher reports, and reference lists were consulted. Selection emphasized mechanisms, acute analgesia, dose interpretation, safety, and longer-term outcomes. Primary reports informed study-specific findings; systematic reviews supplied broader context, including neutral results.

The process was not an exhaustive database search. No registered protocol, duplicate screening, independent risk-of-bias assessment, or new quantitative synthesis was undertaken. Numerical results were included only when available in the consulted report or abstract. Full-text access was incomplete for some studies; a longer-term orthognathic finding identified through secondary citation is distinguished below. The synthesis does not claim identification of every eligible study.

Pharmacology and Proposed Mechanisms

Circadian Timing and Pharmacokinetics

Melatonin conveys temporal information about the light–dark cycle, making administration time relevant to exogenous treatment (5). Identical doses given at different times should not automatically be considered equivalent interventions. Harpsøe and colleagues reviewed 22 pharmacokinetic studies and described substantial exposure variability. Approximate values for immediate-release oral melatonin included a time to peak concentration of 50 minutes, an elimination half-life of 45 minutes, and oral bioavailability of 15% (6). These observations help explain preoperative dosing schedules but do not establish an optimal analgesic regimen.

MT1/MT2 Receptors and Endogenous Opioid Pathways

Mechanistic literature describes spinal and supraspinal effects involving MT1/MT2 receptors, inhibitory neurotransmission, potassium channels, and inflammatory mediators (7). Shavali and colleagues demonstrated melatonin-associated β-endorphin release from cultured mouse pituitary cells, supporting a proposed indirect interaction with endogenous opioid signaling (8). This cellular finding does not establish conventional opioid-receptor agonism or prove the mechanism responsible for postoperative analgesia in humans.

Pain reporting integrates sensory input, attention, emotional state, and expectations. A clinical pain score therefore cannot identify the responsible pathway. Mechanistic claims require complementary measures and a plausible temporal relationship between exposure, pathway activity, and clinical response.

Inflammatory and Oxidative Pathways

Esposito and colleagues studied inflammation-associated thermal hyperalgesia in rats. Intraperitoneal melatonin attenuated hyperalgesia and, at the higher tested dose, reduced tissue injury and protein nitration while affecting cyclooxygenase-2 and inducible nitric oxide synthase expression. The investigators examined mitogen-activated protein kinase and nuclear factor-κB pathways and implicated inhibition of superoxide-driven poly(ADP-ribose) polymerase activation (9).

The translational limitation is substantial: experimentally induced inflammation and high parenteral animal doses differ from surgical injury treated with oral melatonin. Biomarker changes should therefore complement patient-centered outcomes rather than substitute for them. A reduction in a selected inflammatory marker without improvement in pain or function would not establish clinical utility.

Experimental Human Antinociception

Stefani and colleagues randomized 61 healthy adults to placebo or sublingual melatonin at 0.05, 0.15, or 0.25 mg/kg. The two higher doses improved measures of heat and pressure pain sensitivity; sedation also increased. Assessments were performed before treatment and 30 minutes afterward (10). The findings support short-term biological activity, but laboratory thresholds cannot establish effectiveness during mobilization or the duration of benefit after surgical injury.

Sleep and Anxiety

Bjurström and Irwin reviewed 14 perioperative sleep-promotion studies involving 921 participants, including nine melatonin studies. Three melatonin studies reported at least 30% pain reduction with lower opioid consumption during postoperative days 1–2, whereas four found no significant pain effect. Only one of the 14 studies had a low risk of bias, and objective sleep assessment was uncommon (11). Sleep promotion is therefore a possible contributor rather than a proven mediator of analgesia.

Yousaf and colleagues found more consistent evidence for preoperative anxiolysis than for analgesia: five studies reported lower pain or opioid requirements, while three produced conflicting analgesic findings (12). Future mediation studies should distinguish restorative sleep from sedation and assess anxiety separately. Concurrent improvement in sleep and pain alone does not establish causality.

Table 1. Proposed mechanisms and limits of translation

Mechanism	Evidence	Interpretive limit
MT1/MT2 and inhibitory signaling	Experimental and mechanistic literature (7)	Postoperative mediation remains unproven.
Endogenous opioid signaling	β-Endorphin release in cultured cells (8)	Cellular activity does not establish a surgical mechanism.
Inflammatory modulation	Animal hyperalgesia study (9)	Dose, route, and injury model differ from clinical care.
Circadian regulation	Physiological evidence (5)	Temporal activity does not establish analgesic effectiveness.
Sleep and anxiety effects	Perioperative syntheses (11, 12)	Anxiolysis, sleep, sedation, and analgesia require separate assessment.

Clinical Evidence for Acute Postoperative Pain

Hysterectomy and Prostatectomy

Caumo and colleagues compared preoperative melatonin, clonidine, and placebo in a double-blind randomized abdominal hysterectomy study, reporting improvements in postoperative pain and morphine consumption (13). The simultaneous evaluation of anxiety and pain is clinically relevant, but it does not determine whether anxiolysis mediated analgesia. Generalization requires attention to the operation and background analgesic regimen.

Borazan and colleagues randomized 52 prostatectomy patients to placebo or oral melatonin 6 mg on the preceding night and one hour before surgery. Melatonin reduced pain and tramadol consumption and improved reported sleep quality, but extubation and anesthetic recovery took longer, and early sedation scores were higher (14). Reduced rescue medication therefore should be interpreted alongside alertness and functional recovery.

Hernia and Hand Surgery

Lotfy and Ayaad studied 140 inguinal hernia patients receiving placebo, melatonin 3 mg,

melatonin 6 mg, or midazolam. The 6-mg group had more favorable pain and rescue-analgesia outcomes during eight-hour follow-up; preoperative anxiety was the primary outcome (15). These results support further dose comparison but do not establish a universal analgesic dose.

Mowafi and Ismail randomized 40 hand-surgery patients receiving intravenous regional anesthesia to oral melatonin 10 mg or placebo. Melatonin improved tourniquet tolerance, delayed the first postoperative analgesic request, and reduced postoperative diclofenac consumption (16). This broadens the acute evidence while remaining specific to the studied anesthetic context.

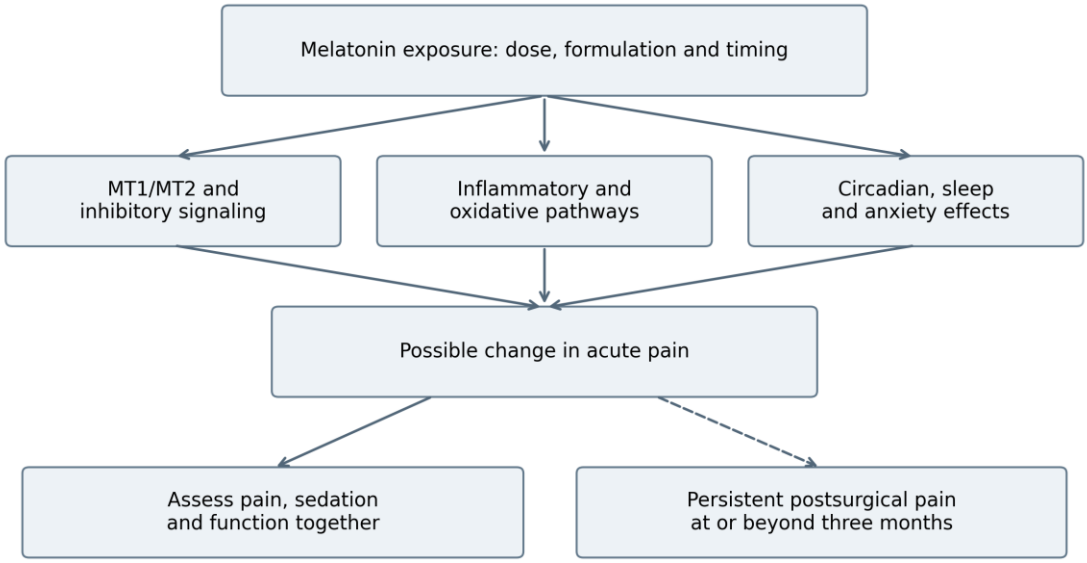

Figure 1. Proposed pathways linking melatonin exposure to postoperative outcomes. This conceptual synthesis does not establish causal mediation. The dashed arrow indicates that prevention of persistent postsurgical pain requires direct long-term testing (2, 5, 7, 8, 9).

Lumbar Surgery and the 2022 Trial

Gholipour Baradari and colleagues, including Samira Sobhani, randomized 80 elective mini-open microdiscectomy patients in Sari, Iran, to oral melatonin 3, 5, or 10 mg or placebo one hour before surgery. Pain was assessed through 24 hours. All melatonin groups had lower pain than placebo, while differences among doses were not significant. Overall opioid consumption differed between groups. No serious adverse effects were reported (17).

Although the authors favored 5 mg, the findings do not establish a clear analgesic dose-response relationship; nonsignificant between-dose comparisons do not prove equivalence. The follow-up supports an acute signal rather than prevention of persistent pain. A future long-term lumbar study would also need to distinguish baseline radicular and back symptoms from newly developed or worsened surgical pain.

Javaherforooshzadeh and colleagues compared melatonin 6 mg, gabapentin 600 mg, and placebo in 90 lumbar-surgery patients. Both active groups had favorable acute outcomes versus placebo. Figure 2 displays published time-to-rescue means from this study (18). This evidence complements the later trial but does not establish equivalence between active treatments or long-term prevention.

Neutral Findings, Inconsistent Evidence, and Evidence Syntheses

Neutral Trials

Gögenur and colleagues randomized 121 laparoscopic cholecystectomy patients to melatonin 5 mg or placebo for three postoperative nights. Sleep latency improved

on the first night, but the remaining measured outcomes did not differ significantly (19). In a separate trial involving 41 cholecystectomy patients, Kücükakin and colleagues found no significant improvement in oxidative-stress variables or C-reactive protein after melatonin (20). Clinical sleep and antioxidant effects therefore cannot be assumed from biological plausibility.

Table 2. Selected randomized trials with favorable acute findings

Study	Setting and sample	Regimen	Main qualification
Caumo et al. (13)	Abdominal hysterectomy	Preoperative melatonin; clonidine and placebo comparators	Acute outcomes in one procedure.
Borazan et al. (14)	Prostatectomy; n=52	6 mg on preceding night and one hour before surgery	Recovery and sedation trade-offs.
Lotfy and Ayaad (15)	Hernia repair; n=140	3 or 6 mg; midazolam and placebo comparators	Anxiety was the primary outcome.
Mowafi and Ismail (16)	Hand surgery; n=40	10 mg orally versus placebo	Intravenous regional anesthesia context.
Gholipour Baradari et al. (17)	Lumbar disc surgery; n=80	3, 5, or 10 mg orally versus placebo	24-hour follow-up; no clear dose response.
Javaherforooshzadeh et al. (18)	Lumbar surgery; n=90	6 mg melatonin, 600 mg gabapentin, or placebo	Acute comparison; no preventive conclusion.

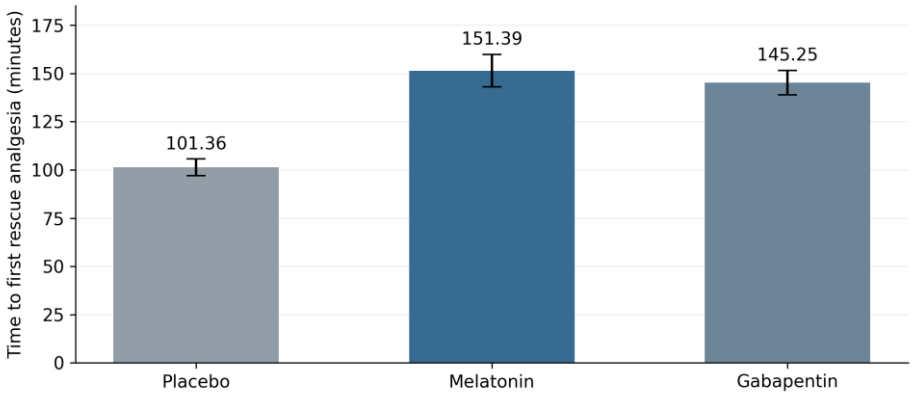

Figure 2. Time to first rescue analgesia after lumbar surgery, redrawn from Javaherforooshzadeh et al. (18). Bars show means; error bars show standard deviations (not confidence intervals). Placebo: 101.36 ± 4.26 minutes; melatonin: 151.39 ± 8.42; gabapentin: 145.25 ± 6.35; n=30 per group. This is a single-trial descriptive graph, not a meta-analysis, and does not establish superiority of melatonin over gabapentin.

Systematic Reviews and Meta-Analyses

Andersen and colleagues included 24 trials with 1,794 participants across multiple perioperative outcomes. Their pain analysis favored melatonin, but extreme heterogeneity (I^2=94%) made the pooled magnitude unreliable (3). The overall participant count is not the number contributing specifically to the pain analysis.

Wang and colleagues analyzed 15 studies involving 1,102 patients. The pooled 24-hour visual analogue pain score favored melatonin, with a mean difference of −0.86 (95% confidence interval, −1.38 to −0.34). Trial sequential analysis supported the pain finding but left the opioid analysis inconclusive. The authors emphasized low-quality evidence and uncertainty about clinical usefulness (4). A pooled mean difference should not be interpreted as a consistent benefit for every procedure.

Saleh and colleagues reviewed eight randomized clinical articles in joint arthroplasty and found variable results across pain, sleep, and delirium outcomes, concluding that robust clinical evidence was lacking (21). Tsukinaga and colleagues analyzed eight studies involving 516 participants for postoperative sleep quality. The pooled difference of −0.75 mm (95%

confidence interval, −4.86 to 3.35 mm) did not demonstrate improvement over placebo (22). Thus, postoperative sleep restoration remains an uncertain explanation for analgesia.

Table 3. Evidence that qualifies favorable acute findings

Source	Outcome or design	Interpretation
Gögenur et al. (19)	Sleep and discomfort after cholecystectomy	First-night sleep latency improved; other measured outcomes did not.
Kücükakin et al. (20)	Oxidative and inflammatory variables	No significant between-group differences.
Andersen et al. (3)	Perioperative systematic review	Extreme heterogeneity limits the pooled pain estimate.
Wang et al. (4)	Meta-analysis and trial sequential analysis	Pain signal; opioid result remains uncertain.
Saleh et al. (21)	Arthroplasty systematic review	Variable outcomes; robust evidence lacking.
Tsukinaga et al. (22)	Postoperative sleep meta-analysis	No demonstrated improvement in VAS sleep quality.

Prevention of Persistent Postsurgical Pain

A preventive intervention must demonstrate an effect on an appropriately defined long-term outcome. The ICD-11 framework requires duration and a relationship to surgery (1). The presence of any pain at follow-up is insufficient. Lower mean pain, improved sensory recovery, and prevention of a new chronic pain condition should remain separate endpoints.

Longer-term literature should not be overlooked. Lotfy and Ayaad cite a triple-blind orthognathic trial by Lee and Curtin describing sensory and pain-related improvement at three months (15, 23). This finding was identified through the secondary account; the original results were not directly available for appraisal here. Numerical estimates are therefore not reproduced, and the trial is not assumed to have measured ICD-11-defined persistent-pain incidence.

It would be inaccurate to state that no longer-term research exists. Nevertheless, the evaluated evidence does not establish a reproducible preventive effect across operations. Acute analgesic trials cannot supply the missing long-term inference, and correlated early and late outcomes do not establish a causal treatment pathway.

Baseline assessment is essential when surgery treats an existing painful disorder. Following lumbar surgery, ongoing symptoms may represent unresolved preoperative pain, newly developed surgical pain, or another condition. Incidence should be accompanied by pain intensity and interference with activity, because preventing mild symptoms and preventing disabling pain have different clinical implications.

A brief perioperative exposure could conceivably influence processes that continue after administration ends. Demonstrating this possibility requires a temporal chain of evidence. Biomarkers, sleep measures, and sensory testing can help explain a clinical effect, but direct assessment of persistent pain must remain central.

Table 4. Outcomes and permissible conclusions

Outcome	What a favorable result supports	What it does not establish
Early pain intensity	Acute benefit at the measured time	Prevention of persistent pain.
Rescue medication use	Possible medication sparing under the study protocol	Better function without corresponding assessment.
Time to first rescue	Delayed need for additional analgesia	Protection over subsequent months.
Sleep latency	Improved sleep initiation	Improved overall sleep quality or analgesia.
Biomarkers	Activity in a measured biological pathway	Clinically meaningful pain relief.
Pain at ≥3 months	Possible durable benefit	Prevention unless surgery-related pain is appropriately defined.
Pain interference	Patient-centered functional information	A specific biological mechanism.

Dose, Formulation, and Safety

Dose and Timing

The reviewed regimens differ in route, timing, and exposure. Single oral doses, repeated preoperative doses, and weight-based sublingual administration should not be considered interchangeable (6, 10, 14, 17). A favorable dose comparison in one procedure cannot resolve conflicting findings in another. Trials should specify formulation, administration time, operative timing, and co-interventions.

Formulation and Product Quality

Erland and Saxena identified substantial disagreement between labeled and measured melatonin content in commercial supplements, with serotonin detected in some samples (24). This supports use of a characterized study product; it does not imply that all preparations are unreliable. Evidence obtained with one formulation cannot automatically validate every commercially available product.

Safety and Tolerability

A safety review by Andersen and colleagues described generally favorable short-term tolerability, with reported adverse effects including sleepiness, dizziness, headache, and nausea (25). Such evidence should be considered alongside procedure-specific recovery outcomes. Small short-term studies cannot reliably exclude uncommon adverse effects or establish safety for all patient groups.

A useful regimen should improve recovery without an unacceptable burden of sedation. Trials should document adverse-event denominators, withdrawals, concomitant sedatives, and readiness for mobilization. Analgesic consumption, pain, alertness, and function should be interpreted together rather than allowing one favorable endpoint to determine the overall conclusion.

Clinical Interpretation

Melatonin has a possible adjunctive role deserving better-defined testing, while routine administration specifically to prevent persistent postsurgical pain is not supported by this synthesis. A placebo-controlled study should establish incremental benefit on top of standardized analgesia; it does not demonstrate that melatonin can replace another treatment.

Opioid sparing is most meaningful when pain control is maintained and patients function as well or better. Equal rescue access, clear administration thresholds, and standardized reporting are essential. Pain during activity should be distinguished from resting pain, since a small resting-score difference may not improve mobilization. Satisfaction, sleep, and discharge readiness can complement but should not obscure a prespecified primary outcome.

Research Priorities and Limitations

Dose finding and definitive prevention may require separate trials. Initial studies can assess exposure, early analgesia, and sedation within one procedure. Subsequent trials can test durable benefit using clinically meaningful effect sizes and plans for attrition. Multicenter recruitment would strengthen generalizability; subgroup analyses of baseline pain or sleep disturbance should be prespecified.

Table 5. Priorities for future randomized trials

Domain	Recommended feature
Population	Define surgery and document baseline pain, function, sleep, and analgesic exposure.
Intervention	Characterize formulation, dose, timing, and duration.
Background care	Standardize analgesia and access to rescue medication.
Acute endpoints	Assess activity-related pain, rescue use, sedation, and recovery.
Prevention	Prespecify new or worsened surgery-related pain at or beyond three months.
Durability	Consider follow-up at six and twelve months.
Analysis	Report absolute effects and confidence intervals; address missing data and multiple comparisons.

Limitations

This narrative review uses selected accessible evidence and is vulnerable to incomplete retrieval and selection bias. Some descriptions rely on abstracts; the orthognathic longer-term finding is included through secondary citation. Assessments of heterogeneity and certainty belong to the cited reviews and were not independently recalculated. Overlapping trial populations prevent simple addition of sample sizes across reviews. These limitations support cautious interpretation and the value of an updated systematic synthesis with direct full-text extraction, especially for persistent-pain outcomes.

Conclusion

Melatonin has a biologically plausible role in perioperative pain modulation and has produced favorable acute findings in several randomized trials, including the 2022 lumbar disc surgery study involving Sobhani. Inconsistent results, uncertainty about dose and opioid sparing, and recovery-related trade-offs limit general recommendations. Available longer-term observations do not establish a reproducible preventive effect on clinically defined persistent postsurgical pain. Future studies should connect mechanistic hypotheses to meaningful patient outcomes and directly test durable prevention.

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Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria

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Use of artificial intelligence

ChatGPT assisted literature retrieval, synthesis, manuscript drafting, and preparation of tables and figures. AI assistance does not replace independent author verification of the scientific content, numerical data, and references. Responsibility for the submitted manuscript rests with the human authors.

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