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Melatonin and its Application in Dentoalveolar Surgery: A Review of Literature

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Abstract: This Review of Literature examines the role of melatonin in pain and anxiety management following impacted mandibular third molar surgery. Impacted third molar surgeries are often associated with unpleasant post-operative sequalae such as pain and anxiety. The mainstay of conventional pharmacological management includes NSAIDs, opioids, and benzodiazepines which carry certain side-effects. Melatonin, an endogenous hormone with antioxidant, anti-inflammatory, and neuromodulatory properties, has been proposed as a promising and safe perioperative adjuvant. The aim of this literature review is to evaluate the efficacy of Melatonin on postoperative pain and preoperative anxiety, gather current evidence on its pharmacological mechanisms and to compare it against existing pharmacological agents

Keywords: *Melatonin, Analgesia, Anxiolytic, Third Molar Surgery.*

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I. INTRODUCTION

Impacted mandibular third molar extraction commonly causes significant postoperative pain and anxiety. Analgesic use and postoperative pain have been found to be strongly predicted by anxiety [1]. It has been proposed that anxiety reduces the threshold for pain [2], makes it easier to overestimate the severity of pain [3], and activates the entorhinal cortex of the hippocampus [4]. Standard analgesics (NSAIDs, opioids) and anxiolytics (benzodiazepines) effectively reduce these symptoms but carry risks (GI ulceration, respiratory depression, sedation, dependence) [5]. Melatonin a pineal hormone (N-acetyl-5-methoxytryptamine) has attracted attention as a novel adjunct for perioperative comfort. Beyond its chronobiotic role, melatonin exerts antioxidant, anti-inflammatory, and neuroactive effects [6]. Importantly, melatonin is relatively safe and non-addictive [7]. It benefits oral surgery by reducing preoperative anxiety and postoperative pain, and improves healing and implant stability [8]. This review critically examines melatonin's pharmacology, analgesic and anxiolytic mechanisms, and clinical evidence focusing on dental surgery and compares it with standard agents.

II. PHARMACOLOGY OF MELATONIN

Melatonin is a small, lipophilic indoleamine readily absorbed orally (though bioavailability varies widely, ~1–74%, due to first-pass metabolism and formulation). Peak serum levels occur ~20–60 minutes after ingestion. It is ~60–80% albumin-bound.7 Hepatic metabolism (primarily CYP1A2, with minor CYP2C19) converts ~90% of melatonin to 6-hydroxymelatonin, which is sulfated or glucuronidated and excreted in urine. Melatonin's elimination half-life is short (roughly 0.5–2 h for immediate-release forms; extended-release preparations have longer apparent half-lives) [9]. Because CYP1A2 metabolizes melatonin, potent CYP1A2 inhibitors (e.g. fluvoxamine) can markedly raise melatonin levels [7].

Melatonin signals primarily via two high-affinity G-protein-coupled receptors, MT1 and MT2, expressed in the brain and periphery. MT1 and MT2 are coupled to inhibitory G proteins; their activation inhibits adenylyl cyclase (lowering cAMP) and modulates other second-messenger pathways [8]. MT1 is widely distributed (suprachiasmatic nucleus, hippocampus, retina, cardiovascular tissues, immune cells), while MT2 is found in the CNS (especially in circadian

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centers) and various organs. Through MT1/MT2 activation and non-receptor actions (e.g. free-radical scavenging), melatonin influences sleep-wake cycles, immune function, and pain and anxiety pathways [7].

A. Analgesic Mechanisms

Melatonin's analgesic effects are multifactorial. First, it dampens surgery-induced inflammation: melatonin is a potent antioxidant and free-radical scavenger, reducing reactive oxygen/nitrogen species after tissue injury [5]. It also downregulates pro-inflammatory cytokines (e.g. TNF-α, IL-6) and prostaglandin production, blunting nociceptor sensitization. By tempering the inflammatory milieu, melatonin indirectly reduces peripheral and central sensitization of pain pathways.

Second, melatonin directly modulates nociceptive neurotransmission through multiple receptor systems. Activation of MT1/MT2 receptors in the spinal cord and brain can inhibit pain signaling. For example, experimental evidence shows melatonin acts via MT1/MT2 at the dorsal horn of the spinal cord, where it interacts with opioid, substance P, and NMDA receptors [10]. Indeed, melatonin's analgesic actions can be blocked by opioid antagonists (e.g. naloxone) or benzodiazepine antagonists, implying it engages endogenous opioid and GABAergic systems [11]. Melatonin also promotes release of endogenous β-endorphins and enhances GABAergic tone, further contributing to analgesia. In essence, melatonin appears to boost the body's intrinsic pain-control mechanisms without the severe side effects of exogenous opioids [5].

➢ *Key Analgesic Actions:*

- Anti-inflammatory/antioxidant: Scavenges free radicals, lowers cytokine and prostaglandin levels after surgery, reducing nociceptor sensitization (dampening hyperalgesia).
- Receptor modulation: Acts via MT1/MT2 in the spinal cord and brain; interacts with opioid, GABA, substance P, and NMDA receptor pathways. These interactions lead to analgesia [5].
- Opioidergic/GABAergic enhancement: Melatonin increases β-endorphins and potentiates GABA-A activity, which parallels mechanisms of common analgesics and anxiolytics (e.g. benzodiazepines, opioids) but with less risk [12].

B. Anxiolytic Mechanisms

Melatonin also exerts calming, anti-anxiety effects through central neuromodulation. It facilitates inhibitory GABAergic transmission: melatonin enhances GABA_A receptor activity, causing neuronal hyperpolarization and reducing the firing of anxiety-related neurons. This mechanism resembles benzodiazepines' action, but melatonin does so without profound sedation or addictive potential [13]. Simultaneously, melatonin stabilizes the stress axis. By acting on MT1/MT2 receptors in the suprachiasmatic nucleus and hypothalamus, melatonin helps normalize circadian and HPA-axis rhythms [14][15]. It tends to suppress excessive HPA activity and cortisol release during stress, attenuating the psychophysiological stress response to surgery. As a result, melatonin reduces preoperative fear and agitation. Importantly, this anxiolysis does not impair cognition: trials report that melatonin lowers anxiety scores without worsening psychomotor or memory tests [13].

➢ *Key Anxiolytic Actions:*

- GABA potentiation: Enhances GABA-A-mediated inhibition in the CNS, similar to benzodiazepines but with milder side effects [5][13].
- HPA-axis modulation: Stabilizes circadian and stress hormone rhythms, reducing cortisol spikes that worsen anxiety and stress-induced hyperalgesia [15][16].
- Sedative synergy: Melatonin promotes sleep and relaxation (via MT1/MT2 in sleep centers) without causing deep sedation; it increases sleep readiness and may improve post-op rest, aiding recovery.

C. Pharmacokinetics and Dosing Considerations

Melatonin's short half-life and variable absorption mean timing and dose are critical. Most dental/operative studies use immediate-release oral melatonin 30–60 minutes pre-procedure. Typical anxiolytic doses range from 3–10 mg; analgesic effects may require higher doses (up to 10–50 mg in some pain studies) [7]. However, trial results vary: for instance, a recent third-molar study used 15 mg sublingual with no benefit, while other surgeries have used 3–6 mg [17]. Optimal dosing remains undefined, in part due to supplement content variability (actual pill content can vary –83% to +478% of label) and individual factors (age, weight, baseline melatonin). Higher doses and repeated dosing regimens may enhance effects but need safety evaluation [18].

III. CLINICAL EVIDENCE IN DENTAL AND SURGICAL SETTINGS

A. Third-Molar Surgery Studies:

Recent randomized trials in wisdom-tooth removal yield mixed findings. Torun et al. (2019) compared 0.4 mg/kg oral melatonin versus midazolam and placebo in third-molar patients. Melatonin significantly reduced anxiety versus placebo, though less than midazolam. Importantly, melatonin did not impair cognitive tests (DSST, TMT) [5]. In contrast, a 2025 trial (Ruppel et al.) found a single 15 mg dose of sublingual melatonin failed to reduce intra- or postoperative pain, swelling or trismus after wisdom-tooth extraction (no difference vs placebo). The authors concluded that "melatonin may have limited effectiveness" for oral-surgery discomfort [17]. Thus, for dental surgery melatonin appears to provide mild anxiolysis but unproven analgesia.

Lotfy and Ayaad (2021) examined melatonin vs midazolam in premedication. In their randomized trial of 140 patients, preoperative melatonin (3 or 6 mg) dose-dependently reduced anxiety and postoperative pain (ΔASSQ and pain scores) [19]. The trial's CONSORT diagram shows anxiety reductions (ΔASSQ) of ~33.4% for 3 mg melatonin and ~45.8% for 6 mg, versus only ~5.1% for placebo (and ~36.4% for midazolam). The 6 mg dose produced significantly greater anxiolysis and lower postoperative pain scores and analgesic requirements than 3 mg or placebo [19]. These findings suggest that adequately dosed melatonin can meaningfully

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reduce perioperative anxiety (nearly matching midazolam at 6 mg) and may have an opioid-sparing analgesic effect. A systematic review by Perdo Henrique Chaves de Oliveira highlighted melatonin's efficacy in improving inflammatory response and anxiety during dental procedures, with mostly positive clinical effects reported in 25 RCTs [20].

Refahee et al. (2023) conducted a double-blind trial in 38 patients, showing that 3 mg melatonin gel applied to the extraction socket after impacted mandibular third-molar surgery significantly reduced postoperative pain at all follow-ups ($P < 0.001$), decreased swelling on day 3 ($P = 0.031$), and improved mouth opening on day 1 ($P = 0.003$) compared with placebo. The authors attributed these benefits to melatonin's anti-inflammatory action. Although no difference in bone density was observed, melatonin demonstrated clear analgesic and anti-inflammatory effects in third-molar surgery [21].

Mukherjee et al. (2025) conducted an RCT in 78 patients showing that 6 mg oral melatonin or 20 minutes of music therapy before impacted third-molar extraction significantly reduced perioperative stress responses, with smaller increases in heart rate and blood pressure than controls ($p < 0.05$). Only melatonin lowered postoperative salivary cortisol (0.42→0.30 pmol/ml), whereas levels rose in the music and control groups, indicating a stronger delayed anxiolytic effect on the HPA axis. The authors concluded that melatonin premedication significantly reduces pre- and postoperative anxiety and indirectly improves pain outcomes in third-molar surgery [22].

B. Other Surgical Contexts

Outside dentistry, meta-analyses and trials generally support melatonin's anxiolytic efficacy but show inconsistent analgesia. A systematic review of perioperative melatonin (Yousaf et al., 2010) found that 9 of 10 trials showed significant preoperative anxiety reduction with melatonin vs placebo [6]. By contrast, its effects on postoperative pain were mixed: some studies showed opioid-sparing or lower pain scores, while others found no difference [6][23]. A 2020 meta-analysis of 30 trials confirmed this pattern: melatonin significantly eased chronic pain conditions, but evidence for acute post-op pain relief was weak. In that analysis, melatonin reduced acute pain scores overall, but when only high-quality trials were pooled, the effect on acute postoperative pain was non-significant. Thus, the consensus is that melatonin is effective for anxiety and chronic pain syndromes, but robust evidence for short-term surgical analgesia is lacking [23].

A prospective randomized control trial by Potturi A et.al found that perioperative use of 10 mg melatonin improved postoperative sensory nerve recovery and reduced pain after surgical treatment of mandibular fractures [24]. Janagarathinam and Rajasekar (2025) evaluated oral melatonin premedication in implant surgery patients and found that it stabilized intraoperative vitals (lower SBP, DBP, and HR) and significantly reduced postoperative pain compared with controls [25]. Sinha et al. (2025) evaluated 3 mg oral melatonin, nitrous oxide, and no sedation in 78 children (ages 5–8) undergoing routine extractions. Both melatonin and N_2O produced marked reductions in anxiety on the Venham scale and significant decreases in FLACC pain scores compared with controls ($p < 0.001$). Salivary cortisol also dropped significantly in both sedated groups ($p < 0.001$), with no reduction in controls. Sedation efficacy and recovery were equivalent between melatonin and N_2O. The authors concluded that oral melatonin effectively reduces anxiety and pain and is a viable alternative to nitrous oxide for pediatric dental procedures [26].

C. Comparative Analysis with Standard Agents

Melatonin's profile contrasts with that of NSAIDs and benzodiazepines. NSAIDs target cyclooxygenase pathways to reduce inflammation-driven pain; benzodiazepines potentiate GABA to relieve anxiety. Unlike NSAIDs, melatonin avoids GI and renal toxicity. Unlike opioids, melatonin does not depress respiration or cause dependence. Compared to benzodiazepines, melatonin causes minimal sedation and no habit-forming risk [7][13]. In practice, melatonin is seldom a sole replacement for standard drugs; rather, it is investigated as an adjunct. Several trials report that melatonin premedication can reduce required opioid or benzodiazepine doses while maintaining comfort. For example, Lotfy & Ayaad noted lower postoperative analgesic consumption with 6 mg melatonin than with midazolam or placebo [19]. Thus, melatonin may allow opioid/benzodiazepine "sparing," diminishing side effects of conventional therapy.

➢ *Comparison Points:*

- NSAIDs/opioids: Melatonin does not inhibit COX enzymes but blunts inflammation via antioxidation and cytokine suppression. It lacks GI bleeding or respiratory depression. As an analgesic, it is milder than NSAIDs/opioids; meta-analyses find it could help chronic pain, but adds little to acute surgical pain relief [23].
- Benzodiazepines: Both melatonin and benzos enhance GABAergic tone, but melatonin's anxiolysis is shorter-acting and less intense. A key advantage is safety: melatonin does not cause the next-day drowsiness or dependency risk of benzodiazepines. Clinical trials consistently note that melatonin reduces anxiety without impairing psychomotor performance [13].

D. Safety Profile and Drug Interactions

Melatonin is remarkably safe. Toxicology studies show extremely low acute toxicity (no LD50 established even at hundreds of mg/kg in animals). In humans, adverse effects are usually mild and transient. Reported side effects (at higher doses) include headache, nausea, dizziness, and occasional vivid dreams or next-day drowsiness [27]. Crucially, melatonin does not cause respiratory depression, has no known abuse liability, and patients do not develop tolerance. Long-term high-dose effects in children or pregnancy are not well-studied, so melatonin is generally avoided in these populations due to limited safety data [7].

Important drug interactions include: because melatonin is metabolized by CYP1A2, co-administration with strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) can raise melatonin levels and potentiate sedation. Conversely, CYP1A2 inducers (e.g. smoking) may reduce melatonin's effect [28]. Melatonin should be used cautiously with other CNS depressants: combining it with benzodiazepines,

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zolpidem, or barbiturates can cause excessive drowsiness [29]. There is also theoretical concern that melatonin's immune-stimulating properties (it can increase interleukin and interferon levels) might be contraindicated in certain autoimmune conditions or transplant patients, though clinical significance is unclear. Overall, melatonin's safety margin is wide, especially for short-term perioperative use, making it attractive as an adjunct [7].

E. Randomized Trials and Meta-Analyses

A growing number of RCTs and meta-analyses have evaluated melatonin around surgery. For dental extraction specifically, evidence is sparse. In addition to the Torun (2019) and Ruppel (2025) trials above, one small study found that 4 mg oral melatonin given one hour before third-molar surgery reduced anxiety and yielded less postoperative pain and analgesic use than placebo [19]. Outside dentistry, systematic reviews support melatonin's anxiolytic efficacy across adult surgeries. A comprehensive Cochrane-like review concluded that melatonin "offers an atoxic alternative to benzodiazepines" for perioperative anxiety in adults [6]. For analgesia, however, trial results are mixed. The 2020 meta-analysis by Oh et al. (1967 patients) found significant melatonin benefit for chronic pain conditions, but consistent with other reviews insufficient evidence that a single preoperative dose reduces acute postoperative pain [23].

Meta-analyses specifically in dental surgery are lacking, but one systematic review of melatonin in dentistry (Zahra et al., 2020) reported that most trials showed reduced preoperative anxiety, whereas outcomes on pain relief were inconsistent. Thus, the literature suggests melatonin reliably eases surgical anxiety, but its analgesic efficacy remains controversial [6][23]. Importantly, many trials note an opioid-sparing trend: several RCTs report that melatonin premedication leads to less postoperative opioid or NSAID consumption, even if pain scores are only modestly affected [17].

Sanidhya et al. (2025), in an F1000Research review, highlighted melatonin's anxiolytic and analgesic potential in dentistry, noting that it effectively reduces preoperative anxiety and postoperative pain in oral surgery. The authors emphasized melatonin as a promising alternative or adjunct to conventional sedatives and analgesics in dental practice [8].

The systematic review by Andersen LP et.al analysed 24 randomised controlled trials involving 1794 patients to evaluate peri-operative melatonin. Eight outcomes were assessed: anxiety, pain control, sleep quality, oxidative stress, emergence behaviour, anaesthetic consumption, steal induction, and safety. Melatonin significantly lowered pre-operative anxiety (SMD 0.88; 95% CI 0.44–1.33) and postoperative pain (SMD 1.06; 95% CI 0.23–1.88) compared with placebo. However, substantial heterogeneity (I^2 = 87% and 94%) limited the reliability of these effect sizes. Narrative findings indicated that melatonin may also enhance sleep quality and emergence behaviour, and potentially reduce oxidative stress and anaesthetic requirements [30].

IV. LIMITATIONS AND FUTURE DIRECTIONS

Current research on melatonin in oral surgery has limitations. Many studies use small samples, varied doses (3-15 mg), and inconsistent timing, making comparison difficult. The negative result in Ruppel et al. (15 mg, single dose) highlights dose-dependency and timing issues: melatonin's short half-life may limit benefit if not re-dosed or combined with other agents [19]. Existing trials often assess only single administrations rather than multi-night premedication, which some evidence suggests could be more effective. Furthermore, outcome measures differ (some use VAS pain, others questionnaires), and placebo controls vary (e.g. multivitamin vs water). Meta-analyses note this heterogeneity: analgesic results are especially inconsistent when only high-quality trials are pooled [6][19]

Fundamentally, more rigorous studies are needed. Future trials should be adequately powered and standardized. Key areas include optimizing dose and formulation (immediate vs prolonged release), scheduling (single pre-op dose vs repeated dosing), and patient selection (e.g. anxious vs non-anxious individuals). Comparative trials against standard sedatives (midazolam, dexmedetomidine) and analgesics (NSAIDs, acetaminophen) are needed. Longitudinal studies could evaluate melatonin's effects on sleep quality and functional recovery after dental surgery.

Finally, mechanistic studies in humans could clarify receptor-specific actions: for instance, does blocking MT2 alter melatonin's analgesia? Such work could guide development of selective melatonergic agents. In summary, while melatonin shows promise as a safe adjunct for perioperative care, high-quality evidence is still emerging; future research must address these gaps to define melatonin's role in dental anesthesia and analgesia [19].

V. CONCLUSION

Melatonin represents a novel, low-risk adjunct to improve comfort after third-molar extraction. It exerts analgesic effects via anti-inflammatory and neuromodulatory actions (involving MT1/MT2, opioid, GABA, and NMDA pathways) and reduces anxiety through GABAergic potentiation and stress-hormone modulation. Clinical trials confirm that melatonin premedication significantly alleviates perioperative anxiety, often with an opioid-sparing benefit, though its standalone analgesic efficacy is less clear. Compared to NSAIDs or benzodiazepines, melatonin's main advantages are safety and lack of sedation/dependence. However, heterogeneity in dosing and study designs means that optimal use is not yet defined. High-quality RCTs specifically in dental surgery are needed to establish evidence-based dosing, timing, and patient selection. Until then, melatonin should be viewed as a promising adjunct one that may modestly improve patient comfort with minimal downside, but not a panacea for post-extraction pain.

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