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Posted Date: 12 March 2025

doi: 10.20944/preprints202503.0827.v1

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The Effects of Non-Steroidal Anti-Inflammatory Drugs Used for Orthodontic Pain Management on Tooth Movement: A Comprehensive Review of the Literature

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Abstract: A common side effect of orthodontic treatment is pain that is typically managed with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). However, the optimal NSAIDs choice for orthodontic pain relief, balancing efficacy and minimal impact on orthodontic tooth movement (OTM), remains unclear. This review investigates the relationship between OTM and orthodontic pain and explores how NSAIDs affect OTM based on a literature search of studies published between 2004 and 2024. Results suggest that ketorolac, nimesulide, and diclofenac may hinder OTM, while aspirin, ibuprofen, meloxicam, and celecoxib show varying effects. Tenoxicam, nabumetone, etoricoxib, and parecoxib appear to have no significant influence on OTM, with etoricoxib presenting as a potentially favorable analgesic. The methodological limitations of the existing studies necessitate further rigorous clinical trials to validate the effects of NSAIDs on OTM in humans.

Keywords: orthodontic pain; orthodontic tooth movement; non-steroidal anti-inflammatory drugs

1. Introduction

Orthodontic pain is an unavoidable consequence and one of the most common side effects of orthodontic treatment. Numerous modalities, including pharmacological and non-pharmacological approaches, have been developed to alleviate orthodontic pain and discomfort in clinical practice [1,2]. The most commonly used pain management drugs for relieving orthodontic pain are acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs) [3].

Acetaminophen is a widely used analgesic, but despite its structural similarity to NSAIDs, it lacks anti-inflammatory effects in peripheral tissues [4]. NSAIDs have been widely shown to be effective in managing orthodontic pain [5,6]. However, there remains an ongoing debate about their potential to slow down the rate of tooth movement and their use in the orthodontic field has been generally discouraged [7–10].

There is no clear scientific recommendation for the best NSAIDs with minimal side effects in orthodontic treatment that allows achieving professional precision and ensuring patient well-being in orthodontic care. Considering this, our study explores the relationship between tooth movement and orthodontic pain, describes NSAIDs used for pain relief, and assesses their impact on tooth movement through a comprehensive literature review.

 doi:10.20944/preprints202503.0827.v1

2. Materials and Methods

An electronic search of the literature was performed using Pubmed and Google Scholar, as detailed in Table 1. This search employed specific keywords in English, which included: "orthodontic pain", "orthodontic tooth movement", "non-steroidal anti-inflammatory drugs". Articles included in the review for the analysis of the effects of NSAIDs on OTM were experimental and clinical studies describing the effects of local or systemic administration of NSAIDs on orthodontic tooth movement (OTM) published between 2004 and 2024 with available full-text access. In contrast, articles were excluded if they were older than the included timeframe or had restricted access. The initial database search yielded a substantial number of articles; however, the rigorous application of our inclusion and exclusion criteria, refined this selection to a final set of 22 articles that met the eligibility requirements.

Table 1. Search strategy summary.

Items	Details
Databases searched	Pubmed, Google Scholar
Search terms used	"orthodontic pain", "orthodontic tooth movement", "non-steroidal anti-inflammatory drugs"
Timeframe	2004-2024
Inclusion criteria	clinical and experimental studies, local or systemic administration of NSAIDs, full text articles, English language only
Exclusion criteria	duplicates, editorials, opinions, correspondences, reviews, full text unavailable, articles not in English language

3. Results

3.1. Characteristics of Orthodontic Pain and Tooth Movement

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [11]. Orthodontic pain, specifically, refers to orofacial discomfort caused by orthodontic tooth movement (OTM) and is commonly characterized as soreness, pressure, and tension in the affected teeth [12,13].

Pain is a subjective experience influenced by factors such as age, gender, and psychological well-being, which explains the variability in how patients perceive it [1]. Surveys of orthodontic patients indicate that pain is frequently reported as one of the most negative aspects of orthodontic treatment and a significant reason for considering discontinuation of care [13–15].

Orthodontic pain can occur at nearly every stage of treatment, including initial wire engagement, banding, wearing elastics, rapid maxillary expansion, braces removal, and separator placement [16]. Research indicates that orthodontic pain typically begins around 12 hours after applying orthodontic forces, peaks within 24 hours, gradually subsides over the next 3 to 7 days, and returns to baseline levels after approximately one month [12,16]. This pain can significantly impact patients' quality of life by impairing chewing and speaking abilities, inducing emotional stress, and even leading to temporary challenges with learning and memory [17,18].

Orthodontic pain is mainly caused by an inflammatory reaction in the periodontium, which accompanies OTM. When force is applied to the crown of a tooth, it is transmitted to the periodontal ligament and alveolar bone. OTM is a process in which the application of a force induces bone resorption on the pressure side and bone apposition on the tension side [19–21]. Under normal

 doi:10.20944/preprints202503.0827.v1

conditions, the movement is highly coordinated and the bone remodeling process is very efficient due to the coupling of bone resorption followed by bone formation. Alveolar bone adaptation to mechanical strains requires a minor reversible injury to the periodontium as part of a physiological process [22].

When orthodontic forces are applied on teeth, a cascade of proinflammatory mediators is activated due to the compression of the periodontal ligament, leading to cellular, vascular, neural and immunological reactions, which ultimately result in orthodontic pain and tooth movement [21]. Orthodontic pain and tooth movement are interrelated and dependent biological events with local inflammation being their common mechanism [17].

When optimal forces are applied on teeth, the vascular vessels are compressed and local ischemia develops [23]. Upon vascular compression and ischemia, anaerobic respiration is activated causing local acidosis. The proton ion H^+ binds to sensory endings and elicits painful sensations which are transmitted to trigeminal neurons [12]. These painful sensations stimulate the release of several neurogenic mediators including but not limited to, substance P, which is responsible for local vascular dilatation and local inflammation [24].

Substance P stimulates the production of RANK-L (receptor activator of nuclear factor-kappa ligand) that plays a critical role in OTM by regulating bone remodeling. It promotes the differentiation and activation of osteoclasts, the cells responsible for bone resorption. During tooth movement, increased RANK-L expression at the pressure sites facilitates bone resorption, allowing the tooth to shift into the desired position [22].

It is well known that the release of these neurogenic mediators stimulates the production of prostaglandins (PGs) in periodontal cells, enhancing inflammation and orthodontic pain, by binding to periodontal sensory endings [25]. Moreover, local acidosis and ischemia stimulate the periodontal cells to release nitric oxide, in order to increase vascular permeability [26]. Once vascular permeability increases, numerous leukocytes such as neutrophils, monocytes and lymphocytes are recruited and release abundant inflammatory mediators, that further amplify local inflammation and bone remodeling due to their ability to stimulate osteoblast and osteoclast differentiation [27].

As orthodontic pain progresses, endogenous opioid molecules are activated to alleviate pain and prevent damage in periodontal tissue, by promoting neovascularization and bone remodeling [28]. When orthodontic forces are reapplied, this process starts over [20,29].

3.2. Effects of NSAIDs on Orthodontic Pain and Tooth Movement

NSAIDs have been used for decades to relieve orthodontic pain. Their effectiveness as analgesic, antipyretic, anti-inflammatory and antiplatelet aggregatory drugs has been confirmed [30]. NSAIDs diminish pain and inflammation by blocking the enzyme cyclooxygenase (COX), which plays a key role in producing PGs. PGs are a group of lipid mediators derived from arachidonic acid, belonging to the family of hormones called eicosanoids. They are pro-inflammatory mediators that induce pain via sensory nerve endings and promote tooth movement by stimulating bone remodeling [2,30]. Among the various types of PGs, prostaglandin E2 (PGE2) is highly effective in promoting vasodilation, vascular permeability, osteoclast activation, and bone resorption, contributing to accelerated tooth movement [8,31]. Certain NSAIDs may reduce this movement by inhibiting PGE2 [32].

PGs are synthesized by two COX isoenzymes: COX-1 and COX-2. COX-1 is a constitutive isoenzyme found in most tissues and organs, where it plays a key role in maintaining general homeostasis and operates without dynamic regulation. In contrast, COX-2 is an inducible isoenzyme that is absent in normal tissues and is expressed only in response to specific environmental stimuli [4,13,20].

There are different types of NSAIDs depending on how they influence the COX-enzyme production [4]. The main NSAIDs identified in the literature for orthodontic pain management are summarized in Table 2.

 doi:10.20944/preprints202503.0827.v1

Table 2. Examples of different types of NSAIDs used for orthodontic pain management.

Types of NSAIDs	Examples
Non selective COX-inhibitors	Aspirin, Ibuprofen, Ketorolac, Tenoxicam
Preferential COX-2 inhibitors	Nimesulide, Diclofenac, Meloxicam, Nabumetone
Selective COX-2 inhibitors	Etoricoxib, Celecoxib, Parecoxib, Rofecoxib

Non-selective COX-inhibitors, are the so-called "traditional NSAIDs" and inhibit both COX-1 and COX-2 isoenzymes. "Traditional NSAIDs" have several advantages such as analgesic and anti-inflammatory efficacy, improved function due to rapid pain relief, reduced side effects on the central nervous system and nevertheless a large variety of agents available on the market. Despite their value, their main disadvantages are related to gastrointestinal toxicity and antiplatelet effect [33].

In order to overcome the unwanted side-effects, especially at the gastric level, but keeping the desired anti-inflammatory effects, preferential and selective COX-2 inhibitors, known as "coxibs" have been developed [4,13]. These drugs specifically inhibit the activity of COX-2 enzyme, which in turn blocks the synthesis of PGs that cause pain and inflammation. Unlike traditional NSAIDs, coxibs do not inhibit COX-1 activity, which is essential for gastrointestinal tract protection and platelet function [34,35]. This clear advantage of coxibs at the gastric level contrasted with a documented increase in cardiovascular risk, which seems to be dose and interval dependent. The negative influence of coxibs seems to be related to a thrombophilic effect due to an imbalance of prothrombotic and antithrombotic factors. However, studies suggest that short-term use of recommended doses of NSAIDs, including coxibs, does not have cardiovascular risks [35,36].

Several studies suggest that conventional NSAIDs may share the cardiovascular risks of coxibs. The MEDAL study compared the COX-2 inhibitor etoricoxib with the preferential COX-2 inhibitor diclofenac in patients with osteoarthritis and rheumatoid arthritis. It found similar cardiovascular thrombosis risks for both drugs during long-term use. Coxibs also showed lower gastrointestinal risk while maintaining comparable efficacy and safety to conventional NSAIDs [35,37].

Inflammatory factors are crucial for tissue remodeling and tooth movement. However, many orthodontic patients take NSAIDs for pain treatment, which suppress COX enzymes and their generation of PGs, decreasing tooth movement rates [22]. This is why acetaminophen has commonly been recommended by many studies to be the best drug in relieving pain associated with orthodontic treatment [5,38]. Acetaminophen has a different mechanism of action compared to NSAIDs and can therefore not be classified as a NSAIDs. Whereas NSAIDs block COX-1 and/or COX-2, acetaminophen is thought to block a third isoform, COX-3, which is expressed only in the brain and the spinal cord, but its mechanism of action is still not completely understood [39]. As a consequence, acetaminophen has minimal effects on PGs synthesis and consequently bone resorption associated with OTM [5,30]. However, pain caused by orthodontic treatment is due to the peripheral inflammation that is much more effectively counteracted by the increased anti-inflammatory effect of NSAIDs.

3.3. Types and Effects of NSAIDs

Several studies investigated the effect of different types of NSAIDs on tooth movement, as compared to control/placebo groups or to administration of other analgesics. In the following section, the details of the included studies are summarized. Acetaminophen has not been described separately as it is not a classical NSAIDs. The results of the databases search, relevant to the topic of this review, are presented in summary in Table 3. A further summary of the effects of the discussed NSAIDs on OTM are detailed in Table 4.

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Table 3. The results of the databases search.

Authors, year	Study group, sample size and distribution	Substance investigated	Applied force, movement	Administration path, Frequency of administration, dosage	Study duration	Method of evaluation of OTM	Outcomes	Conclusion
1. Olteanu *et al.*[40], 2015	Wistar rats, 24, divided into 3 groups of 8 subjects each	Aspirin Algocalmin	25 g from a nickel–titanium closed coil-spring between the inferior first molar and left inferior incisor	Gastric gavage Every 2 days for 10 days, the next day after device application CG (group I): no intervention EG1 (group II): 1.5 mL aspirin (concentration 20 mg/mL) EG2 (group III): 1.2 mL algocalmin (concentration 5 mg/mL)	28 days	Histological study for size of bone areola determination (μm) Distance from the initial position to the final position of M1 (mm)	Reduced size of bone areola in EG1 (74) and EG2 (127) compared to CG (244) Reduced OTM in EG1 (0.03) and EG2 (0.19±0.08) compared to the CG (3.61±0.29)	OTM and bone remodeling were more reduced in the aspirin group
2. Shetty *et al.*[32], 2013	Humans, 42, randomly divided into 3 groups of 14 subjects each	Ibuprofen Acetaminophen	150 g from a nickel-titanium tension spring between the maxillary molars and canines, after extraction of premolars	Oral administration At the appliance activation, for 2 days, 3 times daily CG: no intervention EG1: ibuprofen 400 mg EG2: acetaminophen 500 mg	7 days	Quantitative PGE2 levels in GCF samples from the maxillary canines using ELISA, before (T0) and after spring activation at 24 (T1), 48 (T2), and 168 h (T3)	A statistically significant decrease in PGE2 levels in the EG1 at T1 (p=0.002) and T2 (p=0.011) when compared to CG. A statistically significant difference in the mean concentrations of PGE2 between the two EG at T1 (p=0.006) and T2 (p=0.011)	OTM was more reduced in the ibuprofen group due to inhibition of PGE2 synthesis
3. Arias and Marquez-Orosco [41], 2006	Wistar rats, 36, divided into 4 groups of 9 each	Aspirin Ibuprofen Acetaminophen	35 g from a 3-spin loop made of 0.016-in beta-titanium alloy wire between the incisors	Gastric gavage Every 12 hours for 10 days, diluted in 0.6 mL of reverse osmosis filtered water CG: 0.6 mL of reverse osmosis filtered water EG1: 100 mg/kg aspirin 500 mg EG2: 30 mg/kg ibuprofen 400 mg EG3: 200 mg/kg acetaminophen 500 mg	10 days	Histological analysis of the bone Average tooth movement of the incisors (mm)	Reduced numbers of resorption lacunae/ osteoclasts during OTM in EG1 (1.86 ±1.15/1.83± 1.18) and EG2 (2.00± 1.61/2.48± 2.25) compared with CG (6.09±1.61/ 14.02±5.27) and EG3 (5.86±1.52/ 13.43±4.31) (p<.01) Reduced tooth movement for EG1 (1.32 ±0.28) and EG2 (1.22± 0.29) compared to CG (1.86±0.53) and EG3 (1.80 ±0.41)	OTM and the numbers of resorption lacunae and osteoclasts more reduced in the ibuprofen and aspirin group
4. Tuncer et al. [42], 2014	humans, 48, randomly divided into 3 groups CG-16 subjects	Ibuprofen Acetaminophen	0.014-inch archwire, non-extraction	Oral administration Two tablets, 1 h before the appointment and 6 h after bonding CG (group C): lactose placebo capsule	7 days	Quantitative PGE2 levels (pg/μl) in GCF samples from the maxillary canines with ELISA prior to bonding (T0), right after the	The PGE2 levels in the CG/EG1/EG2 were: T0: 22.33±17.21/ 14.53±13.27/16.14±12.59 T1: 16.81±11.69/9.27±4.81/ 10.89±10.53 T2: 17.33±13.53/19.30±17.25/16. 66±14.39	OTM was not influenced by 1-2 days of ibuprofen use as no time-related differences in PGE2 level were found

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	EG1-17 subjects EG2-15 subjects			EG1 (group A): ibuprofen 400mg EG2 (group B): acetaminophen 500mg	bonding (T1), and on the first (T2), second (T3), third (T4) and seventh day (T5) after bonding	T3: 21.37±24.33/14.52±13.78/21.78±40.11 T4: 17.66±14.90/9.96±7.16/14.63±11.35 T5: 16.18±10.08/11.59±11.84/15.91±13.705	between the groups
5. Rodríguez-Montaño et al.[43], 2024	Humans, 24, randomly divided into 3 groups of 8 subjects each	Ketorolac Acetaminophen	Elastic separator between the upper molar and premolar	Oral administration One capsule every 8 hours for 5 days CG (Group 1): placebo calcined magnesia 500 mg EG1 (Group 2): ketorolac 10 mg EG2 (Group 3): acetaminophen 500 mg	5 days	RANK-L concentrations (pg/µL) from GCF of the right upper first molar mesial zone with ELISA analysis at four time points: before pharmacological intervention (T0), at 24 h (T1), at 48 h (T2), on the 5th day (T3)	Increased RANK-L concentration at T1 in CG (0.146 ± 0.278) compared to EG1 (0.036 ± 0.021) and EG2 (0.047 ± 0.052). RANK-L concentrations at T2 in the 3 study groups did not show a significant difference (CG:0.033, EG1:0.032, EG2:0.033) At T3, RANK-L levels in EG1(0.188 ± 0.446) group remained lower than in CG (0.111 ± 0.118) and EG2 (0.041 ± 0.023) group	OTM may be influenced by ketorolac through a decrease in RANK-L expression
6. Arantes et al. [44], 2009	Humans, 36, randomly divided into 3 groups of 12 subjects	Tenoxicam	Bilateral retraction of the upper canine teeth after premolar extraction with a nickel–titanium spring. Each retraction procedure consisted of three activations that were started on the right side and then alternated between the right and left sides at 14-day intervals	Oral administration, 45 minutes before orthodontic activation, after activation, 24 h and 48 h after activation CG: placebo tablets at all time points EG1 (Group A): 20 mg tenoxicam + placebo + 20 mg tenoxicam at 24 and 48 hours EG2 (Group B): placebo + 20 mg tenoxicam after activation, at 24 and 48 hours. The rescue analgesic offered to the patients in all 3 groups was paracetamol, at a dose of 750 mg, up to four times a day	4 weeks	Measuring the distance between the canine and second premolar teeth with a caliper (mm), prior to activation and 4 weeks later	The orthodontic movement was statistically similar between CG, EG1 and EG2 4 weeks after each orthodontic activation (the distance between the canine and second premolar was between 0.8 and 1 mm in all study groups)	OTM was not influenced by tenoxicam administration
7. Tarvade et al. [45], 2013	Guinea pigs, 28, Group I-24 for biochemical study	Acetaminophen Ibuprofen Nimesulide	A 0.014" spring with two vertical loops between the mandibul	Oral administration, 12 hourly for 3 days CG (Subgroup I and II (a))- no drug administration	3 days	The tooth separation measurements were done between the mesial margins of the incisal edges of the two	At T3, the mean tooth separation was found to be highest in CG (3.70±0.08), while minimal tooth separation was observed in EG2 (2±0.08) and EG3 (1.75±0.148)	OTM, acid phosphatase levels in serum and the rate of bone resorption and

 doi:10.20944/preprints202503.0827.v1

	Group II-4 animals for histological study. Group I and Group II were further divided into 4 subgroups	ar central incisors	EG1 (Subgroup I and II (b)) - acetaminophen suspension EG2 (Subgroup I and II (c)) – ibuprofen suspension EG3 (Subgroup I and II (d))- nimesulide suspension		mandibular incisors using vernier caliper prior (mm) to placement (T0) and 24 h (T1), 48 h (T2) and 72 h (T3) after orthodontic appliance placement Acid phosphatase levels from blood samples 72 h after orthodontic appliance placement Histological study of the bone		appearance of osteoclasts were decreased by ibuprofen and nimesulide administration
8. Knop et al. [46], 2012	Wistar rats, 90, randomly divided into 3 groups of 30 each	Postassium diclofenac Dissodium phosphate	30 g force from a nickel – titanium closed coil spring between the maxillary right first molar and maxillary central incisors. Animals were sacrificed 3, 7, or 14 days after placement of the orthodontic appliance	Intramuscular, daily CG (control): 0.9 % saline solution EG1: 5 mg/kg postassium diclofenac EG2: 2 mg/kg dexamethasone dissodium phosphate	14 days	Histological analysis of the bone at the upper first molars by quantifying osteoclast-like cells, active Howship lacunae, and blood vessels and evaluation of bone neoformation	Reduced numbers of osteoclast-like cells, Howship lacunae and blood vessels throughout all periods studied in the EG1 group compared to CG. Osteoclast-like cells: day 3 (EG1:1.9 ± 0.74, CG: 5.8 ± 1.55), day 7 (EG1:7.5 ± 2.95, CG:16.9 ± 3.35), day 14 (EG1:3.1 ± 1.45, CG:3.3 ± 1.06). Howship lacunae: day 3 (EG1:3.2 ± 1.03, CG:6.4 ± 1.98), day 7 (EG1: 5.8 ± 3.73, CG: 17.8 ± 2.57), day 14 (EG1:5.3 ± 1.95, CG:3.9 ± 1.98). Blood vessels: day 3 (EG1:14.7 ± 2.58, CG:25 ± 3.02), day 7 (EG1:16.8 ± 3.01, CG:7.1 ± 1.45), day 14 (EG1:14.7 ± 3.4, CG:3.1 ± 1.98). At all time-points, EG1 presented lower mature collagen deposition than CG: day 3 (EG1:5.5 ± 2.7, CG:10.78 ± 3.73), day 7 (EG1:29.8 ± 8.13, CG:39.55 ± 4.27), day 14 (EG1:96.9 ± 2.08, CG:100 ± 0)	OTM movement is reduced by potassium diclofenac as it inhibits bone resorption during the initial period of OTM and consequently a delay in collagen maturation during bone neoformation
9. Kirschneck et al. [47], 2017	Fischer-344 rats, 63, randomly divided into three consecutive experiments of 21 animals (A/B/C)	Meloxicam	25 g from a modified nickel-titanium closed coil tension spring. Between the molars	Oral gavage, 10 days prior to orthodontic force CG: no intervention EG1: orthodontic force EG2: orthodontic force with a daily oral 3 mg/kg meloxicam	28 days	Quantification of tooth movement velocity after 14 and 28 days of OTM by means of cone-beam computed tomography	A significantly reduced mean tooth movement velocity was observed both within 14 and 28 days of OTM of M1 (day 14 -64%, day 28 -46%; p<0.001) and for mesialization of M2 (day 14 -51%, day 28 -54%;p<0.001) in EG2. A significant reduction of mesial drift of the third upper left molar in an	Meloxicam reduces PGs synthesis that subsequently causes a corresponding reduction of RANKL/OPG expression ratio and associated osteoclastoge

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	in three experimental groups of 7 animals each. Experiment A quantified tooth movement velocity	and incisors				anterior direction was also observed following meloxicam medication (day 14-40%, day 28–35%)	nesis, thus retarding OTM by about 50%
10. Villa et al. [48], 2005	Humans, 25, CG-16 premolars EG- 34 premolars	Nabumetone	113 g intrusive force on the first premolars from a 0.017x 0.025 stainless steel archwire	Oral administration, 2 days before the orthodontic activation and for 4 more days after CG: two tablets placebo every 24 hours EG: two tablets nabumetone 500 mg every 24 hours	8 weeks	Measurements with a digital Vernier calibrator (mm) on the initial casts of each patient and on casts taken after the orthodontic movement was made	Intrusive movement was: CG: 1.711 and EG:1.449 mm, with p=0.02	The use of nabumetone does not block OTM. There was a decrease of only 0.13 mm per month
11. Kirschneck et al.[49], 2018	Fischer-344 rats, 40, randomly divided into 4 groups of 10 each	Etoricoxib	25 g from a a modified nickel-titanium closed coil tension spring between the first upper left molar and the upper ipsilateral incisor	Oral gavage One week prior to start of OTM and continued daily until day 28 of OTM CG: 1.5ml tap water per day for 5 weeks EG1: normal dose (7.8mg/kg) etoricoxib 3 consecutive days/week EG2: normal dose (7.8mg/kg) etoricoxib 7 days/week EG3: high dose (13.1mg/kg) etoricoxib 7 days/week	35 days	CBCT imaging at the orthodontic left jaw side at the start and end of the experiment	Anterior metric tipping of M1 was significantly inhibited (p=0.046) by about 33% only in EG3 (median=0.5 mm) compared to CG (median=0.8±0.2 mm) with a respective, but insignificant tendency also detectable for the normal dosages	OTM is not influenced by clinically relevant dosage regimens of etoricoxib used in clinical practice to treat dental or orthodontic pain
12. Kirschneck et al. [50], 2020	Fischer-344 rats, 40, randomly divided into 4 groups of 10 each	Etoricoxib	25 g from a a modified nickel-titanium closed coil tension spring between the first upper left molar and the upper ipsilateral incisor	Oral gavage One week prior to start of OTM and continued daily until day 28 of OTM CG: 1.5ml tap water per day for 5 weeks EG1: normal dose (7.8mg/kg) etoricoxib 3 consecutive days/week EG2: normal dose (7.8mg/kg) etoricoxib 7 days/week	35 days	OTM-associated dental root resorptions, osteoclastogenesis, trabecular number and periodontal bone loss were quantified by histomorphometrical, histochemical and microCT analyses of the disected tooth-bearing upper jaw sections	Reduced trabecular number in CG (p=0.0849) and EG1 (p=0.0609), whereas in EG2 (p=0.2449) and EG3 (p=0.5786) this effect was not present. Osteoclastogenesis and osteoclast activity were not significantly increased in any of the groups	Etoricoxib in clinically relevant doses does not affect osteoclasto-genesis, trabecular number in the alveolar bone and remodelling associated with OTM. Only a slight inhibitory effect on bone remodelling is to be

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				EG3: high dose (13.1mg/kg) etoricoxib 7 days/week			expected at high dosages.
13. Abdaljawwad and Al-Groosh [7], 2022	Humans, 40, randomly divided into 4 groups of 10 each	Acetaminophen Ibuprofen Etoricoxib	0.012-inch archwire was placed for alignment as a starting archwire and the usual wire sequence was followed (0.014-inch, 0.016-inch, 18-inch NiTi) at 6 weeks visit intervals	Oral administration, 1h before bonding and archwire placement and continued for 3 days including the bonding day CG: starch capsules once daily EG1: acetaminophen 500mg thrice daily EG2: ibuprofen 400mg thrice daily EG3: etoricoxib 60mg once daily	4 months (24 weeks)	Measuring the Little's irregularity index (mm) in the lower arch, before bonding and at each archwire changing visit which was made every 6 weeks till the end of alignment stage directly in patients' mouth using a four-digit caliper	Mean mesial tooth displacement was: CG:1.3±0.544 EG1: 1± 0.28 EG2: 0.9± 0.155 EG3:1.25 ± 0.866. No statistically significant difference ($p<0.05$) was detected between the experimental groups at any time point	OTM is not influenced by etoricoxib, acetaminophen, and ibuprofen when prescribed with their recommended doses for three days after each archwire placement
14. Hammad et al. [29], 2012	Rats, 40 randomly divided into 4 groups of 10 each	Celecoxib Ketorolac Paracetamol	50 g from a precalibrated closed Sentalloy coil spring between the upper left first molar and the two upper incisors	Gastric gavage, once a day for 2 consecutive months CG: reverse osmosis water EG1: 10 mg/kg celecoxib EG2: 3 mg/kg ketorolac EG3: 150 mg/kg paracetamol	2 months	Measuring the relative separation between M1 and M2 (mm) intraorally using vernier calipers before appliance insertion and immediately after sacrifice Effect on bone resorption using immunohistochemical staining of MMP-13	Mesial tooth displacement was: CG:1.78±0.43 EG1:1.81±0.43 EG2:1.136±0.28; EG3:1.08±0.27. The differences were statistically significant ($p<.001$). The mean number of MMP-13 positive osteoclasts was highest in EG1 followed by CG and was decreased in EG2 and EG3	OTM and bone resorption were not influenced by celecoxib administration
15. Stabile et al. [51], 2009	Wistar rats, 30, distributed in 2 groups of 15 each	Acetaminophen Celecoxib	Activated orthodontic appliance on the upper incisors (30 g on each tooth) that was left for 48 h (appliance group) or was immediately removed after insertion	Oral gavage with 1 ml solution of drug 30 minutes before and 12, 24 and 36 h after fixation of the appliance CG: without orthodontic appliance + carboxymethylcellulose EG1 (CEL): celecoxib 50 mg/kg EG2 (ACET): acetaminophen 200mg/kg EG3 (CMC): carboxymethylcellulose 0.4%	2 days	Quantification of the interincisal gap (mm) by digitalized photographies of the maxilla using the Image J program	In EG1 (1.11 ± 0.05) and EG2 (1.22 ± 0.04) the inter-incisal gap was not affected ($p>0.05$) as compared to the control groups	OTM was not affected by celecoxib use for 2 days

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			(control group)				
16. Jerome et al. [52], 2005	Wistar rats, 20, divided into 3 groups	Celecoxib	80g from a nickel titanium closed coil spring with an additional spring eyelet between the first molar and incisors	Oral administration in the drinking water CG: no treatment EG1: 25 mg/kg celecoxib CG2: 50 mg/kg celecoxib	2 weeks	OTM was measured as the distance between M1 and M2	No differences were found between the three groups of rats (0.5 mm/two weeks)	OTM was not influenced by celecoxib administration
17. Gameiro et al. [53], 2008	Wistar rats, 32, divided into 4 groups: Group I and II – 9 rats each Group III and IV – 7 rats each	Celecoxib	50 g from a closed coil nickel-titanium spring between the maxillary first molar and incisors	Intraperitoneal injections, 2 h before appliance placement and postoperative doses for 2 days CG1 (Group I): saline injections on days 1, 2, and 3 EG1 (Group II): celecoxib (10 mg/kg) twice a day, on days 1,2, and 3 CG2 (Group III): saline injections on days 1 to 14 EG2 (Group IV): celecoxib (10 mg/kg) on days 1 to 14	2 weeks	The distance between the mesial surface of M1 and the distal surface of M3 was measured bilaterally with an electronic caliper under a dental operating microscope The osteoclasts were counted at the alveolar bone surface (compression side) adjacent to the entire mesial root by histochemistry	OTM was significantly reduced in EG1 and EG2 compared to CG (p=.0009). The difference between times of treatment was also significant (p=.0430). The number of osteoclasts did not differ between drugs or times of treatment (p=.1230; p=.4014)	OTM was reduced by both short- and long-term celecoxib administration
18. Sodagar et al. [54], 2013	Rats, 28, divided into 4 groups of 7 each	Celecoxib	60g from a closed nickel-titanium coil spring between the right maxillary first molar and incisors, activated only once at the beginning of the study	Local subperiosteal injections in the buccal mucosa of the upper right M1 at 72 h intervals starting from the first day of appliance insertion to the 18th day (3 days before the end of the study) CG1 (Group 1): no injections EG1 (Group 2): celecoxib (0.3 mg in 0.1 ml saline solution) CG2 (Group 3): normal saline injections (0.1 ml saline solution) CG3 (Group 4): needle penetration	3 weeks	Measuring the space (mm) between the right M1 and M2 with standard interproximal feeler gauge, before appliance removal to avoid any probability relapse Histological study to evaluate root resorption	OTM in EG1 (0.21 ± 0.06) was significantly lower than CG1, CG2 and CG3 (0.54 ± 0.08, 0.51 ± 0.04, 0.58 ± 0.06, respectively). The mean osteoclast counts significantly decreased in EG1 when compared with the other groups	OTM and the number of osteoclasts decreased after celecoxib administration

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				into the subperiosteal space without injecting any solution				
19. Gonzales et al. [39], 2009	Wistar rats, 60, randomly divided into 12 groups of 5 each	Aspirin Acetaminophen Meloxicam Celecoxib Prednisolone	50g from a NiTi closed coil spring between the maxillary left molar and the incisors	Oral administration (via drinking water) CG1 (Negative control): neither pharmacologic treatment/tooth movement CG2 (Positive control): no pharmacologic treatment, but orthodontic treatment EG1: aspirin (high dose 300 mg/kg) EG2: aspirin low dose (60 mg/kg); EG3: acetaminophen (high dose 100 mg/kg) EG4: acetaminophen (low dose 20 mg/kg) EG5: meloxicam (high dose 67 mg/kg) EG6: meloxicam (low dose 13 mg/kg) EG7: celecoxib (high dose 16 mg/kg) EG8: celecoxib (low dose 3.2 mg/kg) EG9: prednisolone (high dose 0.67 mg/kg) EG10: prednisolone (low dose 0.13 mg/kg)	2 weeks	The change in the distance (mm) between the most posterior point of the posterior border of the maxillary first molar crown and the most anterior point of the anterior border of the maxillary second molar crown on digitized lateral cephalometric radiographs	Mean mesial tooth displacement was: CG1: 0 CG2: 0.28 EG1: 0.24 EG2: 0.28 EG3: 0.25 EG4: 0.27 EG5: 0.25 EG6: 0.26 EG7: 0.16 EG8: 0.20 EG9: 0.07 EG10: 0.15	Administration of high-and low-doses of celecoxib reduces OTM in rats, while aspirin, acetaminophen and meloxicam do not seem to affect OTM
20. Sari et al. [31], 2004	Humans, 36, divided into 3 groups of 12 each	Aspirin Rofecoxib	120 g from a nickel-titanium closed-coil spring between the maxillary canines and second	Oral administration CG: no intervention EG1: aspirin 500 mg, 3 times daily, for 2 days EG2: rofecoxib 25 mg on the day of archwire activation and 12.5 mg on the next day	7 days	Evaluating the PGE2 levels (pg/L) in the GCF measured with automated enzyme immunoassay GCF was sampled after the activation of coil spring (T0) and at 24 (T1), 48 (T2), and 168 h (T3)	No statistically significant difference was observed between the rofecoxib and control groups at any time point. PGE2 levels at T1 were: CG: 75.8 EG1: 64.7 EG2: 74.2	OTM was not inhibited by rofecoxib administration in the first day of experiment

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			premolars					
21. De Carlos et al. [55], 2006	Wistar rats, 42, divided into 6 groups of 7 each	Diclofenac sodium Rofecoxib	50 or 100 g from a unilateral closed-coil spring, stretched between the maxillary left first molar and the incisor	injections in the maxillary gingiva, close to the first molar CG1 (CG-50): 50g force and 0.9% saline-solution injections EG1 (R-50): 50g force and 2 injections of 1 mg/kg bw of rofecoxib, on day 1 and day 3 EG2 (D-50): 50g force, 10 mg/kg bw diclofenac CG2 (CG-100): 100g force and same saline solution injection EG3 (R-100): 100g force and same rofecoxib treatment EG4 (D-100): 100g force and same diclofenac treatment	10 days	The distance between the first and second molar (mm) on lateral cranial teleradiographic images	Mesial tooth displacement was: CG1:0.43±0.13 CG2:0.72±0.14 EG3:0.19±0.13 No movement was found in EG1, EG2 and EG4	Using selective COX-2 inhibitors rather than nonspecific COX inhibitors to avoid interference with OTM seems to be no advantage, since both have an inhibitory effect on OTM
22. De Carlos et al.[56], 2007	Wistar rats, 28, divided into 4 groups CG-12 rats EG1-5 rats EG2-6 rats EG3-5 rats	Rofecoxib Celecoxib Parecoxib	50 g from a unilateral closed-coil spring, stretched between the maxillary left first molar and the incisor	3 injections in the maxillary gingiva, close to the first molar, on the day of appliance placement, at day 3 and day 5 by dissolving tablets in saline solution CG: equivolumetric 0.9 per cent saline solution EG1: 0.5 mg/kg bw of Rofecoxib EG2: 8 mg/kg bw Celecoxib EG3: 25 mg/kg bw Parecoxib	10 days	The distance between the first and second molar (mm) on lateral cranial teleradiographic images	Mesial tooth displacement was: CG:0.33±0.07 EG2:0.42±0.09 EG3:0.22±0.04 No movement was found in EG1	Celecoxib and Parecoxib, but not Rofecoxib, are appropriate for discomfort and pain relief while avoiding interference during OTM

bw – bodyweight, CBCT – cone beam computed tomography, COX – cyclooxygenase, CG – control group, CT – computed tomography, EG – experimental group, ELISA - enzyme-linked immunosorbent assay, g – grams, GCF – gingival crevicular fluid, h – hour, kg – kilograms, M – molar, mg- milligrams, mm - millimeters, ml – mililiters, µg – micrograms, MMP- metalloproteinase, OPG – osteoprotegerin, OTM – orthodontic tooth movement, pg/L – picogram/liter, PGE2 – prostaglandin 2, RANK–L - Receptor activator of nuclear factor kappa-B ligand, T - time.

Table 4. Type of included studies and the effects of the discussed non-steroidal anti-inflammatory drugs on orthodontic tooth movement.

NSAIDs	Type of study	Effect on OTM
Aspirin	Clinical [31]	Decreased

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	Experimental (rats) [40,41]	Decreased
	Experimental (rats) [39]	No influence
Ibuprofen	Clinical [32]	Decreased
	Experimental (rats) [41]	Decreased
	Experimental (guinea pigs) [45]	Decreased
	Clinical [7,42]	No influence
Ketorolac	Experimental (rats) [29]	Decreased
	Clinical [43]	Decreased
Tenoxicam	Clinical [57]	No influence
Nimesulide	Experimental (guinea pigs) [45]	Decreased
Diclofenac	Experimental (rats) [46,55]	Decreased
Meloxicam	Experimental (rats) [47]	Decreased
	Experimental (rats) [39]	No influence
Nabumetone	Clinical [48]	No influence
Etoricoxib	Clinical [7]	No influence
	Experimental (rats) [49,50]	No influence
Celecoxib	Experimental (rats) [29,51,52,56]	No influence
	Experimental (rats) [39,53,54]	Decreased
Rofecoxib	Clinical [31]	No influence
	Experimental (rats) [55,56]	Decreased
Parecoxib	Experimental (rats) [56]	No influence

3.3.1. Non Selective COX-Inhibitors

- Aspirin

Aspirin, also known as acetylsalicylic acid, is a powerful NSAIDs that is utilized to effectively reduce pain, fever, inflammation and acts as an antithrombotic. Aspirin acts by irreversibly modifying enzymes COX-1 and COX-2 [30,58].

Olteanu et al. in their study on rats proved the existence of a significant decrease of OTM in the groups in which aspirin and algocalmin were administered, as compared to the control group without drug administration. Moreover, a statistically significant difference was identified by comparison of OTM between the groups in which drugs were administered, the value being more reduced in the group treated with aspirin. The histological study showed that in the control group, the alveolar bone displayed intense bone remodeling associated with orthodontic movement. However, in the group that received aspirin, no signs of bone remodeling were observed [40].

- Ibuprofen

Ibuprofen is a propionic acid derivative and was marketed in 1969 in the United Kingdom as Brufen. It was first used as an alternative to aspirin because of greater tolerance [59]. The anti-inflammatory effect is achieved by blocking the synthesis of PGs in peripheral tissues [30].

Shetty et al., in their study on human subjects, analyzed the effect of ibuprofen and acetaminophen compared to the control group on PGE2 levels in the gingival crevicular fluid (GCF) during OTM. Quantitative evaluation of GCF samples collected from the subjects showed a statistically significant decrease in PGE2 levels in the experimental groups at 24 hours and 48 hours compared to the control group. A highly significant difference in the mean concentrations of PGE2 was observed between the two experimental groups at both time points. This compelling evidence demonstrates that ibuprofen significantly suppresses PGs synthesis in comparison to acetaminophen during the initial and subsequent days of OTM [32].

Arias and Marquez-Orosco compared in their study the effects that aspirin, ibuprofen, and acetaminophen have on OTM and evaluated histologically the differences in bone resorption in the

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pressure area in rats treated with these analgesics. Similar to Olteanu et al.'s study, they concluded that NSAIDs such as aspirin and ibuprofen diminish the number of osteoclasts, probably by inhibiting the secretion of PGs, thereby reducing OTM [41].

However, Tuncer et al. showed in their double-blinded, randomized, placebo-controlled clinical study based on the effects of ibuprofen and acetaminophen on the level of PGE2 during OTM, that there were no statistically significant differences between the two analgesic groups regarding PGE2 levels. The authors concluded that OTM is a multifactorial process which cannot be controlled by only one chemical mediator. Short-term analgesic use during the most painful days of fixed appliance placement does not interfere with OTM. On the other hand, special attention should be given to patients with chronic illnesses such as osteoarthritis, juvenile rheumatoid arthritis or gout where long term analgesic treatment is needed[42].

- Ketorolac

Ketorolac is a NSAIDs commonly used to manage moderate to severe pain, as well as conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, menstrual disorders, and headaches.

Rodríguez-Montaño et al. conducted a double-blinded, randomized clinical trial to compare the effects of of ketorolac and acetaminophen on RANK-L expression in GCF during OTM. They concluded that both ketorolac and acetaminophen may reduce bone remodeling and potentially interfere with OTM. However, they emphasized the need for further studies with larger sample sizes to determine the most suitable analgesic that effectively manages pain without prolonging the duration of orthodontic treatment [43].

- Tenoxicam

Tenoxicam, an NSAIDs with analgesic and antipyretic properties, is used to treat osteoarthritis, backache, rheumatoid arthritis and acute pain [60]. Arantes et al. studied the effect of oral administration of tenoxicam on the OTM of maxillary canines in a randomized controlled double-blinded cross-over study compared to the control group. They concluded that tenoxicam did not influence OTM of the upper canines. The authors selected tenoxicam as an NSAIDs because its long elimination half-life allows for once-daily dosing, providing effective control of acute mild to moderate pain, such as that caused by orthodontic activation, without notable adverse effects [44].

3.3.2. Preferential COX-2 Inhibitors

- Nimesulide

Nimesulide is a mild inhibitor of PGs synthesis and selectively targets COX-2. Its anti-inflammatory effect is achieved by reducing the production of superoxide by neutrophils and inhibiting the synthesis of platelet activating factor [30]. It is used to treat short-term pain after dental surgeries, sports injuries and primary dysmenorrhea [4,30].

A biochemical and histological study conducted by Tarvade et al. in guinea pigs showed that the administration of nimesulide and ibuprofen significantly decreased the rate of OTM and acid phosphatase levels in serum as compared to the acetaminophen and control group. Moreover, administration of nimesulide and ibuprofen significantly modified the appearance of osteoclasts as compared to the control and acetaminophen group, but was not significantly different when compared with each other. A high correlation was found between histological and biochemical findings. Thus, it can be concluded that the level of acid phosphatase in the serum reflects the turnover of alveolar bone during OTM [45].

- Diclofenac

Diclofenac is a monocarboxylic acid derived from acetic acid that inhibits PGs synthesis by acting preferentially on the COX-2 isoenzyme. It has analgesic, antipyretic, and anti-inflammatory properties and it is marketed as sodium and potassium salts for oral administration [61]. It is one of the most widely used NSAIDs, being employed in the treatment of rheumatoid arthritis,

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osteoarthritis, spondylitis, toothache, dysmenorrhea, and inflammatory conditions following trauma or surgery. Diclofenac provides quick relief from pain and swelling [30].

In their study on rats, Knop et al. showed that administration of potassium diclofenac inhibited bone resorption during the initial period of OTM by presenting fewer blood vessels, Howship lacunae, and osteoclast-like cells histologically when compared to the control group. These findings indicate that potassium diclofenac suppresses bone resorption during the early stages of OTM[46]

- Meloxicam

Meloxicam selectively inhibits COX-2 enzyme, having a more favorable side effect profile, compared to both "traditional NSAIDs" and pure COX-2 inhibitors. Although recent clinical research has demonstrated that the analgesic efficacy of meloxicam administered before separator placement is comparable to that of acetaminophen and ibuprofen, there is currently limited information regarding the potential side effects of meloxicam on OTM [62].

In their study on rats, Kirschneck et al. used cone beam computed tomography to quantify the OTM velocity after oral meloxicam administration. By inhibiting PGs synthesis, meloxicam appears to downregulate inflammation and RANKL-induced osteoclastogenesis, resulting in a reduced OTM velocity of about 50%. This effect limits its suitability for use as analgesia during orthodontic therapy. However, the authors concluded that its good gastric tolerance profile suggests potential for future prophylactic use, warranting further study [47].

- Nabumetone

Nabumetone is an effective NSAIDs prodrug that is rapidly converted in the liver into its active metabolite, 6-methoxy-2-naphthyl acetic acid. This active metabolite preferentially blocks COX-2 activity, being responsible for the therapeutic effects of nabumetone [63].

Villa et al. observed in their study on humans pulp-dentinal reactions, root resorption, tooth pain, and tooth movement after the application of a 4-ounce intrusive orthodontic force to human maxillary first premolars in patients given nabumetone. Their results showed that the use of nabumetone does not block OTM when compared to the control group [48].

3.3.3. Selective COX-2 Inhibitors (Coxibs)

- Etoricoxib

Etoricoxib (Arcoxia) is currently the coxib with the highest COX-selectivity available and the only coxib particularly approved for the management of dental postoperative pain [49,64]. It has demonstrated excellent analgesic efficacy with significantly fewer side effects compared to traditional NSAIDs, as confirmed by multiple reviews [65,66]. Moreover, etoricoxib not only has the least inhibitory effect on tooth movement and minimal impact on the gastric mucosa and platelet function, but it also acts as a potent and long-lasting pain reliever during orthodontic treatment, being a potential alternative to acetaminophen [67]. A clinical trial by Gupta et al. that compared the effect of acetaminophen and eterocoxib to a placebo group confirmed that etoricoxib is significantly more effective in managing orthodontic pain than acetaminophen [13].

The experimental study conducted by Kirschneck et al. aimed to investigate the influence of different clinically relevant dosage regimens of etoricoxib on both OTM and cranial growth, since side effects of drugs are generally dose dependent. The study reported that OTM was significantly inhibited by about 33% only in rats receiving high doses of etoricoxib 7 days per week. In relation to its effects on orthodontic treatment, researchers found that it had no impact on the rate of OTM at dosage regimens used in clinical practice to treat orthodontic pain [49].

A further study by Kirschneck et al. found that clinically relevant doses of etoricoxib had minimal impact on osteoclast activity, trabecular number, and bone remodeling during OTM in rats, with only slight inhibition at high doses. They concluded that etoricoxib could be a viable alternative to acetaminophen as an analgesic in orthodontics [50].

Another clinical study conducted by Abdaljawwad et al. aimed to evaluate the effect of ibuprofen, acetaminophen and etoricoxib on pain control and OTM compared to the placebo group.

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The results showed that all three drugs had no influence on the rate of OTM through the whole alignment and leveling period, when used in recommended doses [7].

- Celecoxib

Celecoxib is a highly effective COX-2 inhibitor, with low ulcerogenic potential, used to treat mild to moderate pain, due to its anti-inflammatory, analgesic and antipyretic actions [68].

Hammad et al. studied the effects of different analgesics (celecoxib, ketorolac, and acetaminophen) on OTM and bone resorption compared to a control group using immunohistochemical staining of matrix metalloproteinase-13 (MMP-13) in rats. OTM requires significant remodeling of the periodontium, which is believed to be initiated in the periodontal ligament by MMP. The number of MMP-13-positive osteoclasts was highest in celecoxib-treated group, which means that administration of celecoxib did not decrease bone resorption or impair tooth movement in rats compared with other analgesics tested in this study [29].

Another study by Stabile et al. analyzed the effect of oral administration of acetaminophen and celecoxib on OTM in rats and showed that treatment with both drugs when used for two days did not affect tooth movement. They concluded that short-term treatment with celecoxib may be a safe alternative medication for patients with acetaminophen hypersensitivity or hepatic disease [51]. Similarly, Jerome et al. concluded in their study on rats that oral administration of celecoxib during the application of orthodontic forces does not interfere with OTM and appears to offer some slight protection against root resorption [52].

A recent systematic review with meta-analysis suggested that in the five included studies that analyzed the effect of acetaminophen, aspirin and celecoxib in rats, the short-term (less than one week) use of celecoxib for relieving orthodontic pain might not inhibit OTM [2].

On the other hand, Gameiro et al. in their experimental study on rats rejected the hypothesis that celecoxib administration had no effect on OTM. Although celecoxib did not interfere with the number of osteoclasts, their activity might be reduced, supporting the conclusion that both short- and long-term administration of celecoxib inhibit OTM [53]. Furthermore, another study by Sodagar et al. showed that celecoxib injections decreased OTM and osteoclast count in rats compared to the control groups. They suggested that this might be the result of COX-2 enzyme inhibition and subsequent decrease in PGs production [54].

Gonzales et al. compared in their study on rats the effect of oral administration of high and low doses of aspirin, acetaminophen, meloxicam, celecoxib, and prednisolone in rats compared to the control group. Their result showed that only celecoxib suppressed OTM, while aspirin, acetaminophen, and meloxicam did not seem to interfere with it [39].

- Other coxibs

A clinical study compared the effects of two different NSAIDs, aspirin and rofecoxib, on GCF volume and on PGE2 levels of the GCF during OTM in human subjects as compared to a control group. Rofecoxib was not found to affect PGE2 levels significantly during the experimental period, but aspirin inhibited PGE2 synthesis significantly more than rofecoxib in the first day of the experiment. These results suggest that rofecoxib can be used as an analgesic to control pain without affecting the outcome of orthodontic treatment, but the authors concluded that further studies are recommended [31].

On the other hand, de Carlos et al. showed in their study on rats that rofecoxib and diclofenac both significantly inhibited OTM, partially in the case of rofecoxib and totally in the case of diclofenac. Nevertheless, no statistically significant difference was found between the effects of rofecoxib and diclofenac [55]. A further study by de Carlos et al. compared the effect of injectable administration of rofecoxib, celecoxib and parecoxib on OTM in rats. Their results showed that rofecoxib completely inhibited OTM in rats, whereas celecoxib and parecoxib did not [56].

However, rofecoxib was withdrawn in 2004 from US and European markets by their manufacturer because of reports of increased cardiovascular events and skin rashes, respectively [6].

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4. Discussion and Conclusions

This literature review examines various NSAIDs utilized in managing orthodontic pain during tooth movement. With the growing array of available medications, it is essential for orthodontists to stay informed, particularly about the mechanisms underlying each drug therapy and the clinical management of inflammatory symptoms customized to each patient. Moreover, patients could use NSAIDs for other medical conditions or independently of their orthodontic treatment, highlighting the need for orthodontists to be informed about their potential effects to influence the biomolecular pathways of tooth movement.

Traditional pain management methods rely on the administration of acetaminophen and NSAIDs. Acetaminophen is one of the most widely used analgesics for pain relief. However, its effects at the pain site are relatively weak and insufficient to provide substantial relief. While it has been shown to have no effect on tooth movement, similar to other non-opioid analgesics, acetaminophen exhibits a "ceiling effect," where in increasing doses beyond a certain threshold fails to enhance pain relief.

NSAIDs, on the other hand, achieve analgesia primarily through the peripheral inhibition of PGs synthesis, a key contributor to OTM-associated pain. However, NSAIDs may also reduce the rate of tooth movement. Concerns regarding the side effects of conventional NSAIDs have prompted the development of selective COX-2 inhibitors to mitigate gastrointestinal toxicity.

Findings from reviewed studies indicate that drugs such as ketorolac, nimesulide and diclofenac can decrease tooth movement, while aspirin, ibuprofen, meloxicam and celecoxib yielded inconsistent results. Conversely, tenoxicam, nabumetone, etoricoxib, and parecoxib appear to have no significant influence on OTM. Among these, etoricoxib emerges as a potentially favorable analgesic for orthodontic pain management. It may serve as an alternative to acetaminophen, which, while centrally acting on COX-3, does not impact OTM [39]. Additionally, etoricoxib's longer half-life, requiring only once-daily administration, enhances patient compliance [13]. Its favorable safety profile reduces risks of allergic reactions, rhinitis, asthma, and liver damage often associated with high doses of acetaminophen. However, insufficient clinical evidence limits definitive conclusions about its safety and efficacy.

Variability in study findings likely stems from differences in experimental design, including subject type (humans vs. animals), drug protocols (oral vs. injectable administration), and tooth movement characteristics (analyzed tooth, method of evaluation). Standardizing key factors, such as appliance type, drug dosage, and administration period, is crucial for consistent results. Biological differences between humans and animals further complicate generalizations, highlighting the need for well-designed clinical trials to clarify these medications' effects on OTM.

Author Contributions: Conceptualization, I.M.C.S., H.E., A.P., D.F. and M.G.; methodology, I.M.C.S., A.P., M.S.S. and O.B.; software, A.P.; validation, I.M.C.S., D.F., C.D.O. and M.G.; formal analysis, M.S.S. and O.P.; investigation, I.M.C.S. and A.P.; resources, I.M.C.S. and A.P.; data curation, M.S.S.; writing—original draft preparation, I.M.C.S., A.P., D.F. and M.G.; writing—review and editing, I.M.C.S., M.S.S., C.D.O., M.P. and O.B.; visualization, M.P.; supervision, I.M.C.S., D.F. and M.G.; project administration, I.M.C.S., D.F. and M.G; funding acquisition, I.M.C.S and D.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable. No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

 doi:10.20944/preprints202503.0827.v1

COX	cyclooxygenase
GCF	gingival crevicular fluid
MMP-13	matrix metalloproteinase-13
NSAIDs	non-steroidal anti-inflammatory drugs
OTM	orthodontic tooth movement
PGs	prostaglandins
PGE2	prostaglandin E2
RANK-L	receptor activator of nuclear factor-kappa ligand

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