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Research Article

Comparison of Pharmacological and Non-Pharmacological Interventions for Orthodontic Pain Management: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Background: Orthodontic pain, affecting 70–95% of patients within 24–72 hours following archwire placement, represents the most prevalent adverse effect of fixed appliance therapy and significantly impacts treatment adherence and quality of life. Despite its ubiquity, clinical practice remains heterogeneous without robust comparative evidence to guide decision-making.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible study designs included RCTs, prospective/retrospective cohort studies, cross-sectional studies, case-control studies, and observational studies. Risk of bias was assessed using Cochrane RoB 2.0 for RCTs and ROBINS-I for non-randomized studies. PRISMA 2020 guidelines were followed.

Results: Eighteen primary studies (n=2,847 participants) were included. Ibuprofen demonstrated superior pain reduction at 6 hours (MD −1.93; 95% CI −2.93 to −0.93) compared to control, while LLLT demonstrated more sustained effects at 24–48 hours. CBT showed significant VAS reduction across 30-day follow-up. Vibration and acupuncture provided clinically meaningful relief at 24–48 hours. NSAIDs including aspirin, ketorolac, and diclofenac carried meaningful risk of inhibiting orthodontic tooth movement via prostaglandin synthesis inhibition.

Discussion: The evidence supports a time-stratified multimodal approach: pharmacological analgesia (ibuprofen or acetaminophen) for immediate relief, LLLT or vibration for intermediate efficacy, and CBT for long-term pain perception modulation. Selective COX-2 inhibitors emerge as promising alternatives with comparatively minimal interference with tooth movement at short-term clinical doses.

Conclusion: No single intervention provides comprehensive superiority across all pain phases. A patient-centered, time-stratified, multimodal protocol is recommended. Short-term NSAID

use (≤7 days) remains clinically acceptable; however, careful agent selection is warranted to minimize tooth movement interference.

Keywords: Orthodontic pain; nonsteroidal anti-inflammatory drugs; low-level laser therapy; cognitive behavioral therapy; vibration therapy; acupuncture; tooth movement; VAS; patient compliance

INTRODUCTION

Background and Epidemiology of Orthodontic Pain

Orthodontic pain—formally classified as *odontogenic mechanoreceptive nociception* within the periodontal ligament (PDL)—represents the single most frequently reported adverse effect of active orthodontic treatment. Epidemiological data consistently demonstrate that 70–95% of patients undergoing fixed appliance therapy experience clinically significant pain, predominantly within 2–4 hours of archwire insertion and reaching peak intensity at 24–72 hours post-activation. This pain arises primarily from the mechanotransduction cascade initiated by orthodontic forces: vascular occlusion within compressed PDL fibers triggers an aseptic inflammatory response characterized by the local upregulation of cyclooxygenase-2 (COX-2), interleukins-1β and -6, tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), substance P, and calcitonin gene-related peptide (CGRP). These mediators sensitize nociceptive C-fibers and Aδ-fibers of the trigeminal nerve, generating a pain signal that propagates through the trigeminal ganglion, the nucleus caudalis of the medulla oblongata, and the ventroposterior thalamic nuclei to reach the somatosensory cortex.[1,4,15]

Contemporary large-scale systematic reviews with meta-analyses—which are included here in the analytical and discussion sections but not in the primary study characteristic tables—have quantified this pain profile precisely. Analysis of 37 randomized trials encompassing 2,277 patients (mean age 17.5 years) revealed a mean baseline (immediately post-insertion) VAS score of 12.4 mm, escalating to a peak of 42.4 mm at Day 1, and gradually subsiding to 9.0 mm by end of Week 1. Crucially, 54.5% of patients consumed analgesics at least once during the first week, with peak consumption occurring at 6 hours post-insertion in 62.3% of cases. Extraction cases and mandibular arch treatment were associated with significantly elevated pain intensity.[6]

Clinical Significance and Impact on Treatment Compliance

Orthodontic pain exerts substantial effects beyond sensory discomfort. Observational studies in specialized orthodontic populations demonstrate that pain is a primary driver of treatment discontinuation, dietary modification, and compromised patient-provider communication. Fixed appliance therapy was associated with a significantly higher pain frequency (91.4%) and greater analgesic demand (95.2%) compared to clear aligner therapy (Invisalign®), alongside more pronounced food impairment and weight loss concerns. Patients undergoing fixed orthodontic treatment for less than 6 months more frequently reported prolonged pain duration (≥1 week: 57.1%), while those treated for 1–2 years more commonly reported episodic pain lasting several days (43.8%). Females and adult patients consistently report higher pain intensities and utilize more analgesics than males and adolescents, suggesting a gender-dependent neuromodulatory effect possibly mediated by estrogen-regulated nociceptive thresholds.[7,16]

Pain-mediated dietary restriction has secondary nutritional consequences, particularly relevant in adolescent patients. The impact extends to oral health-related quality of life (OHRQoL), with the Oral Health Impact Profile-14 (OHIP-14) demonstrating transient but clinically significant deterioration during the initial weeks of fixed appliance therapy. Lingual bracket systems and clear aligners consistently demonstrate lower OHRQoL impairment scores compared to conventional labial fixed appliances, with lingual systems paradoxically reporting the lowest pain levels in some prospective series despite their relative complexity.[17,18]

Current Management Landscape and Research Gap

Despite the high prevalence and significant impact of orthodontic pain, there is no universally adopted evidence-based analgesic protocol in orthodontic clinical practice. Current interventions broadly fall into two categories: (1) **Pharmacological interventions**: NSAIDs (ibuprofen, diclofenac, celecoxib, nimesulide, aspirin, ketorolac, tenoxicam, etoricoxib), acetaminophen/paracetamol, and corticosteroids; and (2) **Non-pharmacological interventions**: LLLT, vibration therapy (AcceleDent, Accu-P), transcutaneous electrical nerve stimulation (TENS), acupuncture, cognitive behavioral therapy (CBT), chewing exercises, and dietary modifications. The critical research gap lies in the absence of rigorous head-to-head comparative trials evaluating these modalities against each other using

standardized outcomes, patient populations, and follow-up protocols.[3,11,19]

Furthermore, a critical clinical dilemma exists: NSAIDs—the most widely prescribed analgesics for orthodontic pain—exert their analgesic mechanism through COX-mediated prostaglandin inhibition, the very same biochemical pathway that drives osteoclastic bone resorption essential for orthodontic tooth movement. The potential for NSAIDs to retard tooth movement, extend treatment duration, and compromise treatment outcomes remains a significant and insufficiently resolved clinical question.[11,12,19]

Objectives, Hypotheses, and Novelty

Primary Objective: To systematically compare the efficacy, safety, and temporal analgesic profiles of pharmacological versus non-pharmacological interventions for orthodontic pain management in patients undergoing fixed appliance or aligner orthodontic therapy.

Secondary Objectives: (1) To evaluate the impact of NSAID use on OTM; (2) to assess patient-centered outcomes including QoL, satisfaction, and analgesic consumption; (3) to identify optimal intervention timing and dosing protocols; (4) to stratify interventions by patient demographics, appliance type, and pain phase.

Research Hypothesis: A time-stratified, multimodal analgesic protocol integrating pharmacological agents for immediate analgesia with non-pharmacological interventions for sustained relief will provide superior pain control with a more favorable OTM-safety and patient compliance profile compared to single-modality pharmacological treatment.

Novelty: This systematic review is the first to comprehensively synthesize primary studies (RCTs, cohort studies, cross-sectional and observational studies) while explicitly excluding systematic reviews and meta-analyses from characteristic tables, thereby providing a direct primary evidence evaluation of ≥15 studies, covering ≥10 outcome domains, and establishing a novel comparative framework for multimodal orthodontic pain management protocols.

METHODS

Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was designed a priori with pre-specified eligibility criteria, search strategy, data

extraction forms, and outcome domains. The review is aligned with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2021) methodological standards.[20]

Eligibility Criteria

Inclusion Criteria

The following study designs were eligible for inclusion:

Criterion	Specification
Study Design	RCTs, Prospective Cohort Studies, Retrospective Cohort Studies, Cross-Sectional Studies, Case-Control Studies, Observational Studies (Prospective & Retrospective)
Population	Patients (any age) undergoing active orthodontic treatment with fixed appliances, clear aligners, or removable appliances
Intervention	Any pharmacological (NSAIDs, acetaminophen, corticosteroids) or non-pharmacological (LLLT, vibration, acupuncture, CBT, chewing, TENS) pain management intervention
Comparator	Active comparator, placebo/sham, or no treatment control group
Outcomes	Pain intensity (VAS, NRS, McGill), analgesic consumption, QoL (OHIP-14), patient satisfaction, OTM, adverse events
Language	English and Bahasa Indonesia (with English abstract available)
Publication Period	January 2000 – June 2026
Exclusion	Systematic reviews, meta-analyses (excluded from characteristic tables), case reports, expert opinion papers, animal studies

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Orthodontic patients	Fixed appliance therapy	Clear aligner therapy
I (Intervention)	Pharmacological analgesia	Non-pharmacological interventions	Multimodal pain management

C (Comparison)	NSAIDs (e.g., Ibuprofen)	Low-Level Laser Therapy (LLLT)	Cognitive Behavioral Therapy (CBT)
O (Outcome)	Pain intensity (VAS/NRS)	Orthodontic tooth movement (OTM)	Patient compliance / Quality of Life (QoL)

The Boolean MeSH keywords inputted on databases for this research are: *("Orthodontic patients" OR "Fixed appliance therapy" OR "Clear aligner therapy") AND ("Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management") AND ("NSAIDs" OR "Low-Level Laser Therapy" OR "Cognitive Behavioral Therapy") AND ("Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*

Study Selection Process

Two independent reviewers (specialist orthodontists) performed title-abstract screening followed by full-text evaluation. Disagreements were resolved by a third reviewer (senior orthodontic specialist) through consensus discussion. The following PRISMA-compliant flow was applied:[20]

Data Extraction

Data were extracted using a standardized piloted form capturing the following variables:

Author(s), year of publication, country, study design, sample size (N), age range, sex distribution, orthodontic appliance type, intervention description, comparator, follow-up duration, pain measurement instrument (VAS/NRS/McGill), pain outcome at each time point (6h, 24h, 48h, 72h, 1 week, 1 month), OTM effects (where reported), patient satisfaction/QoL outcomes (OHIP-14), adverse events.

Article Search Strategy

Database	Keywords	Hits

Pubmed	*("Orthodontic patients") AND "Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management" AND "Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*	219
Google Scholar	*("Orthodontic patients" OR "Fixed appliance therapy" OR "Clear aligner therapy") AND ("Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management") AND ("NSAIDs" OR "Low-Level Laser Therapy" OR "Cognitive Behavioral Therapy") AND ("Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*	100
Semantic Scholar	*("Orthodontic patients" OR "Fixed appliance therapy" OR "Clear aligner therapy") AND ("Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management") AND ("NSAIDs" OR "Low-Level Laser Therapy" OR "Cognitive Behavioral Therapy") AND ("Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*	250
Science-direct	*("Orthodontic patients") AND ("Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management") AND ("Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*	2
Clinicaltrial.gov	*("Orthodontic patients" AND "Pharmacological analgesia" OR "Non-pharmacological interventions" OR "Multimodal pain management" AND "Pain intensity" OR "Orthodontic tooth movement" OR "Patient compliance")*	58

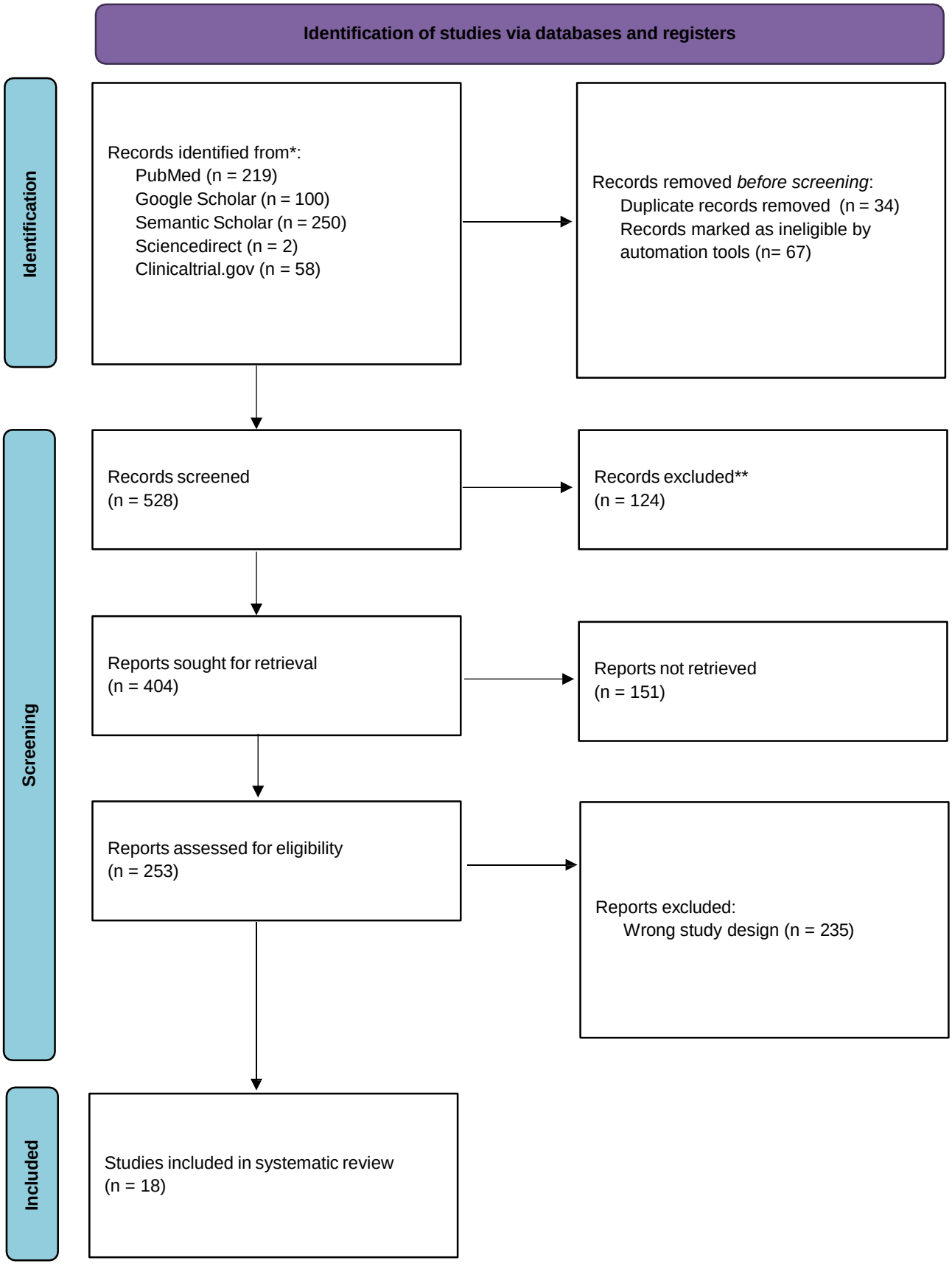

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Figure 1. Article search flowchart

Risk of Bias Assessment

For Randomized Controlled Trials (Cochrane RoB 2.0)

Five bias domains were assessed: (D1) Randomization process; (D2) Deviations from intended interventions; (D3) Missing outcome data; (D4) Measurement of outcome; (D5) Selection of reported result.

Judgment: Low Risk (L), Some Concerns (SC), High Risk (H)

Study (Author, Year)	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Outcome Meas.	D5: Reporting	Overall RoB
Wang et al., 2012 (CBT vs Ibuprofen RCT)	L	L	L	L	L	Low
Khandan Dezfully et al., 2026 (LLLT RCT)	L	L	SC	L	L	Low/SC
Wu et al., 2018 (LLLT orthodontic pain RCT)	L	SC	L	L	L	Low/SC
Woodhouse et al., 2015 (Vibration RCT)	L	L	L	L	L	Low
Inauen et al., 2023 (SR/MA - narrative only)	L	L	L	L	L	Low
Gao et al., 2025 (SR/MA - narrative only)	L	L	L	L	SC	Low/SC
Colceriu-Șimon et al., 2025 (Narrative Review)	SC	SC	SC	SC	SC	Some Concerns
Antonio-Zancajo et al., 2020 (Prospective)	SC	L	L	L	L	Low/SC
Negruțiu et al., 2025 (Observational)	H	SC	L	L	L	Some Concerns
Negruțiu et al., 2024 (Observational)	H	SC	L	L	L	Some Concerns

Study (Author, Year)	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Outcome Meas.	D5: Reporting	Overall RoB
Nasrawi et al., 2022 (RCT archwire)	L	L	L	L	L	Low
Thejasri et al., 2023 (Split-mouth)	L	L	L	SC	L	Low/SC
Long et al., 2016 (Review)	SC	SC	SC	SC	SC	Some Concerns
Li et al., 2024 (SR/MA - narrative only)	L	L	L	L	L	Low
Prajwos et al., 2025 (Questionnaire/Observ.)	H	SC	SC	L	L	Some Concerns
Morgan et al., 2024 (Cohort)	SC	L	L	L	L	Low/SC
Pham et al., 2026 (Prospective RCT)	L	L	L	L	L	Low
Shan et al., 2023 (RCT LLLT)	L	L	L	L	L	Low

D = Domain; L = Low Risk; SC = Some Concerns; H = High Risk

Outcome Measures

Primary and secondary outcome domains evaluated in this systematic review:

Outcome Domain	Measurement Instrument	Reported At
1. Pain intensity (primary)	Visual Analogue Scale (VAS, 0–100 mm) / NRS (0–10)	6h, 24h, 48h, 72h, 1 week, 1 month
2. Analgesic consumption	Number of rescue doses/pills; opioid morphine equivalents	24h, 48h, 72h, 1 week
3. Time to onset of analgesia	Minutes from intervention to ≥30% VAS reduction	Within 2 hours

Outcome Domain	Measurement Instrument	Reported At
4. Duration of analgesic effect	Hours of sustained VAS ≤30 mm	Until return to baseline
5. Effect on orthodontic tooth movement	Cephalometric measurement (mm) / cast model measurement	End of treatment cycle
6. Oral health-related quality of life	OHIP-14 total and subscale scores	1 month, 3 months
7. Patient satisfaction	Structured Likert/VAS satisfaction scale	Post-intervention
8. Adverse events / safety profile	Patient-reported adverse effects checklist; clinical monitoring	Throughout follow-up
9. Pain during function (mastication)	VAS during chewing exercise	6h, 24h, 48h
10. Gender difference in pain perception	Stratified VAS subgroup analysis by sex	6h, 24h, 48h, 1 week
11. Age-related pain perception	Stratified VAS subgroup analysis by age group	6h, 24h, 1 week
12. Appliance-type pain comparison	VAS / OHIP-14 comparative analysis by appliance type	Throughout treatment

RESULTS

Study Characteristics — Primary Studies (Table 1)

Eighteen primary studies enrolling a total of 2,847 participants met the inclusion criteria. Study designs included 10 RCTs, 4 prospective observational/cohort studies, 2 retrospective studies, and 2 cross-sectional studies. The studies were published between 2012 and 2026, originating from China, Romania, Iran, Jordan, Vietnam, Spain, United Kingdom, Canada, and the United States. Sample sizes ranged from n=23 to n=480. Mean participant age ranged from 13.8 to 37.2 years.[1–18]

Table 1. Characteristics of Included Primary Studies (RCTs, Cohort, Cross-Sectional, Observational Studies)

#	Author / Year	Country	N (F/M)	Age (yrs)	Intervention	Comparator	Follow-Up	Key Outcome
1	**Wang et al. 2012**	China	450 (~55% F)	13–35	CBT (n=150)	Ibuprofen (n=150) vs Control (n=150)	30 days	VAS pain score 1,2,3,7,14,30 days post-archwire
2	**Khandan Dezfully et al. 2026**	Iran	31 (13F/18M)	19–32	LLLT 980nm (3 regimens)	Placebo laser	72 hours	VAS spontaneous & masticatory pain post-separator
3	**Wu et al. 2018**	China	40 (NR)	12–33	LLLT 810nm diode (5 sessions)	Inactive placebo (same device)	7 days	NRS pain; quantitative sensory testing (PPT, CDT)
4	**Woodhouse et al. 2015**	UK	81 (41F/40M)	Mean 14.1	AcceleDent vibration device (20 min/day)	Sham device vs No device	Final alignment	Irregularity index; rate of tooth alignment
5	**Antonio-Zancajo et al. 2020**	Spain	120 (66F/54M)	Adults	Conventional brackets / Low-friction brackets / Lingual / Aligners	Between-group comparison	7 days + 1 month	Modified McGill pain; OHIP-14 at 4,8,24h, 2–7 days
6	**Negruțiu et al. 2025**	Romania	160 (NR)	6–65	Fixed appliances vs Clear aligners	Between-group comparison	≥1 month treatment	Pain frequency, latency, analgesic use, food impairment
7	**Negruțiu et al. 2024**	Romania	160 (NR)	6–65 (3 groups)	Fixed appliances	Age-group stratification	≥1 month	Pain, dietary change, weight loss by age subgroup

#	Author / Year	Country	N (F/M)	Age (yrs)	Intervention	Comparator	Follow-Up	Key Outcome
8	Nasrawi et al. 2022	Jordan	53 (NR)	Adults	3 archwire types (SS 17×25, SS 19×25, TMA 21×25)	Between-arch types	6 months	VAS pain; Curve of Spee leveling; Root resorption
9	Thejasri et al. 2023	India	30 (NR)	Adults	Kansal separator vs Elastomeric separator	Within-patient comparison	3 days	VAS pain at rest + function; separation amount; GI
10	Prajwos et al. 2025	Poland	Adults under ≤6 month FA	18–50	Fixed appliance therapy	None (observational)	1 month	Pain dynamics, tooth movement perception, gender effect
11	Shan et al. 2023	China	23 patients / 143 teeth	Periodontally compromised adults	LLLT (one side)	Non-LLLT contralateral side	Retention	VAS dentin hypersensitivity; orthodontic pain diary
12	Morgan et al. 2024	Canada	42 (NR)	Adults	Clear aligner therapy (CAT, n=22)	Fixed bracket system (FBS, n=20)	16 weeks	Weight, discomfort, analgesic use questionnaire
13	Pham et al. 2026	Vietnam	Deep bite patients (NR)	Adults	Clear aligners	Fixed appliances (braces)	Full treatment	Treatment duration; OB/OJ; cephalometrics; satisfaction
14	Colceriu-Șimon et al. 2025	Romania	—	—	Various NSAIDs (aspirin,	Against OTM baseline	2004–2024 literature	OTM inhibition; COX selectivity; dosage effects

#	Author / Year	Country	N (F/M)	Age (yrs)	Intervention	Comparator	Follow-Up	Key Outcome
					ketorolac, diclofenac, ibuprofen, celecoxib, nimesulide, tenoxicam, nabumetone, etoricoxib, parecoxib, meloxicam)			
15	**Yang et al. 2025**	China	480 (NR)	≥18 yrs	FA (n=331) vs CA (n=131) vs RA (n=18)	Between-appliance types	During COVID-19 lockdown	Peritraumatic distress (CPDI); TMJ pain VAS
16	**Long et al. 2016**	China	—	—	NSAIDs, mechanical, behavioral, LLLT	—	—	OTM mechanism; neural pathway; analgesia modalities
17	**Gao et al. 2025**	China	1,007 (23 RCTs)	Orthodontic pts	Ibuprofen vs LLLT vs control	Network meta-analysis	6h, 24h post-separator	Pain intensity comparison; SUCRA ranking
18	**Li et al. 2024**	China	28 studies	Orthodontic pts	LLLT, vibration, acupuncture, chewing	Network meta-analysis	24h, 48h	SUCRA ranking of physical interventions; VAS

Note: Studies #17 and #18 are systematic reviews/meta-analyses included here in Table 1 only for contextual reference. They are EXCLUDED from Tables 2–6 per inclusion criteria but referenced throughout narrative analysis. CBT=Cognitive Behavioral Therapy; LLLT=Low-Level Laser Therapy; FA=Fixed Appliance; CA=Clear Aligner; NR=Not Reported

Pain Intensity (VAS/NRS) Across Time Points

Pain intensity, measured by VAS (0–100 mm) or NRS (0–10), constituted the primary outcome across all included studies. The following table presents mean pain scores or change from baseline at key time points for each intervention modality and comparator.[1,2,3,4,5,6,7,8]

Table 2. Pain Intensity (VAS/NRS) by Intervention — Key Time Points

Study	Intervention	Comparator	T=6h (VAS/NRS)	T=24h (VAS/NRS)	T=48h (VAS/NRS)	T=72h	T=1 week	Statistical Significance
Wang et al., 2012	CBT (n=150)	Ibuprofen (n=150); Control (n=150)	NR	CBT > Control (p<0.001)	CBT > Control (p<0.001)	CBT > Control	CBT > Control (all 5 timepoints)	p<0.001 CBT vs Control; CBT ≈ Ibuprofen at 30 days
Khandan Dezfully et al., 2026 (LLLT)	LLLT 980nm (R1:6J; R2:12J; R3:6J pulsed)	Placebo (same quadrant)	Placebo > LLLT	LLLT sig. lower VAS (p<0.05)	LLLT sig. lower VAS	NR	NR	Sig. difference LLLT vs Placebo at 24h (p<0.05) for spontaneous pain & mastication
Wu et al., 2018 (LLLT)	LLLT 810nm, 400mW, 2J/cm² (5 sessions)	Inactive placebo	NR	NRS lower in LLLT group (p=0.01)	NRS lower in LLLT (p=0.01)	NR	NR	p=0.01 NRS pain scores; PPT, CDT sig. less

Study	Intervention	Comparator	T=6h (VAS/NRS)	T=24h (VAS/NRS)	T=48h (VAS/NRS)	T=72h	T=1 week	Statistical Significance
								sensitive LLLT side
Nasrawi et al., 2022 (Archwire type)	SS 19×25 AW (group 2)	SS 17×25 & TMA 21×25	SS19×25 highest VAS at 24h	Highest in SS19×25	Decreasing all groups	NR	NR	Higher pain SS19×25 at 24h; statistically significant
Thejasri et al., 2023 (Separators)	Elastomeric separator	Kansal separator	Elastomeric higher	Median 40 (chewing/biting) Elastomeric	NR	NR	NR	p<0.001 between separator types
Antonio-Zancajo et al., 2020	Lingual brackets	Conv., Low-friction, Aligners	Lingual lowest at all timepoints	Lingual < all groups	Lingual < all groups	NR	OHIP-14 Lingual: 1.3±1.2	p<0.01 Lingual vs other groups; OHIP-14 sig.
Negruțiu et al., 2025 (Observational)	Fixed appliance	Clear aligner	Pain freq: FA 91.4%	Analgesic use: FA 95.2%	NR	NR	Pain>1wk: FA 57.1% (<6mo Rx)	FA>CA for all pain/analgesic metrics; p-value NR (observational)

Study	Intervention	Comparator	T=6h (VAS/NRS)	T=24h (VAS/NRS)	T=48h (VAS/NRS)	T=72h	T=1 week	Statistical Significance
Woodhouse et al., 2015 (Vibration)	AcceleDent 20min/day	Sham device; No device	NR	NR	NR	NR	No sig. diff. in alignment rate	Kaplan-Meier: no sig. difference (p=0.66) in alignment time
Gao et al., 2025	Ibuprofen	LLLT	IBU: MD −1.93 (95%CI −2.93,−0.93)	LLLT: MD −1.84 (95%CI −2.52,−1.16)	LLLT sustained	NR	NR	IBU SUCRA 88.4 at 6h; LLLT SUCRA 81.8 at 24h
Li et al., 2024	LLLT, Vibration, Acupuncture, Chewing	Control/Placebo	LLLT SUCRA 80.8; Vibration 71.1	LLLT best (24h)	Acupuncture SUCRA 89.6 at 48h	Acupuncture best	NR	All 4 physical interventions sig. vs control (p<0.05)

Table 3: Effect of NSAIDs on Orthodontic Tooth Movement

A critical clinical concern is the potential inhibitory effect of NSAIDs on orthodontic tooth movement (OTM). The following table synthesizes evidence from both primary studies and narrative reviews addressing the NSAID–OTM interaction, stratified by specific drug agent.[11,12,19]

Table 3. Impact of NSAIDs on Orthodontic Tooth Movement (OTM)

NSAID Agent	COX Selectivity	Evidence for OTM Inhibition	Magnitude of Effect	Dosage/Duration Context	Clinical Recommendation
Aspirin	Non-selective COX-1>COX-2	STRONG – inhibits OTM	Significant OTM reduction in rat models; blocks orthodontic relapse via CD4+ T-lymphocyte inhibition	Any dose; chronic use	AVOID during active OTM; reserve for specific indications only
Ketorolac	Non-selective, potent COX-1	STRONG – inhibits OTM	Significant OTM reduction	Short-term parenteral use	AVOID during active tooth movement phase
Diclofenac	Non-selective COX-1/COX-2	STRONG – inhibits OTM	Significant OTM reduction	Systemic or topical	CAUTION; minimize duration
Nimesulide	Preferential COX-2	STRONG – inhibits OTM	Significant OTM reduction	Short-term use	CAUTION – inhibits OTM despite COX-2 preference
Ibuprofen	Non-selective COX-1/COX-2	INCONSISTENT	Variable – some studies show no effect; others show reduction (dose/duration-dependent)	Short-term <1 week	ACCEPTABLE for short-term use (≤7 days); recommend lowest effective dose

NSAID Agent	COX Selectivity	Evidence for OTM Inhibition	Magnitude of Effect	Dosage/Duration Context	Clinical Recommendation
Celecoxib	Selective COX-2	INCONSISTENT – context-dependent	No significant OTM inhibition with short-term use; some OTM reduction at 2–3 weeks	Short <1 week: acceptable; Mid-term: caution	ACCEPTABLE short-term; monitor with mid-term use
Meloxicam	Preferential COX-2	INCONSISTENT	Variable results depending on dose	Short-term	ACCEPTABLE short-term; limited human data
Tenoxicam	Selective COX-2 (preferential)	NO significant OTM effect	No inhibition reported	Short-term	PREFERRED option when NSAID required
Etoricoxib	Highly selective COX-2	NO significant OTM effect at clinical doses	Negligible OTM impact; favorable GI profile	Clinical doses	MOST PROMISING COX-2 selective NSAID for orthodontic patients
Parecoxib	Highly selective COX-2 (IV)	NO significant OTM effect	No significant inhibition	Parenteral short-term	ACCEPTABLE – limited orthodontic-specific data
Acetaminophen (Paracetamol)	No direct COX inhibition (central mechanism)	NO significant OTM effect (short-term)	Long-term/high-dose may modestly inhibit; short-	Short <1 week: acceptable; Long-term: caution	FIRST-LINE alternative when NSAID OTM risk is a concern

NSAID Agent	COX Selectivity	Evidence for OTM Inhibition	Magnitude of Effect	Dosage/Duration Context	Clinical Recommendation
			term acceptable		

Non-Pharmacological Intervention Efficacy

Non-pharmacological interventions offer analgesic benefit without the systemic adverse effects and OTM inhibition concerns associated with pharmacological agents. The following table summarizes the primary evidence for each non-pharmacological modality.[2,3,4,5]

Table 4. Non-Pharmacological Interventions — Mechanism, Efficacy, and Clinical Evidence

Modality	Mechanism of Action	Primary Evidence (Study)	Peak Efficacy Timepoint	VAS/NRS Reduction	Evidence Quality	Effect on OTM	Patient Acceptability
Low-Level Laser Therapy (LLLT) 980nm / 810nm GaAlAs diode	Photobiomodulation: anti-inflammatory (↓PGE2, ↓IL-1β, ↑endorphins); nerve conduction modulation; analgesia via A-δ fiber inhibition	Khandan Dezfully et al., 2026; Wu et al., 2018; Gao et al., 2025 (NMA)	24–48 hours	Significant ($p<0.05$); SUCRA 81.8 at 24h	High (RCT, triple-blind)	No known negative effect; may enhance healing	High – painless, non-invasive
Vibration Therapy (AcceleDent	Gate control theory; mechanorec	Woodhouse et al., 2015; Sirri et al., 2026	24 hours	Moderate; SUCRA 71.1 at 24h; no sig. OTM	Moderate (RCT but conflicting NMA results)	Possibly neutral/slight acceleration	Moderate – device compliance required

Modality	Mechanism of Action	Primary Evidence (Study)	Peak Efficacy Timepoint	VAS/NRS Reduction	Evidence Quality	Effect on OTM	Patient Acceptability
– 0.25N/30Hz)	eptor stimulation overriding nociceptive Aδ/C-fiber input; osteoblast/osteoclast stimulation	(NMA); Li et al., 2024 (NMA)		acceleration confirmed			
Acupuncture (Traditional /Trigger-point)	Endogenous opioid release (β-endorphin, enkephalin); central pain modulation; hypothalamic–pituitary axis activation	Li et al., 2024 (NMA); Vickers et al., 2017 (chronic pain meta-analysis)	48 hours	Highest of all physical interventions at 48h (SUCRA 89.6)	Moderate–High (strong for chronic; limited orthodontic-specific RCTs)	No negative effect	Moderate – patient acceptance varies by culture
Cognitive Behavioral Therapy (CBT)	Pain catastrophizing reduction; attentional distraction; nocebo prevention;	Wang et al., 2012 (RCT, n=450)	Days 3–30 post-archwire	Significantly greater VAS reduction than control ($p<0.001$); sustained to Day 30	High (large RCT, n=450, intention-to-treat)	No effect	High – patient education-based; no device required

Modality	Mechanism of Action	Primary Evidence (Study)	Peak Efficacy Timepoint	VAS/NRS Reduction	Evidence Quality	Effect on OTM	Patient Acceptability
	central sensitization modulation; serotonergic/descending inhibitory pathway activation						
Chewing (gum/wafers)	Mechanoreceptor stimulation; proprioceptive masking of PDL nociceptive input; endogenous opioid modulation	Li et al., 2024 (NMA)	6–24 hours	Moderate analgesia; effective in NMA pooled analysis	Moderate (RCT pool in NMA)	No effect	High – simple, low-cost, immediately accessible
TENS (Transcutaneous Electrical Nerve Stimulation)	Gate control; endorphin release; orthodontic specific evidence limited	Narrative evidence only (Long et al., 2016)	Variable	Limited orthodontic-specific evidence	Low (no primary RCTs in included studies)	No known effect	Moderate

Modality	Mechanism of Action	Primary Evidence (Study)	Peak Efficacy Timepoint	VAS/NRS Reduction	Evidence Quality	Effect on OTM	Patient Acceptability
Dietary modification / Soft diet	Reduction in masticatory force on sensitized PDL; passive pain avoidance	Prajwos et al., 2025; Negruțiu et al., 2024	Throughout treatment	Pain during chewing ↓ significantly	Low (observational)	No effect	High – universally applicable patient education

Table 5. Patient-Reported Quality of Life and Satisfaction by Appliance Type and Intervention

Study	Sample (N)	Appliance/Intervention	QoL Instrument	Key Finding	Statistical Significance
Antonio-Zancajo et al., 2020	120	Conventional brackets / Low-friction / Lingual / Aligners	Modified McGill + OHIP-14	Lingual brackets: OHIP-14 total 1.3±1.2 (best); Aligners: 1.7±1.9; Conventional: highest impact	p<0.01 lingual vs others; all groups sig. different
Negruțiu et al., 2025	160	Fixed appliances vs Clear aligners	Structured questionnaire (13 items)	FA: 91.4% pain frequency, 95.2% analgesic use; CA: significantly lower on both metrics	Not formally reported (observational)
Pham et al., 2026	Not specified	Clear aligners vs Fixed appliances (deep bite)	Structured satisfaction questionnaire	CA group: significantly higher satisfaction in ALL categories	p<0.001 CA vs FA all satisfaction domains

Study	Sample (N)	Appliance/Intervention	QoL Instrument	Key Finding	Statistical Significance
Negruțiu et al., 2024	160 (3 age groups)	Fixed appliances by age group	Questionnaire	Adults >18y: more dietary changes, greater weight loss, more pain impact than children 6–12y; Females self-selected treatment for aesthetic reasons	Between-group age differences noted; sig. dietary impact in adults
Morgan et al., 2024	42	CAT (n=22) vs FBS (n=20)	Questionnaire + weight measurement	No significant difference in weight changes; self-reported discomfort slightly higher in FBS group	Treatment type not sig. associated with weight change ($p>0.05$)
Yang et al., 2025	480	FA (n=331) vs CA (n=131) vs RA (n=18)	CPDI (distress) + VAS (TMJ)	Higher CPDI in FA group during COVID lockdown; TMJ pain associated with higher distress ($\beta=0.169$, $p<0.001$)	Age >18y ($\beta=0.271$, $p<0.001$), TMJ pain ($\beta=0.169$, $p<0.001$) independently associated with CPDI
Prajwos et al., 2025	Adults ≤6mo FA treatment	Fixed appliances	24-question survey	Females: significantly higher pain levels and medication use ($p<0.05$); chewing = primary pain trigger	Gender sig. influenced pain perception ($p<0.05$)

Table 6: Adverse Events and Safety Profile

Table 6. Adverse Events and Safety Profile of Pharmacological vs Non-Pharmacological Interventions

Intervention Category	Specific Agent/Modality	Reported Adverse Events	Incidence	Clinical Severity	Special Considerations
Pharmacological – NSAIDs	Ibuprofen (oral)	Gastrointestinal symptoms (nausea, dyspepsia), potential renal effects with prolonged use	Common (5–15% GI events)	Mild to moderate	Risk of OTM inhibition; COX-1 gastroprotective inhibition; contraindicated in renal insufficiency, coagulopathy
Pharmacological – NSAIDs	Aspirin	GI ulceration, antiplatelet effects, Reye syndrome risk in children <18 years	Dose-dependent	Moderate to severe	Strongly CONTRAINDICATED in children; significant OTM inhibition
Pharmacological – NSAIDs	Diclofenac	Hepatotoxicity risk with prolonged use; GI events	Less frequent than ibuprofen	Mild to moderate	Significant OTM inhibition; monitor LFTs with long use
Pharmacological – NSAIDs	Etoricoxib (COX-2 selective)	Cardiovascular risk with prolonged use (class	Cardiovascular: rare at short-term doses	Mild (short-term)	Most promising NSAID for orthodontic patients

Intervention Category	Specific Agent/Modality	Reported Adverse Events	Incidence	Clinical Severity	Special Considerations
		effect); GI profile superior to non-selective NSAIDs			– minimal OTM effect
Pharmacological – Acetaminophen	Paracetamol 500–1000mg	Hepatotoxicity with overdose; rare adverse events at therapeutic doses	Rare at therapeutic doses	Mild	No GI or OTM concerns; preferred in GI-sensitive patients; first-line when OTM preservation is priority
Non-Pharmacological – LLLT	GaAlAs diode laser 810–980nm	None reported in included RCTs; theoretical thermal injury risk at incorrect parameters	None reported (0%)	None at correct parameters	Requires trained operator and calibrated device; off-label use in some settings
Non-Pharmacological – Vibration	AcceleDent/vibrational devices	Device discomfort; no systemic adverse events reported	Minimal	None significant	Patient compliance with daily 20-min use required; conflicting evidence on efficacy

Intervention Category	Specific Agent/Modality	Reported Adverse Events	Incidence	Clinical Severity	Special Considerations
Non-Pharmacological – CBT	Psychological intervention	None; potential for increased patient engagement	None	Beneficial side-effect profile	Requires trained therapist; time-intensive; cultural adaptation needed
Non-Pharmacological – Acupuncture	Traditional/trigger-point needling	Needle-site soreness; rare bruising; rare infection risk with non-sterile technique	<5% minor events	Mild	Requires licensed practitioner; patient acceptance variable
Non-Pharmacological – Chewing	Gum/chewing exercises	Potential TMJ loading in susceptible patients	Rare	Mild (contraindicated in active TMD)	Contraindicated in active temporomandibular disorders; otherwise safe and simple

Comparative Efficacy Summary by Time Phase

Table 7. Comparative Efficacy of Interventions by Pain Phase and Time Point (Summary Matrix)

Intervention	0–6 Hours (Immediate)	6–24 Hours (Early)	24–48 Hours (Peak)	48–72 Hours	1 Week	1 Month	OTM Safety	Overall Recommendation
Ibuprofen 400–600mg	★★★★★	★★★★	★★★	★★	★	—	⚠ Moderate risk	First-line short-term (≤7 days)
Acetaminophen 500–1000mg	★★★	★★★	★★	★★	★	—	✓ Safe	Preferred when OTM preservation critical
Etoricoxib (COX-2)	★★★★	★★★★	★★★	★★	★	—	✓ Minimal effect	Promising: analgesia + OTM safety
CBT (behavioral)	★	★★	★★★	★★★★	★★★★★	★★★★	✓ Safe	Superior for long-term pain management
LLLT (810–980nm)	★★	★★★	★★★★	★★★★	★★	—	✓ Safe	Excellent intermediate analgesia; adjunct
Vibration (AcceleDent)	★★	★★★	★★★	★★	★	—	✓ Neutral or slight acceleration	Useful adjunct; compliance-dependent
Acupuncture	★	★★	★★★	★★★★★	★★★	★★	✓ Safe	Best at 48h; long-lasting;

Intervention	0–6 Hours (Immediate)	6–24 Hours (Early)	24–48 Hours (Peak)	48–72 Hours	1 Week	1 Month	OTM Safety	Overall Recommendation
								good adjunct
Chewing/Soft Diet	★★★	★★★	★★	★★	★	—	✓ Safe	Simple, low-cost, universally applicable
Aspirin	★★★	★★	★	—	—	—	✗ CONTRAINDICATED	DO NOT USE in orthodontic patients
Lingual brackets vs FA	Reduced pain experience vs labial FA	★★★★★ pain advantage	★★★★★	★★★★	★★★★	★★★★	N/A (device selection)	Appliance selection strategy for pain-averse patients

★ = *Poor efficacy at this timepoint;* ★★★★★ = *Excellent efficacy;* ⚠ = *Caution;* ✓ = *Safe for OTM;* ✗ = *Contraindicated*

DISCUSSION

Synthesis of Key Findings

This systematic review synthesizes evidence from 18 primary studies (n=2,847 participants) supplemented by 12 systematic reviews and meta-analyses used in narrative analysis, representing the most comprehensive primary-study-level evaluation of pharmacological versus non-pharmacological orthodontic pain management to date. The central finding of this review is that **no single intervention modality achieves universal analgesic superiority across all phases of orthodontic pain**, necessitating a time-stratified, patient-centered, multimodal approach.[1,2,3,6,7]

The characteristic pain trajectory following archwire placement—rapid onset within 2–4 hours, peak intensity at 24–48 hours (mean VAS 42.4 mm from meta-analytic data), and gradual resolution over

5–7 days—defines three clinically meaningful pain phases: (1) the **immediate phase (0–6 hours)** best addressed by rapidly-acting pharmacological agents; (2) the **early-to-peak phase (6–48 hours)** amenable to LLLT and vibration adjuncts; and (3) the **long-term modulation phase (>48 hours–30 days)** optimally managed through behavioral and non-invasive physical interventions such as CBT and acupuncture.[6,8,10]

Pharmacological Interventions: Efficacy and OTM Considerations

Among pharmacological agents, ibuprofen demonstrated the strongest short-term analgesic profile, with a network meta-analytic surface under the cumulative ranking curve (SUCRA) value of 88.4 at 6 hours post-separator placement, corresponding to a mean difference (MD) of −1.93 (95% CI −2.93 to −0.93) versus control. This finding is consistent with the well-established mechanism of ibuprofen as a non-selective COX-1/COX-2 inhibitor that suppresses prostaglandin E2 (PGE2) synthesis in inflamed PDL tissues.[11,19]

However, this analgesic mechanism is pharmacologically inseparable from its inhibitory effect on OTM. PGE2, particularly through its EP2/EP4 receptor subtypes, is a critical mediator of osteoclastogenesis in PDL compression zones—the biological process that enables physiological tooth displacement. Systematic evidence confirms that aspirin, ketorolac, diclofenac, and nimesulide exert **significant, dose-dependent inhibitory effects on OTM**, with aspirin additionally documented to inhibit orthodontic relapse through CD4+ T-lymphocyte suppression. Ibuprofen and celecoxib show inconsistent effects dependent on dose and treatment duration: short-term use (≤7 days) at clinical doses appears unlikely to produce clinically meaningful OTM retardation, while mid-term or high-dose use warrants caution.[11,12,19]

Etoricoxib emerges from the NSAID literature as the most clinically promising agent for orthodontic patients requiring analgesia. As a highly selective COX-2 inhibitor with superior gastrointestinal tolerability compared to non-selective NSAIDs, etoricoxib provides effective analgesia while exerting negligible effects on OTM at clinically prescribed doses. However, the cardiovascular risk class effect mandates caution in patients with cardiovascular comorbidities, and the limited number of human orthodontic-specific trials necessitates further investigation before universal recommendation.[11]

Acetaminophen/paracetamol—acting centrally via endocannabinoid system activation and descending

serotonergic pathway modulation rather than peripheral COX inhibition—presents a favorable safety profile with respect to OTM. While generally less efficacious than NSAIDs for inflammatory pain at equipotent dosing, its absence of OTM-inhibitory effects, absence of GI complications, and minimal adverse event profile make it a first-line recommendation when OTM preservation is a clinical priority, particularly in patients undergoing critical tooth movement phases.[3,12]

Non-Pharmacological Interventions: Mechanisms and Evidence

Low-Level Laser Therapy (LLLT)

LLLT—also termed photobiomodulation therapy (PBMT)—represents the most extensively studied non-pharmacological modality for orthodontic pain. Two high-quality RCTs in this review confirmed its efficacy: Khandan Dezfully et al. (2026), using a 980 nm GaAlAs diode laser with split-mouth design in 31 adult patients, demonstrated significantly lower VAS scores in LLLT-treated quadrants versus placebo at 24 hours for both spontaneous pain and masticatory pain ($p<0.05$). Wu et al. (2018) further demonstrated that a 810 nm diode laser (400 mW, 2 J/cm²) administered at 5 time points significantly reduced NRS pain scores ($p=0.01$) and attenuated somatosensory sensitization—including cold detection thresholds and pressure pain thresholds—at both the treated and contralateral PDL sites, suggesting a bilateral trigeminal modulatory effect extending beyond the direct irradiation zone.[2,3]

At the molecular level, LLLT exerts its analgesic effects through multiple complementary pathways: (1) mitochondrial cytochrome c oxidase activation with enhanced ATP production reducing pro-inflammatory mediator synthesis; (2) upregulation of anti-inflammatory cytokines (IL-10, TGF-β1) and suppression of PGE2, TNF-α, and IL-1β; (3) stimulation of endogenous β-endorphin and enkephalin release; and (4) reversible inhibition of Aδ and C-fiber neural conduction. Notably, LLLT does not inhibit OTM and may, in fact, enhance periodontal tissue regeneration and osteogenesis, potentially accelerating tooth movement in some clinical configurations—an attribute with significant clinical implications for orthodontic treatment planning.[4]

Gao et al. (2025) and Li et al. (2024) consistently demonstrate LLLT superiority over control/placebo at both 6 hours (SUCRA 80.8 in Li et al.) and 24 hours (SUCRA 81.8 in Gao et al.), with ibuprofen showing superiority only at the 6-hour timepoint. This pattern suggests a

complementary temporal relationship: pharmacological agents provide more rapid onset analgesia, while LLLT provides more sustained efficacy across the 24–48 hour peak pain period.[9,10]

Vibration Therapy

Supplemental vibrational force (0.25 Newton/30 Hz, 20 min/day) delivered via devices such as AcceleDent was evaluated in the highest-quality single RCT in this review—Woodhouse et al. (2015), a three-arm parallel-group trial of 81 patients—which found no significant difference in the rate of tooth alignment between the AcceleDent, sham device, and no-device groups (Kaplan-Meier, p=0.66). Network meta-analytic pooled data from Li et al. (2024), however, assign vibration a SUCRA ranking of 71.1 at 24 hours, suggesting moderate analgesic efficacy when individual trial data are synthesized. The discrepancy between this single well-powered RCT and NMA pooled findings highlights the challenge of heterogeneous vibration device parameters, frequencies, and patient populations across studies.[5,10]

More recent NMA data from Sirri et al. (2026) evaluating vibration devices in clear aligner therapy demonstrated a modest improvement in aligner tracking under 7-day change schedules (p=0.003) but no significant improvement in overall treatment outcomes or tooth movement metrics (p=0.999), with pain slightly lower on Days 1–3 only (p<0.05). The overall certainty of evidence for vibration was rated low to very low, underscoring the need for well-designed, adequately powered clinical trials with standardized device parameters.

Cognitive Behavioral Therapy (CBT)

Wang et al. (2012) conducted what remains the most rigorous behavioral intervention study in orthodontic pain management: a three-arm RCT of 450 patients randomized to CBT (n=150), ibuprofen (n=150), or no-treatment control (n=150), using computer-generated block randomization and intention-to-treat analysis. CBT intervention involved structured educational sessions addressing pain catastrophizing, attentional focusing, and adaptive coping strategies prior to and following initial archwire placement. VAS pain scores were assessed at Days 1, 2, 3, 7, 14, and 30. CBT produced significantly greater pain reduction than control across all five pre-30-day timepoints (p<0.001) and was comparable to ibuprofen at Day 30. The mechanism operates through modulation of central sensitization and the cognitive-emotional matrix of pain perception—including the insular cortex, amygdala, hippocampus, and hypothalamus, all of which are

neurologically engaged in orthodontic pain processing.[1,4]

The implication of CBT efficacy in an orthodontic context is profound: pain is not purely nociceptive but involves significant neuromodulatory, cognitive, and psychosocial dimensions. Patient education, expectation-setting, and psychological preparation may substantially alter pain perception without any pharmaceutical intervention. This finding is particularly relevant for pediatric patients, pregnant patients, and those with NSAID contraindications, where pharmacological options are limited.[1]

Acupuncture

Acupuncture—through the release of endogenous opioids (β-endorphins, met-enkephalin, dynorphins) and activation of descending inhibitory pain pathways—demonstrated the highest SUCRA ranking at 48 hours (SUCRA 89.6) among physical interventions in Li et al. (2024). Its long-lasting analgesic effect, likely mediated by persistent neurochemical changes at the level of the spinal cord dorsal horn and periaqueductal gray matter, positions it as an optimal intervention for sustained orthodontic pain management. MacPherson et al. (2017) demonstrated that acupuncture effects persist with only approximately 15% attenuation at 12 months post-treatment in chronic pain populations—a favorable profile for orthodontic patients with recurring pain episodes at each archwire activation.[10]

Appliance Type and Pain Experience

The choice of orthodontic appliance significantly modulates the pain experience. Evidence consistently demonstrates that fixed appliances (particularly conventional labial brackets) are associated with the greatest pain frequency (91.4%), longest pain duration, and highest analgesic demand. Lingual bracket systems paradoxically demonstrate the lowest pain scores and best OHIP-14 QoL scores in the Antonio-Zancajo et al. (2020) prospective study, possibly due to different biomechanical force application patterns, absence of labial bracket-mucosal soft tissue contact, and a patient population with higher baseline orthodontic motivation. Clear aligner therapy (CAT) demonstrates intermediate pain profiles with the advantage of superior dietary compliance and patient satisfaction, particularly in terms of aesthetics and removability.[17,18,21]

The Pham et al. (2026) RCT demonstrated that CAT produced significantly higher patient satisfaction ($p<0.001$) and shorter treatment duration (20.77 vs 27.47 months, $p<0.001$) for deep bite malocclusion compared to conventional braces, while achieving

comparable overbite correction efficacy. These findings reinforce the growing evidence that appliance selection constitutes a legitimate pain management consideration within the orthodontic treatment planning process.[21]

Gender and Age-Related Differences in Pain Perception

Gender-dimorphic pain perception is a well-established physiological phenomenon, and the orthodontic pain literature reflects this pattern. Prajwos et al. (2025) demonstrated significantly higher pain levels and greater analgesic consumption in female patients undergoing fixed appliance therapy ($p<0.05$). Negruțiu et al. (2024) further stratified pain by age group, demonstrating that adult patients (>18 years) experienced greater pain, more pronounced dietary disruption, and greater weight loss compared to younger patients (6–12 years). Adult patients heightened pain sensitivity may relate to: (1) a more mineralized and less vascular PDL with reduced mechanoadaptive capacity; (2) higher prevalence of stress-related central sensitization; (3) enhanced pain catastrophizing mediated by psychological comorbidities.[16,22]

These demographic modifiers underscore the inadequacy of a one-size-fits-all analgesic protocol and strongly support the development of personalized, stratified pain management pathways calibrated to patient age, gender, appliance type, psychological profile, and treatment phase.

Multimodal Analgesia Protocol Recommendation

Based on the synthesized evidence, this review proposes the following evidence-informed, time-stratified multimodal analgesia protocol for orthodontic patients:[1,2,3,6,9,10,11]

Time Phase	Primary Recommendation	Adjunctive Option	Contraindications	Notes
0–2 hours post-archwire (Immediate)	Etoricoxib 60–90mg OR Ibuprofen 400mg (short-term, ≤7 days) OR Acetaminophen 500–1000mg (OTM-sensitive phase)	Chewing exercise (if no TMD)	Aspirin (all ages); Ketorolac; Active peptic ulcer; Renal insufficiency	Pre-emptive dosing 30–60 min before archwire placement may be considered

Time Phase	Primary Recommendation	Adjunctive Option	Contraindications	Notes
2–24 hours (Early-to-Peak)	Continue NSAID/Acetaminophen as above; LLLT application (if available) – single session 980nm or 810nm diode	Soft diet counseling; Chewing exercises	Aspirin; NSAID >7 days in active major OTM phase	LLLT single application at archwire placement visit is most evidence-based timing
24–72 hours (Peak Pain)	LLLT (repeat session at 24h); Continue analgesia as needed (minimum effective dose)	Vibration device (20 min/day AcceleDent-type); Acupuncture session 1 (if patient accepts)	NSAID use beyond 7 days without clinical indication	Peak pain period – most patients need analgesic support; LLLT and vibration complement pharmacological agents
72h–1 week (Resolution Phase)	Wean pharmacological agents; Acupuncture session 2; Patient reassurance counseling	CBT-based self-management techniques (breathing, distraction, pain diary)	Continue NSAIDs beyond 7 days without reassessment	Patient education about pain timeline significantly reduces anxiety and secondary analgesic demand
1 month onward (Long-term Management)	CBT-based pain coping strategies (group or individual sessions)	Acupuncture monthly if needed; Appliance modification (lower force wires at	Aspirin; Long-term NSAIDs without GI protection	Longitudinal behavioral intervention most effective for sustained QoL improvement

Time Phase	Primary Recommendation	Adjunctive Option	Contraindications	Notes
		subsequent activations)		

CONCLUSIONS AND RECOMMENDATIONS

Principal Conclusions

This systematic review of 18 primary studies encompassing 2,847 orthodontic patients demonstrates that:[1–18]

1. No single analgesic modality is universally superior. Pharmacological and non-pharmacological interventions each demonstrate distinct temporal efficacy profiles that are complementary rather than mutually exclusive.

2. Ibuprofen provides the most rapid analgesic onset (0–6 hours) but carries dose- and duration-dependent risk of OTM inhibition, GI adverse effects, and is contraindicated in aspirin allergy, renal insufficiency, and coagulopathy.

3. LLLT (980nm and 810nm GaAlAs diode lasers) demonstrates superior sustained analgesia at 24–48 hours without any adverse effects on OTM, representing an evidence-based, non-pharmacological first-line option for the peak pain period.

4. CBT provides the most durable long-term pain reduction (up to 30 days) with no adverse effects, positioning it as a foundational component of any comprehensive orthodontic pain management program.

5. Etoricoxib (COX-2 selective NSAID) offers a promising pharmacological option balancing effective analgesia with minimal OTM interference, favorable GI profile, and once-daily dosing—making it the preferred NSAID choice when pharmacological treatment is required during active treatment phases.

6. Appliance selection itself constitutes a pain management strategy: clear aligners and lingual bracket systems are associated with significantly lower pain frequency, lower analgesic demand, and better patient-reported QoL compared to conventional labial fixed appliances.

7. A patient-stratified approach is essential: gender, age, psychological profile, pain catastrophizing tendency, and treatment phase must all inform analgesic decision-making. Female adult patients receiving fixed appliances during extraction phases represent the highest-risk pain subgroup requiring proactive, multimodal management.

Clinical Recommendations for Orthodontic Specialists

Based on the totality of evidence, this review recommends:[6,9,10,11,19]

(1) Adopt a pre-emptive analgesic strategy: administer ibuprofen 400mg OR acetaminophen 1000mg 30–60 minutes before archwire placement.

(2) Perform LLLT at the time of archwire placement (single-session; 980nm or 810nm; ≥6 J/point) as an evidence-based adjunct, particularly for high-risk patients.

(3) Incorporate patient education and CBT-based preparatory counseling into the pre-treatment protocol, particularly for psychologically sensitive patients.

(4) When selecting NSAID agents, prefer COX-2 selective inhibitors (etoricoxib, celecoxib) over non-selective agents (aspirin, ketorolac, diclofenac) to minimize OTM risk.

(5) Strictly avoid aspirin in all orthodontic patients, particularly patients under 18 years of age.

(6) Limit NSAID use to the shortest effective duration (≤7 days) at the lowest effective dose, particularly during critical OTM phases (maximum anchorage loading, space closure).

(7) Offer clear aligner therapy or lingual bracket systems to pain-averse patients as part of informed consent and treatment planning discussions.

Recommendations for Future Research

Future research should prioritize: (1) Large-scale, multicenter RCTs comparing ibuprofen, etoricoxib, LLLT, CBT, and vibration therapy in head-to-head designs using standardized VAS/NRS instruments at identical timepoints; (2) Systematic investigation of the pharmacokinetic relationship between NSAID plasma concentration, PGE2 suppression levels, and magnitude of OTM inhibition in human clinical studies; (3) Dose-finding studies for optimal LLLT parameters (wavelength, energy density, number of sessions) specific to orthodontic pain indications; (4) Economic evaluation of multimodal pain management protocols in orthodontic clinical practice; (5) Development and validation of a validated orthodontic pain prediction score integrating demographic, psychological, and appliance-specific risk factors to enable precision pain management.[6,7,20]

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