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REVIEW

Pharmacological Modulation of Orthodontic Tooth Movement: Mechanisms, Clinical Implications, and Emerging Therapeutic Approaches. A Review

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Introduction: Orthodontic tooth movement is a biologically mediated process involving inflammatory signaling and coordinated bone remodeling in response to mechanical force. Increasing evidence suggests that systemic and locally administered pharmacological agents can modulate this process by influencing cellular and molecular pathways regulating osteoclastogenesis and osteogenesis.
Objective: To analyze the role of various medications in orthodontic tooth movement by describing their mechanisms of action, clinical implications, and emerging therapeutic applications.
Methods: A narrative literature review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library databases. Publications in English from January 2010 to October 2025 were screened. Original studies in humans and animal models, in vitro investigations, clinical trials, and relevant systematic reviews addressing drug-related modulation of OTM were included. Non-peer-reviewed publications, incomplete reports, and unrelated studies were excluded. A total of 70 studies met the inclusion criteria and were analyzed through qualitative synthesis.
Results: Pharmacological agents were categorized as inhibitors or accelerators of OTM. Nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, corticosteroids, and certain hormonal therapies were consistently associated with reduced osteoclastic activity and slower tooth movement. Conversely, prostaglandins, vitamin D metabolites, thyroid hormones, and selected molecular modulators demonstrated acceleration effects, primarily in preclinical models. Emerging approaches, including selective estrogen receptor modulators, monoclonal antibodies, and localized drug delivery systems, show promising potential; however, most evidence remains experimental and heterogeneous.
Conclusion: Pharmacological modulation represents a biologically relevant adjunct to orthodontic biomechanics. Nevertheless, current evidence is predominantly derived from animal and preclinical studies, limiting direct clinical extrapolation. Careful assessment of patients' pharmacological profiles is essential for individualized treatment planning, and further controlled clinical trials are required before routine therapeutic implementation.
Keywords: orthodontic tooth movement, pharmacological agents, bone remodeling, drug-tissue interaction, narrative review

Introduction

Orthodontic tooth movement (OTM) is a highly dynamic biological process, resulting from the controlled application of mechanical forces on the teeth.[1,2] These forces are transmitted to the supporting tissues, mainly the periodontal ligament (PDL) and the alveolar bone, causing a complex tissue response involving mechanical, inflammatory, cellular, and

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molecular phenomena.[3] The bone remodeling that underlies this process involves resorption in the pressure zone and bone formation in the tension zone, mediated respectively by osteoclasts and osteoblasts.[4]

However, this process does not occur in isolation; multiple local and systemic factors can modify the speed and quality of tooth movement. Among these, the administration of commonly used drugs is of particular importance, as they can significantly alter the cellular and molecular responses involved in bone remodeling.[5,6]

The increase in demand for orthodontic treatments, especially in adult patients, has coincided with a growing exposure to systemic medications, both prescription and over-the-counter.[7–9] Various drugs have the ability to alter the biological response to treatment, either by inhibiting, slowing down, or even accelerating orthodontic tooth movement.[6,10,11] Through systemic circulation, the active ingredients can reach the paradental environment and modify the molecular pathways that regulate cellular activity and bone remodeling.[4,11]

From a clinical perspective, it is essential to distinguish between conventional medications—those used for general therapeutic purposes, but which unintentionally affect orthodontic tooth movement—and medications designed or adapted to specifically modulate this process. Conventional medications such as nonsteroidal anti-inflammatory drugs (NSAIDs),[11] corticosteroids, bisphosphonates,[12] or hormonal contraceptives[13] can significantly interfere with the kinetics of orthodontic treatment. For example, the widespread use of NSAIDs has been shown to reduce the synthesis of prostaglandins, key elements in osteoclast activation, thus slowing tooth movement.[10,14,15] In contrast, drugs such as vitamin D3,[16] exogenous prostaglandins,[17] thyroid hormones[18] and other cellular modulators[4] are currently being investigated as potential agents to accelerate orthodontic treatment. Localized administration through controlled delivery systems, such as nanoparticles, microcapsules or pharmacological ligatures, allows for localized action in the periodontal ligament, minimizing systemic adverse effects and thus maximizing clinical efficiency.[19]

This duality of effects makes medications a crucial clinical consideration for orthodontists, both as a potential risk factor and as a possible therapeutic adjunct. Integrating the patient's pharmacological profile into orthodontic treatment planning is therefore essential within the framework of increasingly individualized, safe, and evidence-based practice.

Despite the expanding body of literature addressing pharmacological influences on orthodontic tooth movement (OTM), a significant proportion of the available evidence is derived from animal models and in vitro investigations, with comparatively few high-quality randomized clinical trials conducted in humans. In addition, previous reviews have frequently examined either inhibitory or accelerating agents in isolation, without clearly differentiating between systemic and localized drug administration or between short-term biological responses and long-term treatment outcomes. These distinctions are clinically relevant, as systemic medications may exert cumulative or unintended effects on bone remodeling, whereas localized delivery systems are designed to achieve targeted modulation while minimizing systemic exposure.

Therefore, the objective of this narrative review is to analyze the role of various medications in orthodontic tooth movement, describing their mechanisms of action, clinical implications, and emerging therapeutic applications, while critically appraising the level of available evidence and clarifying the boundaries between clinically applicable knowledge and experimental pharmacological strategies.

Materials and Methods

This study was conducted as a structured narrative literature review aimed at critically synthesizing current evidence on the pharmacological modulation of orthodontic tooth movement (OTM).

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. Publications in English from January 2010 to October 2025 were considered. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including "orthodontic tooth movement," "pharmacological agents," "drug effects," "bone remodeling," "NSAIDs," "bisphosphonates," "prostaglandins," "vitamin D," "corticosteroids," and "hormones," using Boolean operators (AND, OR) to optimize retrieval.

Eligible studies comprised original research conducted in humans and animal models, randomized and non-randomized clinical trials, in vivo and in vitro experimental studies, and systematic reviews directly addressing the influence of pharmacological agents on OTM. Exclusion criteria included duplicate records, non–peer-reviewed

publications, conference abstracts without full-text availability, editorials, letters to the editor, and studies not specifically focused on drug-mediated modulation of orthodontic tooth movement.

The initial search identified 101 records. After removal of duplicates and screening of titles and abstracts according to predefined eligibility criteria, 70 studies were selected for full-text review and qualitative synthesis.

Due to substantial heterogeneity in study design, populations, pharmacological agents, dosage regimens, routes of administration, and outcome measures, quantitative meta-analysis was not feasible. Therefore, a narrative synthesis approach was adopted. Particular emphasis was placed on level of evidence (human clinical data versus animal or in vitro studies), mechanism of action, route of administration (systemic versus local), duration of pharmacological exposure (short-term versus long-term), and reported clinical implications.

Results

Biological Foundations of Orthodontic Movement

Orthodontic tooth movement is an adaptive response of the periodontal tissues to a sustained mechanical force applied to the teeth.[20,21] This stimulus generates changes at the cellular and molecular level in the PDL and alveolar bone, which allows bone resorption in the pressure zone and bone formation on the tension side, fundamental processes for controlled tooth movement.[22]

The PDL acts as a primary mechanical sensor. Upon application of orthodontic forces, cells such as fibroblasts, osteocytes, and endothelial cells activate signal transduction mechanisms that trigger the release of local inflammatory mediators.[23] These include prostaglandins, cytokines such as IL-1, IL-6, and TNF-α, as well as growth factors, which modulate the differentiation of osteoclastogenic and osteoblastic precursors, facilitating bone remodeling.[22,24]

In the early stages of OTM, an acute inflammatory response is observed, characterized by local vasodilation, increased vascular permeability, and migration of immune cells to the stimulus area.[25,26] At the molecular level, the RANK/RANKL/OPG pathway stands out as the regulatory axis of the balance between bone resorption and formation. This pathway modulates osteoclast activity and can be altered by both physiological factors, such as the patient's hormonal profile, and by drugs that act on bone tissue.[27]

Furthermore, it is evident that orthodontic force modifies blood flow in the periodontal space, generating transient tissue hypoxia. This hypoxia stimulates the expression of angiogenic and cellular adaptation factors, which act as key signals for the initiation of bone remodeling.[3] Thus, OTM is not a purely mechanical phenomenon, but a complex interaction between physical stimuli and biological responses that depend on multiple individual variables.[1,28]

The magnitude, direction, and duration of the applied force, as well as the patient's systemic condition and the potential influence of medications, are determining factors for the effectiveness of orthodontic treatment. Therefore, a comprehensive understanding of the biological mechanisms of orthodontic tooth movement allows not only for optimizing clinical outcomes but also for anticipating potential pharmacological interferences that may alter the rate or quality of tooth movement.[29] The following section describes medications that can inhibit and accelerate orthodontic movement.

Drugs That Slow Down or Inhibit Orthodontic Movement

Orthodontic tooth movement depends on a delicate balance between bone resorption and formation.[27] This balance can be modulated by various medications that, by interfering with inflammatory signals, bone metabolism, or cellular activity, can slow, inhibit, or alter the normal course of tooth movement.[21] Commonly used medications with inhibitory effects include nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, systemic corticosteroids, and some hormonal therapies.[30–32]

NSAIDs are one of the most relevant pharmacological groups in this context. Their mechanism of action is based on the inhibition of the cyclooxygenase (COX) enzyme, especially the COX-2 isoform, which leads to a reduction in the synthesis of prostaglandin E2 (PGE2), key mediators in osteoclast activation and, therefore, in bone resorption.[33] Clinical studies have shown that the use of ibuprofen and naproxen during orthodontic treatment can significantly decrease the rate of orthodontic tooth movement. In a multicenter trial, patients who received ibuprofen for post-adjustment pain

management had lower rates of tooth movement compared to those who used alternative methods, such as chewing gum.[14] Similarly, another study with naproxen reported that treated patients exhibited a statistically significant reduction in the rate of tooth displacement compared to unmedicated controls, confirming that the inhibitory effect is dose-dependent and more pronounced in prolonged therapies.[15] In contrast, acetaminophen, which acts primarily on the central nervous system without inhibiting peripheral prostaglandins, appears to have minimal impact on this process. For this reason, it would be considered a safer analgesic alternative for patients undergoing orthodontic treatment.[34,35]

Bisphosphonates, used primarily for the treatment of osteoporosis and bone metastases, have one of the most potent inhibitory effects on orthodontic tooth movement.[12,36] These molecules integrate into bone tissue and decrease osteoclast activity by inducing apoptosis, directly blocking the bone resorption necessary for OTM.[37] Preclinical studies in animal models have shown that even at low doses, tooth movement becomes clinically imperceptible, while in patients with osteoporosis treated with alendronate, a marked reduction in the rate of tooth movement was observed. This finding presents a significant therapeutic challenge, especially in older adults and cancer patients.[38]

Regarding systemic corticosteroids, such as prednisone, their action is complex and dual. While they can induce an initial phase of bone resorption, their prolonged use leads to suppression of osteoblastic activity, inhibiting bone formation and disrupting remodeling homeostasis.[39] In the long term, this results in slow, irregular tooth movement and an increased risk of periodontal complications.[40]

It is also important to consider the adverse effects of sex hormones, particularly estrogens.[41] These hormones reduce bone resorption by inducing apoptosis of osteoclasts and inhibiting the differentiation of their precursors.[21] In women receiving hormone replacement therapy or during physiological stages such as pregnancy, a decrease in the speed of OTM has been reported. Clinical studies have documented those patients under estrogen treatment exhibited significantly slower tooth movement compared to controls, confirming its protective effect against bone loss.[42,43] This type of hormonal influence underscores the importance of a comprehensive assessment of the patient's systemic and hormonal status before starting treatment.[44]

Finally, other drugs with potential inhibitory effects, although less studied, include antihistamines, immunosuppressants, statins, and certain antiepileptics.[29,45] Their mechanism of action may involve the suppression of inflammatory pathways, immunomodulation, or alteration of bone metabolism, which could subtly but cumulatively interfere with OTM.[46]

Current evidence indicates that most of these drugs affect orthodontic movement by reducing osteoclastic activity, inhibiting local inflammation, or decreasing bone turnover.[47] In clinical practice, their prolonged or combined use can compromise therapeutic goals, necessitating constant adjustments to the orthodontic treatment plan.[48] Therefore, a complete and up-to-date medication history is essential to anticipate potential interferences, individualize treatment, and ensure predictable and safe results.[49]

Drugs That Accelerate Orthodontic Movement and Emerging Therapies

The duration of orthodontic treatment is a constant concern for both professionals and patients. Therefore, in recent years, research has intensified into pharmacological agents capable of accelerating OTM, to optimize clinical results and reduce treatment time.[16,50] These drugs act through different mechanisms, such as: stimulation of bone resorption, increased local inflammatory response, activation of pro-remodeling pathways, or enhancement of angiogenesis.[51]

One of the most promising agents in this context is vitamin D3, particularly its active form 1,25-dihydroxyvitamin D. This substance plays a key role in bone homeostasis and the regulation of calcium metabolism and has been shown to stimulate osteoclast differentiation through RANKL expression. Local administration of vitamin D has been evaluated in animal and human models, demonstrating a significant acceleration of osteoclast differentiation without relevant systemic adverse effects.[44,52]

Prostaglandins, especially prostaglandin E2 (PGE2), have also been the subject of multiple studies.[26,53] These molecules promote bone resorption by activating specific receptors that increase osteoclastic activity.[14] Exogenous application of PGE2 to orthodontic pressure zones has been shown to increase the rate of OTM, although its clinical use is limited by possible side effects such as excessive inflammation, pain, or loss of periodontal support. To overcome these barriers, controlled release systems are being developed that allow for safe, localized dosing.[24] Among the most studied strategies are injectable microdeposits, biodegradable hydrogels, and polymeric nanoparticles that enable slow

and sustained release of PGE2 into periodontal tissues.[53,54] These delivery vehicles not only aim to maintain stable therapeutic concentrations at the application site but also to reduce the risk of excessive inflammation, post-injection pain, or periodontal attachment loss. Furthermore, the combination of PGE2 with bioactive matrices and controlled-release systems represents a promising approach to achieving a balance between clinical efficacy and biosafety in accelerating orthodontic tooth movement.[55,56]

Among the hormones with therapeutic potential are the thyroid hormones, particularly triiodothyronine (T3).[54] This hormone increases the metabolic rate and stimulates bone resorption by activating osteoclasts.[20] In preclinical studies, its application has been shown to double the rate of OTM compared to control groups. However, due to its systemic effects, its clinical use is still in the experimental phase and under evaluation.[26,51,57]

Another modulator under study is nitric oxide (NO), a molecule with vasodilatory and pro-inflammatory functions.[55] Nitric oxide (NO) has been shown to indirectly stimulate osteoclastic activity, promoting bone remodeling in hypoxic environments such as those generated by orthodontic forces. Its localized release, using nanostructured systems, has been evaluated with promising results in animal models, where a significant increase in the speed of OTM has been reported, accompanied by greater osteoclastic activity and without relevant systemic adverse effects.[55,56]

Additionally, benzodiazepines such as diazepam and certain opioids have been explored, which could enhance OTM by modulating the neuroinflammatory response to mechanical stimulation.[10] Although these findings come mainly from studies in rodents, they open new lines of research on the role of the central nervous system in the orthodontic response.[58]

On the other hand, and somewhat controversially, non-therapeutic compounds such as nicotine and alcohol have also shown the ability to accelerate tooth movement due to their pro-inflammatory effect. However, their negative impact on periodontal tissues and their association with adverse systemic effects preclude any clinical recommendations in this regard.[59]

Currently, the most innovative efforts are focused on the development of localized delivery systems, such as microcapsules, nanoparticles, or bioactive ligatures.[60] These systems allow for the controlled administration of agents such as vitamin D, prostaglandins, or hormonal modulators directly into the periodontal ligament, reducing systemic exposure and enhancing clinical effectiveness. Studies with PGE2 microcapsules have demonstrated a doubling of the speed of OTM compared to controls.[17] Similarly, nanoparticles designed to release nitric oxide have shown localized osteoclastic stimulation in animal models,[56] and recent reviews highlight their additional potential in friction reduction and antibacterial activity.[23,58] In the case of bioactive ligatures with incorporated drugs, they have been shown to release mediators in a sustained manner that enhance orthodontic tooth movement, with better clinical safety profiles.[16,53] These systems allow the controlled administration of various agents, reducing systemic exposure and enhancing clinical effectiveness at the site of action.[56] This strategy represents an important step towards pharmacologically assisted, personalized and safer orthodontics.[23]

In another study, one of the most disruptive proposals is the application of monoclonal antibodies. For example, denosumab, which specifically inhibits the RANKL ligand, preventing osteoclast differentiation. Although its use during the active phase of orthodontic treatment is contraindicated due to its potent antiresorptive effect, it has shown potential utility in the retention phase, helping to stabilize teeth after treatment is completed.[61]

The use of selective estrogen receptor modulators (SERMs), such as raloxifene, has also begun to be explored.[62] These compounds were initially developed to prevent osteoporosis in postmenopausal women, but it has been suggested that they could act as regulators of orthodontic tooth movement without completely inhibiting it. Their dual action on bone and periodontal tissues makes them promising therapeutic candidates, although further clinical research is still needed to confirm their applicability.[16,63] Another emerging area of research is cannabinoids such as cannabidiol (CBD), which has demonstrated anti-inflammatory and analgesic properties without the psychotropic effects of tetrahydrocannabinol (THC). CBD could represent an alternative for managing orthodontic pain, with the added advantage of not negatively interfering with bone remodeling. While its use is still in the early stages of research, preliminary results suggest its potential future integration into orthodontic practice.[58,64]

In summary, emerging pharmacological therapies offer a new vision for orthodontic treatment: orthodontics guided not only by mechanics, but also by molecular biology and precision pharmacology. The possibility of modulating tissue

response with high specificity opens a promising clinical horizon, although their incorporation must be accompanied by rigorous protocols and a thorough understanding of their mechanisms of action.

Drugs and Their Influence on the Orthodontic Movement

Table 1 presents a summary of the main pharmacological groups evaluated in relation to OTM, detailing their effect on the dynamics of tooth displacement, the most relevant clinical considerations for orthodontic practice, and the type of scientific evidence available that supports these findings.

Clinical Implications for Orthodontists

Contemporary orthodontic practice demands an approach that transcends the mechanical and considers the systemic, biological, and pharmacological environment of the patient.[78] It is becoming increasingly clear that drugs administered for reasons unrelated to orthodontic treatment can significantly influence the tissue response to tooth movement, affecting the effectiveness, duration, and predictability of the treatment.[2,78,79]

Table 1 Pharmacological Agents and Their Influence on Orthodontic Tooth Movement

Type of Compounds	Drugs	Effect on OTM	Clinical Considerations	Type of Evidence	References
NSAIDs	Ibuprofen, naproxen, indomethacin	Slows OTM	Caution in prolonged use during active treatment	Human, Animal	[11,14,15,32,34,35,57,65]
	Etoricoxib	Minimal impact	May preserve remodeling balance	Animal	[66]
Analgesic	Acetaminophen	Minimal or no effect	Preferred analgesic during orthodontics	Human	[32,34,35,57,65]
Antiresorptive	Bisphosphonates (alendronate, risedronate, clodronate)	Slows OTM	May significantly delay treatment	Human, Animal	[37,67]
	Denosumab	Variable	It can be considered as a tool to reinforce anchorage during complex orthodontic treatments	Human (limited)	[61]
Corticosteroids	Chronic corticosteroid treatment	Accelerates OTM	Chronic administration of corticosteroids (such as prednisone or equivalents)	Animal	[40]
Anabolic steroids	Testosterone Cypionate Testosterone undecanoate	Accelerates OTM	They enhance bone and periodontal remodeling	Animal	[39]
Immunomodulators	Cyclosporine A	Accelerates OTM	Risk of gingival hyperplasia	Animal	[68]
Hormones	Estrogens	It influences the speed of OTM	Estrogen and progesterone levels influence bone metabolism and periodontal ligament	Human, Animal	[41,44]
	Thyroxine	Accelerates OTM	There is a lack of solid clinical evidence in humans	Animal, Limited human	[18,54]

(*Continued*)

Table 1 (Continued).

Type of Compounds	Drugs	Effect on OTM	Clinical Considerations	Type of Evidence	References
Vitamins	Vitamin D	Accelerates OTM	Clinical modulator potential of OTM	Animal, Limited human	[52]
	Vitamin C	Slight acceleration	It could accelerate periodontal remodeling	Animal	[69,70]
	Vitamin E	There was no significant effect	It influences bone biology more than speed	Animal	[69,70]
Beta-blockers	Propranolol	Slows OTM	They can decrease the speed of tooth movement due to less bone remodeling	Animal	[71]
Benzodiazepines	Diazepam	Acceleration OTM	Limited evidence	Animal	[10]
Normothymic	Lithium	Slows OTM	It can affect the duration of orthodontic treatment	Animal	[72]
Angiotensin II receptor antagonists (ARA-II)	Losartan	Slows OTM	Significant decrease in the number of osteoclasts	Animal	[73]
Experimental agents	Nitric oxide	Slows OTM	Reduction of root resorption and changes in the vascularization of the periodontal ligament	Animal	[56]
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine	Accelerates OTM	Decreased bone density	Animal	[74]
Selective Estrogen Receptor Modulators (SERMs)	Raloxifene	Modulatory effect	Potential retention application	Animal, Limited human	[62]
Osteoprotegerin	OPG-Fc (a form of recombinant osteoprotegerin)	It reduces orthodontic relapse	It reduces tooth relapse by inhibiting osteoclasts and bone resorption	Animal	[27]
Cannabinoids	CBD and other cannabinoids	It could slow down OTM	Inhibitory effect on bone resorption	Animal	[58,64]
Non-therapeutic	Nicotine, alcohol	Accelerates OTM	Contraindicated Tissue damage	Animal	[59,75]
	Caffeine	Slows OTM	Its influence on osteoclast numbers	Animal	[76]
Fatty acids	Omega-3	Slows OTM	Inhibition of osteoclastic activity	Animal	[77]

In this context, the medical history should go beyond the traditional orthodontic diagnosis and include a detailed pharmacological evaluation, considering both chronic medications and occasional treatments, supplements, hormonal products and phytotherapeutics.[5,80] It is essential to identify those compounds that can interfere with bone metabolism or

modulate the inflammatory response, since their presence can alter the rate of tooth displacement or the quality of remodeling.[81]

The diagnostic and planning phase should incorporate this analysis, anticipating possible variations in the speed or direction of OTM associated with certain medications. Patients taking bisphosphonates, corticosteroids, or immunomodulators, for example, may exhibit a significantly slower response to treatment, requiring adjustments to the biomechanical design, a longer treatment duration, or even a reassessment of the orthodontic indication.[6,11,78]

In more complex cases, an interdisciplinary approach becomes indispensable. Collaboration with treating physicians such as endocrinologists, rheumatologists, gynecologists, oncologists, or immunologists, as appropriate, allows for safer and more personalized treatment decisions. This synergy not only promotes orthodontic efficiency but also the patient's overall health, consolidating comprehensive, high-quality care. Furthermore, advances in pharmacological technologies have opened new opportunities to optimize orthodontic treatment.[82] The use of drug ligatures, nanoparticles, and localized delivery systems allows for the direct introduction of active ingredients into the periodontal ligament, accelerating tooth movement or stabilizing it, depending on the clinical objective. These strategies are still undergoing preclinical evaluation or limited trials,[19,53,54] but they point to a future in which orthodontics will be not only mechanical but also molecularly guided.[65]

In this regard, the often-underestimated retention phase could also benefit from pharmacological strategies. Administering bone remodeling inhibitors, such as denosumab, or using raloxifene, could help prevent relapse in patients at high risk of post-treatment instability.[27,62] These therapies, however, must be carefully evaluated, considering systemic factors, the risk of adverse effects, and specialized medical coordination. Orthodontic clinical decisions should be based not only on tooth position or skeletal pattern but also on the patient's pharmacological environment. Active pharmacovigilance, informed clinical judgment, and continuous professional development allow us to act with greater precision, adaptability, and safety, reaffirming our role as specialists who understand orthodontics as a profoundly biological, individualized, and constantly evolving discipline.[2,78]

Discussion

The analyzed results demonstrate a marked influence of certain drugs on orthodontic tooth movement (OTM), either accelerating, slowing, or modulating post-treatment stability. This variability in the pharmacological response is explained by the diversity of pathophysiological mechanisms involved in bone remodeling, including osteoclastogenesis, inflammatory metabolism, and modulation of periodontal collagen.

Regarding the agents that accelerate orthodontic tooth movement, the local administration of prostaglandins stands out,[17,53] as well as the active form of vitamin D3, which promotes osteoclastic activity.[83]

Similarly, hormones such as levothyroxine[17,18] and vitamin E[69,70] increase the rate of orthodontic tooth movement by stimulating bone metabolism. Accelerating effects have also been described in animal models with exposure to nicotine,[59] alcohol,[75] and cyclosporine A;[68] however, these latter substances compromise bone and periodontal quality, which represents a significant limitation for their clinical use. In contrast, the combined use of vitamin C, involved in collagen synthesis, showed a slight but positive acceleration of orthodontic tooth movement.[70]

On the other hand, a considerable group of pharmacological agents has been shown to slow OTM, particularly those with anti-inflammatory or antiresorptive effects. Traditional NSAIDs such as ibuprofen, indomethacin, naproxen, and diclofenac inhibit prostaglandin synthesis, decreasing the osteoclastic response to orthodontic forces.[32,57,65,84] This effect has also been observed with the use of antibiotics such as doxycycline at sub-inflammatory doses[85] and chemically modified tetracycline,[53] as well as with the use of calcitonin[52] and lithium,[72] all of which are associated with a significant reduction in osteoclastogenesis.

Bisphosphonates such as alendronate and clodronate induce apoptosis in osteoclasts and have demonstrated potent inhibition of OTM.[67,86] Similarly, psychotropic drugs antidepressants,[74,87] lithium carbonate,[72] as well as anticonvulsants such as phenytoin[88] have been associated with a reduction in the rate of orthodontic movement, due to their effects on bone remodeling and periodontal tissues.

However, some drugs have shown a neutral or clinically safe profile, notably acetaminophen, which does not significantly interfere with prostaglandin synthesis or osteoclastic activity.[65] Likewise, the use of etoricoxib, a selective COX-2 inhibitor, appears to maintain analgesia without compromising the efficiency of orthodontic treatment.[66]

A particularly interesting aspect is the use of drugs with beneficial effects during the retention phase, reducing post-treatment relapse. In this regard, simvastatin, administered both locally and systemically, has been documented to improve treatment stability by decreasing bone resorption.[46,89,90] Relaxin has also demonstrated a regulatory role in collagen metabolism, preventing teeth from returning to their original position.[91] Alendronate and propranolol are other agents that promote post-treatment stability, with the latter being especially useful due to its action on the sympathetic response.[6,71,92]

It should be noted that most of the reviewed studies were conducted in animal models or in vitro assays, which limits their direct extrapolation to clinical practice. However, the observed patterns allow for a better understanding of how the systemic and local pharmacological environment can significantly modify orthodontic response.

Limitations of Current Evidence

Despite the growing body of literature addressing pharmacological modulation of orthodontic tooth movement (OTM), the overall certainty of the available evidence remains limited due to methodological and translational constraints.

A substantial proportion of the published data is derived from preclinical research, including animal models and in vitro experimental systems. While these investigations provide critical mechanistic insights into osteoclastogenesis, cytokine signaling, RANK/RANKL/OPG pathways, and bone remodeling dynamics, their external validity for human clinical application is inherently restricted. Interspecies biological variability, differences in bone turnover rates, pharmacokinetic profiles, and controlled experimental conditions introduce a significant translational gap. Consequently, although internal validity within experimental models may be acceptable, the direct clinical applicability of these findings remains uncertain.[2,6,8,11,32]

Methodological heterogeneity further reduces the strength of the cumulative evidence. Studies vary considerably with respect to pharmacological class, route of administration (systemic versus localized delivery), dosage regimens, exposure duration, orthodontic force magnitude, and outcome assessment parameters. Such variability limits comparability across investigations and precludes quantitative synthesis. From an evidence hierarchy perspective, much of the literature corresponds to lower levels of evidence, with limited standardization and potential sources of bias, including small sample sizes and short follow-up periods.

High-quality randomized controlled trials in human populations remain scarce, particularly for emerging therapeutic approaches such as monoclonal antibodies, nitric oxide–releasing systems, selective estrogen receptor modulators (SERMs), and cannabinoid-based compounds. In many instances, promising preclinical outcomes to have not yet undergone rigorous clinical validation. The absence of long-term safety data, standardized endpoints, and adequately powered trials further restricts the certainty of conclusions and prevents formulation of definitive clinical guidelines.

Potential biological trade-offs also warrant consideration within a risk–benefit framework. Pharmacological strategies designed to enhance osteoclastic activity and accelerate OTM may increase susceptibility to adverse events such as root resorption, alveolar bone loss, or periodontal instability if not precisely controlled. Conversely, antiresorptive or anti-inflammatory agents may prolong treatment duration and compromise therapeutic efficiency. These considerations underscore the necessity of individualized clinical decision-making grounded in cautious interpretation of the current evidence base.

Taken together, the available literature reflects a field in active development but characterized predominantly by preclinical data and limited high-level clinical evidence. From an evidence-based medicine standpoint, the overall certainty of the evidence may be considered low to moderate, primarily due to indirectness, heterogeneity, and limited long-term human data. Future research should prioritize well-designed, adequately powered randomized clinical trials, standardized outcome measures, transparent reporting, and comprehensive safety evaluation to strengthen the evidence hierarchy and support clinical translation.

Conclusions

Pharmacological modulation of orthodontic tooth movement constitutes a biologically grounded field with meaningful clinical implications, particularly in the context of patients receiving systemic medications. Robust evidence indicates that commonly prescribed drugs—such as nonsteroidal anti-inflammatory agents, corticosteroids, and antiresorptive therapies—can alter bone remodeling dynamics and thereby influence the rate and predictability of orthodontic tooth movement. These effects are supported by both experimental and clinical observations and should be considered during routine orthodontic treatment planning.

Conversely, pharmacological strategies specifically designed to accelerate orthodontic tooth movement—including targeted molecular therapies, monoclonal antibodies, nitric oxide–releasing systems, selective estrogen receptor modulators, and cannabinoid-based compounds—remain largely investigational. The majority of supporting data originates from preclinical or animal studies, and high-quality human clinical trials evaluating long-term safety, dosage standardization, and therapeutic efficacy remain limited. Consequently, these approaches cannot yet be recommended as established clinical protocols.

At present, the clinical relevance of pharmacological modulation lies primarily in understanding how existing systemic medications may inadvertently influence orthodontic biomechanics, rather than in actively prescribing adjunctive pharmacological agents to modify treatment outcomes. Until stronger human evidence becomes available, pharmacological modulation should be regarded as a promising but experimental adjunct to conventional orthodontic strategies.

Future research must prioritize rigorously designed randomized clinical trials, standardized outcome parameters, and comprehensive safety assessments to bridge the current translational gap and define the precise role of pharmacological interventions within evidence-based and personalized orthodontic practice.

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Disclosure

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