Available Online: 20 August 2026 DOI: 10.54254/3049-5458/2026.36248

Multimodal analgesic management for acute postoperative pain: drug selection, safety and clinical pathways

Linhang Qin

Clinical Medical College, North Sichuan Medical College, Nanchong, China

q15826141860@163.com

Abstract. Acute postoperative pain management in oral surgery remains challenged by several persistent issues: irrational opioid prescribing, insufficient analgesia from single-agent regimens, and the absence of standardized stratified care pathways tailored to different surgical procedures. Multimodal analgesia achieves superior pain relief while reducing opioid exposure by simultaneously targeting peripheral inflammation, nociceptive input, and central pain modulation. This narrative review systematically examines oral pain pathways and grading systems, first-line non-opioid analgesics, centrally acting analgesics, perioperative strategies for different surgical approaches, safety risks, and sustained-release drug delivery systems. Available clinical evidence supports Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used alone or in combination with acetaminophen as first-line therapy for pain following most dental extractions, root canal treatments, and implant surgeries. Opioid agents should be reserved for short-term use only in a small subset of patients with severe breakthrough pain who fail to respond to non-opioid treatments. Tramadol is not recommended as a routine alternative analgesic, and gabapentinoids are not advised for routine use in inflammatory postoperative oral pain. A 2026 systematic review focused on third molar surgery indicates that pregabalin may provide limited pain relief, but with high study heterogeneity and a significantly increased risk of adverse events, which does not support its routine use as a first-line agent. Liposomal and other sustained-release delivery systems can prolong local drug release, however, their real clinical benefits, tissue safety, cost-effectiveness, and standardized preparation in dental practice still require further high-quality clinical evidence. A multimodal clinical pathway based on preoperative risk screening, intraoperative long-acting local anesthesia, and postoperative step-up/step-down analgesic adjustment guided by pain and functional impairment grading can provide a reference for oral surgeons to develop short-course, opioid-sparing, and re-evaluable analgesic regimens.

Keywords: postoperative pain in the oral cavity, multimodal analgesia, non-opioid analgesics, central analgesics, slow-release drug delivery system

1. Introduction

Acute postoperative oral pain frequently impairs oral intake, sleep quality, mouth-opening exercises, and wound healing, and represents a common clinical issue that affects patients' healthcare experience and postoperative treatment compliance. Its intensity is determined not only by the degree of surgical tissue

Copyright: © 2026 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

damage, but also by multiple factors including preoperative baseline pain, inflammatory load, anxiety, sleep quality, and prior analgesic exposure. Two key challenges persist in current clinical practice. On one hand, although opioids are not first-line agents for common inflammatory dental pain, excessive prescribing, leftover drug diversion, and initial opioid exposure in adolescents may elevate the risk of subsequent persistent use and misuse [1, 2]. On the other hand, empirical analgesic prescriptions are often uniformly applied to patients undergoing different surgical procedures, experiencing varying pain severity, and with diverse comorbidities, there remains a lack of standardized care pathways covering etiological treatment, analgesic step-up/step-down adjustment, and treatment discontinuation.

Tissue injury triggers the release of prostaglandins, bradykinins, cytokines, and neuropeptides, which induce peripheral sensitization. Sustained nociceptive input can further undergo amplification in the trigeminal sensory nucleus and cortical pain networks. Therefore, simply escalating analgesic dosage based solely on pain scores tends to overlook the underlying inflammatory mechanisms, neuropathic features, and inherent safety risks of analgesic drugs.

Systematic reviews and meta-analyses have demonstrated that ibuprofen provides superior early pain relief after third molar surgery compared with acetaminophen alone, and the combination of the two agents can further reduce the need for rescue analgesia. Network meta-analyses of post-root-canal treatment pain also support the use of NSAIDs alone or combined with acetaminophen, but fail to show consistent advantages for opioid agents [3, 4]. Accordingly, 2024 evidence-based clinical guidelines position non-opioid drugs as the cornerstone of acute dental pain management, while opioids are reserved only for short-term use when first-line treatments are ineffective or contraindicated [5].

This article sequentially reviews the nociceptive conduction pathways and pain stratification of oral postoperative pain, the clinical positioning of non-opioid and centrally acting analgesics, perioperative care pathways for different surgical procedures, adverse reaction management, and prescription control. It also discusses emerging sustained-release delivery systems and a stratified clinical decision-making framework, with the aim of providing a basis for the standardization of postoperative oral analgesia and the reduction of unnecessary opioid use.

2. The neural conduction pathways and grading of oral pain

2.1. Peripheral conduction, central sensitization and descending modulation

The Aδ fibers in the dental pulp and periodontal tissues mainly transmit sharp, localized, rapid pain, while the C fibers are involved in slow, diffuse, and persistent pain. Inflammatory mediators can sensitize Transient Receptor Potential Vanilloid 1 (TRPV1), acid-sensitive ion channels and sodium channels. The nociceptive signals are transmitted through the trigeminal nerve into the brainstem and project to the thalamus, somatosensory cortex and limbic network, completing pain localization, intensity encoding and emotional experience [6]. Continuous peripheral input may promote central sensitization through N-Methyl-D-Aspartate Receptors (NMDAR), glial cells and inflammatory signals. Studies on pathological pain of the trigeminal nerve suggest that the descending monoaminergic and endogenous opioid pathways may also be involved in pain modulation. However, the role of these pathways in acute postoperative pain of the oral cavity still requires more direct evidence for verification [7].

2.2. Mild, moderate and severe dental pain

This article, for the purpose of facilitating the initial clinical screening, uses the NRS scale with scores of 1-3, 4-6, and 7-10 to represent mild, moderate, and severe or extremely severe pain, respectively. This operational

stratification is based on studies after third molar surgery and is not a uniform verification standard applicable to all types of oral surgeries [8]. Simple tooth extraction, routine periodontal procedures, and single implant procedures are mostly associated with mild to moderate short-term inflammatory pain. For impacted third molars, flap debridement and bone removal, as well as multiple implants or bone grafting, are usually moderate in severity. Orthognathic, maxillofacial trauma and reconstruction surgeries are usually of moderate to severe severity and require a monitored multimodal analgesic approach. Drug decisions should also take into account eating habits, sleep patterns, mouth opening capabilities, and the extent of limitations in daily activities. When severe, progressive or prolonged pain exceeds the expected duration, one should first rule out infections, bleeding, alveolar osteitis, hematoma, occlusal trauma and nerve damage, rather than directly equating it with an increase in pain medication dosage.

3. Classification and characteristics of analgesic drugs

3.1. A first-line non-opioid painkiller

Non-opioid drugs are the first-line choice for most acute postoperative pain in the oral cavity. NSAIDs reduce peripheral inflammatory sensitization by inhibiting prostaglandin synthesis, while acetaminophen mainly participates in central pain relief. The two mechanisms complement each other. When a single drug is insufficient and there are no corresponding contraindications, using them in combination can increase the rate of adequate pain relief and reduce the need for opioid rescue [4, 5, 9, 10]. Table 1 lists the adult short-term reference plans, their characteristics and applicable scenarios. After the symptoms and functions have improved, it should be promptly reduced to a single drug for as-needed use and then discontinued. Table 1 summarizes the mechanism of action of first-line non-opioid analgesics, adult short-term reference protocols and clinical indications. Relevant evidence can be found in references [4, 5, 9, 10].

Table 1. The mechanisms of action of first-line non-opioid analgesics and their matching with clinical situations

Category	Representative Drug	Mechanism of Action	Function Characteristics	Matching Clinical Situation
NSAIDs	Ibuprofen	Inhibit COX-1/COX-2, reduce prostaglandin synthesis, thereby reducing peripheral sensitization and inflammatory pain.	It takes effect quickly. There is sufficient evidence for the occurrence of acute dental pain.	Suitable for mild to moderate pain dominated by inflammation. It should be used in a short-term manner in combination with gastrointestinal tract, renal function, bleeding and cardiovascular risk considerations [5, 10].
	Naproxen	Like ibuprofen, naproxen inhibits COX-1/COX-2 and lowers prostaglandin production, reducing peripheral sensitization and inflammatory pain.	The half-life is relatively long, which enables an extension of the dosing interval and a reduction in the frequency of administration.	Suitable when inflammatory pain is expected to continue overnight or through the first postoperative day. Limit treatment duration after assessing gastrointestinal, renal, bleeding, and cardiovascular risks.

Table 1. Continued

NSAIDs	Aspirin	Inhibit COX and prostaglandin synthesis, At the same time, it also irreversibly inhibits platelet COX-1.	It has analgesic and anti-inflammatory effects, but its antiplatelet effect limits its routine use during the perioperative period.	Perioperative period is usually not regarded as the first choice for routine treatment [5, 10].
Non-NSAID	Acetaminophen	The active metabolite AM404, TRPV1, and the descending 5-hydroxytryptamine pathway are involved in central analgesia. The anti-inflammatory effect at the periphery is relatively weak.	Can be used as an alternative or combined medication for NSAIDs, The total dosage of the compound preparation needs to be calculated, and attention should be paid to the risk of liver damage.	Suitable for patients who are contraindicated for NSAIDs or who need to avoid their peripheral effects [5, 10].
Mechanism complementation combination	NSAID + Acetaminophen	At the same time, it inhibits peripheral inflammation and enhances central analgesia, achieving complementary mechanisms.	It usually offers a good balance between efficacy and safety in acute dental pain, and can reduce the need for opioid rescue medications.	It is applicable to those with insufficient medication and without any contraindications, especially when pain has affected eating, sleep, or mouth opening [4, 5, 10].

3.2. Central analgesics and anesthetic adjuncts

Opioid drugs: Only used for a small number of severe breakthrough pains that cannot be controlled after adequate short-term treatment with NSAIDs and acetaminophen, and where the underlying cause has been addressed. The choice should be made based on immediate-release formulations, the minimum effective dose and the fewest number of tablets. The treatment course should be as short as possible and rarely exceed 3 days, and no automatic renewal of prescriptions should occur [5].

Tramadol: It possesses both weak μ receptor agonistic and monoamine reuptake inhibitory effects. However, studies on third molars have not shown that it has a stable advantage over NSAIDs. Therefore, it is not used as a routine alternative drug in dentistry [11].

Gabapentin-like drugs: A systematic review in 2026 showed that pregabalin might slightly alleviate postoperative pain after third molar extraction, but the study had high heterogeneity, the results were influenced by individual studies, and adverse events increased. The current benefit-risk evidence does not support its use as a routine first-line drug for postoperative pain in inflammatory oral conditions [12].

Anesthesia adjunct drugs: Ketamine, dexmedetomidine, etc. can be considered as potential components of multimodal analgesia for complex maxillofacial surgeries under the supervision of the anesthesia team. However, at present, there is insufficient direct evidence specific to dentistry, and this review does not propose specific routine medication regimens based on this.

4. The combination of painkillers for different dental surgeries

The evidence bases for different surgical procedures are not consistent: extraction and third molar models have relatively sufficient evidence, while evidence for implantation, bone grafting, and large-scale maxillofacial surgeries is relatively limited. Therefore, the main body of this section merely highlights the key differences among the various surgical procedures. The complete perioperative process is presented in Table 2.

4.1. Simple tooth extraction and third molar surgery

Simple tooth extraction usually causes short-term mild to moderate pain. The flap resection, bone removal and operation duration for impacted third molars can increase the early postoperative pain. This surgical procedure has the most solid evidence. The key point is to provide non-opioid analgesia before the local anesthesia wears off. For complex tooth extractions, long-acting local anesthesia can be considered, and opioids are used only for a few cases of severe breakthrough pain [4, 5, 13].

4.2. Root canal treatment and related dental pulp surgeries

Post-root canal treatment pain relief primarily depends on debridement, drainage, and necessary occlusal adjustments. The medication is only used as an auxiliary measure after the cause of the disease has been addressed. If the pain continues to worsen, one should re-examine the residual pulp, the occlusal high points or the infection, rather than repeatedly increasing the dosage of painkillers [3].

4.3. Periodontal surgery and implant surgery

The trauma caused by periodontal flap surgery, single implantation, and multiple implantations or bone grafting is quite different. The current studies show significant heterogeneity in terms of surgical methods, medication use, and outcome indicators, and are not sufficient to determine a unified optimal combination and treatment course. Therefore, adjustments should be made on an individualized basis according to the severity of the trauma and the patient's risk [14].

4.4. Orthognathic, trauma and maxillofacial reconstruction surgeries

Orthognathic, maxillofacial trauma and reconstruction surgeries usually require the supervision of the anesthesia team, combined with regional block, local infiltration and multimodal systemic analgesia. The current number of specific studies is limited and the quality of the evidence is low. Some of the recommendations still come from extrapolation based on general perioperative principles. The evaluation of the orthognathic surgery system also indicates that the evidence for preventive analgesia is of relatively low certainty [15]. Table 2 compares the expected pain, perioperative procedures and drug placement in different oral clinical scenarios, based on the comprehensive organization of guidelines and systematic review evidence [3-5, 13-15].

Table 2. Expected pain characteristics, preferred strategies, and drug placement in different oral clinical scenarios

Different Clinical Scenarios	Expected Characteristics of Pain	Priority Strategy	The Localization of Different Drugs
Simple tooth extraction	Mostly mild-to-moderate and short-duration inflammatory pain, It often occurs after the local anesthesia wears off.	First, address the cause of the problem and take local measures. When there are no contraindications, a single non-opioid drug should be used as the initial treatment.	Ibuprofen or naproxen are the first-line options, When NSAIDs are contraindicated, acetaminophen can be used instead. Opioids are not used regularly [5].
Resecting the impacted third molar surgery	Most cases are moderate in severity. Flap removal and bone removal can exacerbate the pain. It peaks within a few hours after the surgery and continues to increase on the first day.	Long-acting local anesthesia + NSAID/acetaminophen, Only provide short-term rescue for the few cases of severe and life-threatening situations.	There is ample evidence for ibuprofen. NSAID + acetaminophen is preferred over opioid-containing combinations. Aspirin should not be routinely used due to the risk of bleeding. Opioids should only be used for short-term relief [4, 5,13].
Root canal treatment and related pulp surgeries	Usually mild to moderate. Preoperative pulpitis, periapical inflammation and instrument irritation can cause the pain to increase within 6 to 24 hours.	The foundation lies in thorough debridement, drainage, or bite adjustment. The drugs are administered as either NSAIDs alone or in combination with acetaminophen.	NSAID is the core medication for inflammatory pain. Acetaminophen is used as an alternative or in combination, Opioids and glucocorticoids did not show consistent advantages. Antibiotics cannot replace pain relief and the treatment of the underlying cause [3].
Periodontal flap surgery or single implant placement	Mostly presenting as mild-to-moderate and localized inflammatory pain, with the duration usually being relatively short.	Local anesthesia combined with individualized non-opioid analgesia, Select the medication based on the bleeding risk, renal function and gastrointestinal history.	When there are no contraindications, NSAIDs should be used first. Acetaminophen is an alternative or combined medication, Usually, a regular opioid prescription is not necessary [14].
Multiple implants, bone grafting or full arch restoration	The tissue damage and edema are more obvious, the pain is usually moderate and lasts for a long time, and the individual differences increase.	Long-acting local/regional anesthesia combined with a planned non-opioid multimodal approach, and re-evaluation based on recovery status.	The core component consists of NSAID and acetaminophen. Adjust the single drug when there are restrictions. Only consider short-term central rescue drugs after the diagnostic re-evaluation [14].

Table 2. Continued

Orthognathic surgery, facial trauma or reconstruction surgery	Moderate to severe pain is common in hospital settings. The injury is severe and may be accompanied by a high risk of respiratory depression.	Multimodal analgesia under supervision: regional block/local infiltration + acetaminophen + NSAID when there are no contraindications.	Multimodal analgesia was administered by the anesthesia team under monitoring. The specific drug combination should be tailored to the individual. Currently, there is limited and of low quality evidence specifically for oral and maxillofacial surgery [15].
Severe, progressive or abnormally prolonged pain	The pain does not match the normal healing process, which may indicate infection, bleeding, alveolar abscess, hematoma, occlusal trauma or nerve damage.	First, re-evaluate and address the complications, and do not simply increase the dosage of painkillers as a substitute for the treatment of the underlying cause.	Non-opioid drugs can be used for symptom control, Central-prescription drugs are only used after a clear indication and risk screening have been conducted. Repeated changes to the prescription should be regarded as a warning sign of diagnosis [5].

Note: The evidence bases for different surgical procedures are not consistent. The evidence for tooth extraction is relatively sufficient, while the evidence for implantation, bone grafting, and major maxillofacial surgeries is relatively limited.

5. Main safety risks and prescription management

5.1. Abuse, continuous use and prescription diversion

Before prescribing central analgesics, it is necessary to confirm the indications and assess the patient's previous exposure to analgesics, substance use history, mental and psychological factors, sleep apnea, and concurrent central depressants. For adolescents and high-risk patients, non-opioid treatment options should be given priority. When opioids are truly necessary, they should be administered at the lowest effective dose, with the smallest quantity and the shortest course of treatment. No automatic renewal of prescriptions should occur, and education on safe storage, education on the prohibition of drug donation and disposal of leftover medications [1, 2, 5].

Gabapentin derivatives also have the potential for misuse, with the risks being concentrated among individuals with a history of opioid or poly-substance use disorders, especially when used in combination with opioids, benzodiazepines, or alcohol [16]. When there are no clear neurologically-based indications for its use, it should not be regarded as a "safe opioid substitute".

5.2. Gastrointestinal tract, liver and kidney, and bleeding risks

Before using NSAIDs, one should assess for peptic ulcers or bleeding, renal insufficiency, dehydration, cardiovascular risks, aspirin-induced asthma, and anticoagulant or antiplatelet therapy. High-risk patients should avoid using the drug or use the lowest effective dose and the shortest course of treatment. Acetaminophen should be the total dose of prescription drugs and over-the-counter combination preparations, and should be used with caution in patients with liver disease, excessive alcohol consumption or malnutrition. When there is suspected gastrointestinal bleeding, acute kidney injury or liver injury, the relevant drugs should be immediately discontinued and an urgent clinical assessment should be conducted [17, 18].

5.3. Neurological, mental and respiratory side effects

Opioids, tramadol and gabapentin can cause sedation and respiratory depression. The combined use of tramadol with certain monoamine-based drugs may also increase the risk of epilepsy or serotonin syndrome. When combining opioids, benzodiazepines, alcohol, or when there are respiratory risk factors, gabapentin should be avoided or strictly limited. When severe sedation, consciousness disorders or respiratory depression occur, the relevant drugs should be immediately discontinued and emergency assessment and supportive treatment should be initiated [11, 16, 19].

6. New sustained-release and local analgesic delivery systems: future prospects

The potential value of the new local sustained-release technology lies in prolonging regional anesthesia in the surgical area and reducing systemic medication. However, the clinical evidence in dentistry mainly comes from small-scale studies of liposomal bupivacaine. The third molar random trial showed that it only provided a slightly smaller early pain reduction compared to conventional bupivacaine, with the maximum between-group difference being approximately 0.75 NRS points. The clinical perceptibility and additional costs still need to be evaluated [20, 21]. Other delivery systems such as nanoparticles are currently mainly at the stage of materials science, animal testing, or early translational research. Reference [22] describes a non-dental model of sciatic nerve injury in mice, and it cannot be regarded as a direct basis for the clinical effectiveness in dentistry. Future studies should compare its incremental benefits with those of conventional long-acting local anesthetics and mature non-opioid regimens, and evaluate the safety of tissues and nerves, cost-effectiveness, and operational feasibility. Such technologies should be used as optional adjuncts before obtaining high-quality, multi-center and long-term evidence.

7. Clinical decision-making framework based on pain grading

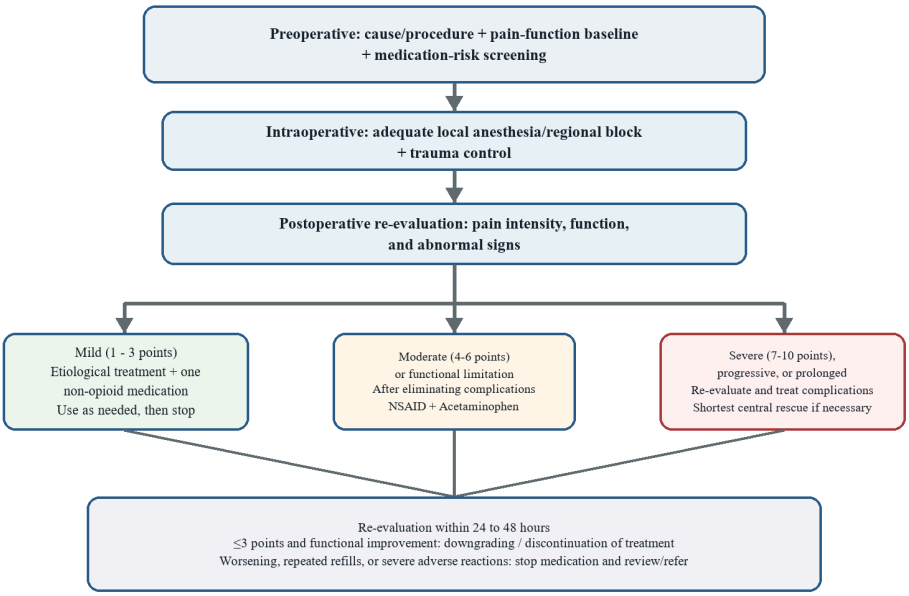

Figure 1. Clinical decision flowchart for multimodal analgesia after oral surgery

Based on the available evidence, this article proposes a suggestive operational framework. The core of this framework is to first determine whether the pain is in line with the normal postoperative process, then combine the NRS, functional impairment, surgical trauma and duration for assessment, and after screening for contraindications, interactions and abuse risks, select a non-opioid-based priority plan. The upgrade node refers to the pain that persists and affects functionality even after the cause has been addressed. The downgrade node, on the other hand, indicates that the pain and functionality continue to improve. Severe, progressive or pain that exceeds the expected timeline should trigger a re-diagnosis, rather than automatically increasing the dosage of medication. Figure 1 summarizes the specific branches. The thresholds of "pain ≤ 3 points", "pain ≥ 7 points", and "re-evaluation 24-48 hours later" are merely suggested standards for ease of clinical operation. They should be adjusted in combination with the surgical method, postoperative time, and individual risks, and cannot be regarded as a verified unified clinical guideline.

8. Conclusion

For most cases of acute postoperative oral pain, management should prioritize etiological treatment, adequate local anesthesia, and non-opioid-based analgesic regimens. In the absence of contraindications, NSAIDs used alone or in combination with acetaminophen offer a favorable benefit-risk profile. Once pain and functional impairment improve, the regimen should be gradually stepped down to as-needed dosing before complete discontinuation. Opioids, tramadol, gabapentinoids, and analgesic adjuvants must be prescribed only to patients with clear indications who have undergone formal risk screening and can receive regular reassessment and monitoring. These agents should be administered at the lowest effective dose for the shortest possible duration, and automatic prescription refills should be avoided. Sustained-release local anesthetics and biodegradable delivery systems are currently regarded as optional adjunctive or investigational tools, and cannot replace etiological treatment and established first-line analgesic approaches.

Currently, the majority of supporting evidence is derived from dental extraction study models. There is considerable heterogeneity across different surgical procedures in terms of optimal dosage, treatment duration, and outcome measures. The long-term tissue safety, cost-effectiveness, and real-world efficacy of sustained-release delivery systems remain to be fully clarified. Future research should conduct multicenter studies stratified by surgical procedure and patient risk profile, and adopt unified patient-reported outcome measures and functional endpoints. The multimodal analgesic framework proposed in this article can serve as a reference for clinical decision-making after oral surgery, but cannot replace formal clinical practice guidelines or individualized patient assessment.

References

[1] Harbaugh, C. M., Nalliah, R. P., Hu, H. M., Eng, B., & Waljee, J. F. (2018). Persistent opioid use after wisdom tooth extraction. *JAMA, 320*(5), 504–506.

[2] Schroeder, A. R., Dehghan, M., Newman, T. B., Bentley, J. P., Park, K. T., & Chaudhary, R. (2019). Association of opioid prescriptions from dental clinicians for US adolescents and young adults with subsequent opioid use and abuse. *JAMA Internal Medicine, 179*(2), 145–152.

[3] Zanjir, M., Sgro, A., Lighvan, N. L., Azarpazhooh, A., & Lawrence, H. P. (2020). Efficacy and safety of postoperative medications in reducing pain after nonsurgical endodontic treatment: A systematic review and network meta-analysis. *Journal of Endodontics, 46*(10), 1387–1402.e4.

[4] Bailey, E., Worthington, H. V., van Wijk, A., Yates, J. M., Coulthard, P., & Afzal, Z. (2013). Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database*

of Systematic Reviews, 2013(12), CD004624.

[5] Carrasco-Labra, A., Polk, D. E., Urquhart, O., Brignardello-Petersen, R., Azarpazhooh, A., & Carrasco-Labra, A. (2024). Evidence-based clinical practice guideline for the pharmacologic management of acute dental pain in adolescents, adults, and older adults. *Journal of the American Dental Association, 155*(2), 102–117.e9.

[6] Ong, C. K. S., & Seymour, R. A. (2003). Pathogenesis of postoperative oral surgical pain. *Anesthesia Progress, 50*(1), 5–17.

[7] Bista, P., & Imlach, W. L. (2019). Pathological mechanisms and therapeutic targets for trigeminal neuropathic pain. *Medicines, 6*(3), 91.

[8] Mota de Almeida, F. J., Kindlund, Y. A., Lundqvist, R., & Lantto, A. (2025). Postoperative pain of impacted mandibular third molar surgery performed by general dental practitioners: A multicenter study. *Journal of Clinical and Experimental Dentistry, 17*(8), e989–e994.

[9] Mallet, C., Desmeules, J., Pegahi, R., & Eschalier, A. (2023). An updated review on the metabolite (AM404)-mediated central mechanism of action of paracetamol (acetaminophen): Experimental evidence and potential clinical impact. *Journal of Pain Research, 16*, 1081–1094.

[10] Moore, P. A., Ziegler, K. M., Lipman, R. D., Aminoshariae, A., & O'Brien, M. (2018). Benefits and harms associated with analgesic medications used in the management of acute dental pain: An overview of systematic reviews. *Journal of the American Dental Association, 149*(4), 256–265.e3.

[11] Isiordia-Espinoza, M. A., Pozos-Guillén, A. J., & Aragon-Martinez, O. H. (2014). Analgesic efficacy and safety of single-dose tramadol and non-steroidal anti-inflammatory drugs in operations on the third molars: A systematic review and meta-analysis. *British Journal of Oral and Maxillofacial Surgery, 52*(9), 775–783.

[12] Li, J., & Wang, A. (2026). The effect of pregabalin for pain after third molar surgery: A systematic review and meta-analysis. *BMC Anesthesiology*. Advance online publication.

[13] Au, A. H. Y., Choi, S. W., Cheung, C. W., & Leung, Y. Y. (2015). The efficacy and clinical safety of various analgesic combinations for post-operative pain after third molar surgery: A systematic review and meta-analysis. *PLOS ONE, 10*(6), e0127611.

[14] Melini, M., Forni, A., Cavallin, F., Parotto, M., & Zanette, G. (2021). Analgesics for dental implants: A systematic review. *Frontiers in Pharmacology, 11*, 634963.

[15] Alyahya, A., Aldubayan, A., Swennen, G. R. J., & Al-Moraissi, E. (2022). Effectiveness of different protocols to reduce postoperative pain following orthognathic surgery: A systematic review and meta-analysis. *British Journal of Oral and Maxillofacial Surgery, 60*(7), e1–e10.

[16] Evoy, K. E., Sadrameli, S., Contreras, J., & Moeller, K. E. (2021). Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs, 81*(1), 125–156.

[17] Salvo, F., Fourrier-Réglat, A., Bazin, F., & Robinson, P. (2011). Cardiovascular and gastrointestinal safety of NSAIDs: A systematic review of meta-analyses of randomized clinical trials. *Clinical Pharmacology & Therapeutics, 89*(6), 855–866.

[18] U.S. Food and Drug Administration. (2025). *Acetaminophen.*

[19] U.S. Food and Drug Administration. (2019). *Neurontin, Gralise, Horizant (gabapentin) and Lyrica, Lyrica CR (pregabalin): Drug safety communication—Serious breathing problems.*

[20] Hamilton, T. W., Athanassoglou, V., Mellon, S., & Trivella, M. (2017). Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. *Cochrane Database of Systematic Reviews, 2017*(2), CD011419.

[21] Youn, S., Scheker, K., Sheridan, S., & Kim, Y. (2025). Does liposomal bupivacaine reduce postoperative pain following third molar extractions? A double-blinded randomized controlled trial. *Journal of Oral and Maxillofacial Surgery, 83*(5), 592–600.

[22] Mohan, P., Sobhanan, J., Gaffney, & C. M. (2025). Local delivery of non-opioid analgesic microparticles to modulate post-surgical pain. *Pharmaceutical Research, 42*(9), 1573–1585.