

Pharmacological Modulation of Orthodontic Tooth Movement: Recent Advances in Drug-Based and Targeted Delivery Approaches

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ABSTRACT

Orthodontic tooth movement is a biologically regulated process involving coordinated remodeling of the periodontal ligament and alveolar bone in response to mechanical loading. Although conventional orthodontic mechanics remain the principal means of controlling tooth movement, pharmacological modulation of bone remodeling has emerged as a potential adjunct for accelerating tooth movement, enhancing anchorage, reducing relapse, and managing treatment-related complications. Increasing understanding of the receptor activator of nuclear factor-kappa B ligand/receptor activator of nuclear factor-kappa B/osteoprotegerin (RANKL/RANK/OPG) axis, prostaglandin signaling, osteogenic pathways, inflammatory mediators, and cellular mechanotransduction has provided opportunities for targeted pharmacological intervention.

This review critically examines recent advances in drug-based modulation of orthodontic tooth movement, with particular emphasis on the transition from systemic pharmacological exposure toward localized and controlled drug-delivery strategies. Evidence concerning non-steroidal anti-inflammatory drugs, corticosteroids, bisphosphonates, vitamin D, parathyroid hormone, prostaglandins, statins, osteoprotegerin/RANKL-related approaches, growth factors, and emerging molecular targets is discussed. Particular attention is given to local delivery systems including liposomes, sustained-release formulations, biomaterial-based carriers, microneedle systems, and targeted biological delivery. Recent experimental evidence demonstrates that local delivery of biological molecules can alter osteoclastogenesis and tooth movement while potentially reducing systemic exposure. However, most emerging approaches remain supported predominantly by animal or preclinical evidence, and questions concerning dose, delivery route, tissue specificity, safety, and long-term effects remain unresolved.

The future of pharmacological modulation in orthodontics is likely to depend less on systemic administration of conventional drugs and more on precise, site-specific delivery of biologically active agents. Such strategies may permit controlled modification of alveolar bone remodeling while minimizing unwanted systemic effects. Translational research integrating drug-delivery technology with orthodontic biomechanics may therefore provide a foundation for personalized pharmacological adjuncts to orthodontic treatment.

Keywords: orthodontic tooth movement; pharmacological modulation; drug delivery; RANKL; osteoclastogenesis; bone remodeling; local drug delivery; bisphosphonates; vitamin D; orthodontic anchorage.

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1. INTRODUCTION

Orthodontic tooth movement (OTM) is a consequence of coordinated remodeling of the periodontal ligament (PDL), alveolar bone, vascular tissues, and surrounding cellular environment following application of mechanical force. The biological response involves an inflammatory phase followed by coordinated osteoclastic bone resorption on the pressure side and osteoblastic bone formation on the tension side. The magnitude and rate of movement therefore depend not only on the magnitude and duration of orthodontic force but also on the biological responsiveness of the supporting tissues.

At the cellular level, osteoclast differentiation and activity are strongly influenced by the receptor activator of nuclear factor-kappa B ligand (RANKL), its receptor RANK, and the decoy receptor osteoprotegerin (OPG). Mechanical loading alters the local inflammatory and molecular environment, resulting in changes in RANKL/OPG balance and osteoclastogenesis. Osteocytes have also been identified as an important source of RANKL during orthodontic tooth movement.

These biological mechanisms have generated considerable interest in pharmacological modulation of OTM. Drugs and biologically active molecules may theoretically be used either to accelerate movement or to inhibit unwanted

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movement. Potential applications include reduction of treatment duration, enhancement of anchorage, prevention of post-treatment relapse, control of root resorption and management of alveolar bone limitations.

Conventional pharmacological approaches, however, have an important limitation. Systemic administration exposes multiple tissues to the drug and may produce adverse effects unrelated to orthodontic treatment. This has shifted research toward localized administration and targeted delivery systems capable of concentrating active molecules at the orthodontic site.

Recent evidence has expanded the field beyond conventional drugs to include biologically active proteins, signaling molecules, nucleic-acid-related approaches, nanoparticles and biomaterial-based delivery systems. A particularly important development is the use of degradable microneedle systems capable of delivering molecules such as RANKL directly to local tissues.

The objective of this review is therefore to critically examine recent developments in pharmacological modulation of OTM, with particular emphasis on drug-delivery technology, site-specific administration and translational potential.

2. BIOLOGICAL BASIS OF PHARMACOLOGICAL MODULATION

2.1 Periodontal ligament and inflammatory response

Mechanical orthodontic force produces areas of compression and tension within the PDL. Compression is associated with vascular changes, inflammatory mediator release and osteoclast recruitment, whereas tension promotes cellular proliferation and osteogenic activity.

Prostaglandins, cytokines, chemokines and growth factors participate in this response. Consequently, pharmacological agents capable of altering inflammatory or osteoclastogenic pathways can influence the rate of tooth movement.

2.2 RANKL/RANK/OPG pathway

The RANKL/RANK/OPG signaling system is one of the principal molecular regulators of osteoclastogenesis. RANKL binds to RANK on osteoclast precursor cells and promotes their differentiation and activation. OPG acts as a soluble decoy receptor and reduces RANKL-mediated osteoclastogenesis.

Mechanical force during OTM alters the local RANKL/OPG environment. Therefore, pharmacological enhancement or inhibition of this pathway offers an attractive mechanism for controlling tooth movement.

Experimental local administration of OPG-Fc has demonstrated marked inhibition of orthodontic tooth movement in animal models. Local OPG-Fc reduced osteoclast numbers and significantly inhibited tooth movement, demonstrating the potential of site-specific modulation of osteoclastogenesis.

2.3 Osteocytes as therapeutic targets

The recognition that osteocytes contribute substantially to RANKL production during orthodontic force application has broadened the potential therapeutic target beyond the

PDL fibroblast and osteoclast. Future therapies may therefore target osteocyte-mediated mechanotransduction and bone remodeling rather than directly targeting osteoclasts.

3. PHARMACOLOGICAL AGENTS THAT MAY ALTER ORTHODONTIC TOOTH MOVEMENT

3.1 Non-steroidal anti-inflammatory drugs

NSAIDs are commonly prescribed for orthodontic pain. Their inhibition of cyclooxygenase and prostaglandin synthesis makes them effective analgesics but may also alter the inflammatory component of OTM.

Recent evidence suggests that the effects are drug-, dose-, and duration-dependent. Aspirin, ketorolac, diclofenac and nimesulide have been associated with reduction in tooth movement, whereas findings for ibuprofen, meloxicam and celecoxib have been less consistent.

This creates an important clinical dilemma: an analgesic that effectively suppresses inflammation may potentially interfere with the biological response required for efficient orthodontic movement.

Rather than considering NSAIDs simply as inhibitors of OTM, future research should examine whether dose optimization and localized analgesic delivery can achieve pain control without significantly suppressing the desired remodeling response.

3.2 Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. Their potential influence on orthodontic movement is clinically relevant because an increasing number of adults undergoing orthodontic treatment may have previous or ongoing exposure to antiresorptive medication.

Recent evidence continues to support an inhibitory effect of bisphosphonates on OTM. A 2026 umbrella review found that all included systematic reviews reported reduced OTM following bisphosphonate administration, although much of the evidence originated from animal studies and methodological limitations remain.

The clinical implication is that orthodontic treatment planning should consider antiresorptive drug history. However, systemic discontinuation or modification of antiresorptive therapy cannot be recommended solely to facilitate orthodontic movement and requires medical coordination.

Local delivery of antiresorptive agents represents a potentially different strategy. Experimental studies using locally administered zoledronate demonstrate that site-specific intervention can modify bone remodeling during tooth movement.

3.3 Vitamin D

Vitamin D has attracted considerable attention because of its effects on calcium metabolism, osteoblast differentiation and osteoclastogenesis.

A 2024 systematic review and meta-analysis of randomized clinical trials found that systemic or local vitamin D

administration was associated with enhanced OTM, although the limited number of eligible human studies prevented definitive conclusions regarding broader clinical outcomes such as root resorption.

Vitamin D therefore represents an interesting example of a pharmacological agent where promising biological findings have progressed toward human clinical research.

Future research should investigate whether localized vitamin D delivery can provide predictable enhancement of tooth movement while avoiding unnecessary systemic exposure.

3.4 Parathyroid hormone

Parathyroid hormone (PTH) has complex skeletal effects that depend on dose, duration and route of administration. Intermittent exposure can produce anabolic effects, whereas sustained exposure has different biological consequences.

Experimental orthodontic studies have investigated PTH as an accelerator of tooth movement through modulation of bone turnover. However, translation into routine orthodontic treatment requires determination of appropriate dose, delivery route and safety profile.

The concept is particularly relevant to drug delivery because local controlled release may potentially reproduce desired tissue effects without requiring systemic exposure.

3.5 Prostaglandins

Prostaglandins are important mediators of orthodontically induced bone remodeling. Local administration of prostaglandin-related agents has demonstrated potential to increase the rate of tooth movement in experimental models.

However, the clinical use of prostaglandins is limited by their inflammatory and systemic effects. The development of localized formulations could theoretically improve the therapeutic index by concentrating the active compound around the desired tooth.

3.6 Corticosteroids

Corticosteroids influence inflammatory responses and bone metabolism and may consequently modify orthodontic movement. Their effects are influenced by dosage, duration and systemic exposure.

Because long-term corticosteroid use can negatively influence skeletal health, systemic administration solely to modify orthodontic movement is not clinically justified. Their importance in this field lies mainly in understanding the relationship between inflammatory suppression, bone turnover and OTM.

3.7 Statins

Statins have emerged as potential modulators of bone metabolism because of their osteogenic, anti-inflammatory and immunomodulatory properties.

Experimental studies suggest that simvastatin can increase anchorage and suppress osteoclastogenesis. Local simvastatin delivery has been investigated as a means of maintaining tooth anchorage during orthodontic movement.

More recent experimental work has also examined simvastatin in combination with photobiomodulation, demonstrating that simvastatin reduced tooth movement compared with some laser-treated groups and altered markers associated with bone remodeling.

Despite promising preclinical findings, the absence of robust human trials remains a major limitation.

4. PHARMACOLOGICAL ACCELERATION OF ORTHODONTIC TOOTH MOVEMENT

The concept of accelerating OTM is attractive because orthodontic treatment frequently requires months or years of treatment. Pharmacological acceleration attempts to enhance the rate of bone remodeling while maintaining controlled biomechanics.

A systematic review of locally administered biofunctional molecules identified calcitriol, prostaglandins, RANKL, growth factors, PTH and other molecules as potential accelerators of OTM. However, the evidence remains heterogeneous and many candidate agents have been investigated only in animal models.

An important recent development is the use of RANKL-containing microneedle patches. A hyaluronic acid/alginate microneedle system was developed for sustained local RANKL delivery. The experimental system demonstrated favorable biocompatibility, sustained release and increased osteoclastogenesis, with accelerated tooth movement in rats.

This represents a conceptual shift from conventional drug administration toward engineered delivery of an active biological molecule at the precise anatomical site where bone remodeling is required.

5. PHARMACOLOGICAL INHIBITION OF TOOTH MOVEMENT

Acceleration is only one potential application of pharmacological modulation.

Inhibition of tooth movement may be clinically useful for:

- enhancing orthodontic anchorage;
- reducing unwanted reciprocal movement;
- controlling relapse;
- stabilizing teeth during complex biomechanics;
- protecting vulnerable alveolar bone regions.

OPG-Fc provides an experimental example. Local OPG-Fc administration markedly reduced orthodontic movement by inhibiting osteoclastogenesis.

Local OPG-Fc administration has also been investigated during the retention phase. Experimental evidence demonstrated substantial reduction of post-treatment relapse, supporting the concept that pharmacological modulation of bone maturation could eventually complement conventional retention.

However, these findings should not be interpreted as evidence for routine clinical use. Most such approaches remain experimental.

6. LOCAL DRUG DELIVERY: THE MOST IMPORTANT EMERGING DIRECTION

The major limitation of systemic pharmacological modulation is lack of tissue specificity.

A drug administered orally or intravenously reaches multiple tissues. In contrast, a local delivery system may concentrate the active compound near the PDL and alveolar bone.

Potential advantages include:

- Reduced systemic exposure.
- Higher local drug concentration.
- Controlled release.
- Reduced dosing frequency.
- Improved biological specificity.
- Potential reduction in systemic adverse effects.

Local delivery has already been investigated using injections, liposomes, sustained-release polymers and biomaterial carriers.

An early experimental study demonstrated that local EGF delivered through liposomes increased RANKL expression, osteoclastogenesis and tooth movement in rats. This study provided an early proof-of-concept that a drug-carrier system could be used to alter the biological response to orthodontic force.

Similarly, local delivery of matrix metalloproteinase inhibitors has been shown to inhibit orthodontic movement, demonstrating that extracellular matrix remodeling can also be pharmacologically targeted.

7. LIPOSOMAL AND NANOCARRIER SYSTEMS

Nanotechnology offers several opportunities for orthodontic drug delivery.

Liposomes can encapsulate active molecules and potentially improve local retention. Nanoparticles may provide controlled release, protect biologically unstable molecules and permit modification of surface characteristics for tissue targeting.

However, translation from experimental models to clinical orthodontics requires careful assessment of particle size, surface charge, biodegradability, release kinetics, tissue penetration, immunogenicity, local toxicity and systemic distribution.

Nanocarriers should therefore not be considered inherently safer than conventional drugs. Their safety profile depends on both the active molecule and the carrier system.

8. MICRONEEDLE-BASED DELIVERY

Microneedle technology represents one of the most promising developments for local orthodontic delivery.

The recent hyaluronic acid/alginate/RANKL microneedle patch demonstrates how a biodegradable delivery platform can provide sustained release of a biological molecule while producing a measurable biological response in experimental OTM.

The major potential advantage of microneedles is that they may provide a less invasive alternative to repeated injections while maintaining localized delivery.

Future systems may incorporate RANKL or RANKL-modulating agents, growth factors, osteogenic peptides, antiresorptive drugs, nucleic-acid-based therapeutics and anti-inflammatory molecules.

Nevertheless, clinical translation will require development of standardized dosing, predictable release kinetics and patient-friendly application methods.

9. DRUG DELIVERY FOR ORTHODONTIC ANCHORAGE

Anchorage control remains one of the fundamental challenges in orthodontic treatment.

Conventional methods include extraoral appliances, intraoral anchorage devices, temporary anchorage devices and differential biomechanics.

Pharmacological anchorage enhancement represents a complementary concept.

Local simvastatin delivery has demonstrated increased tooth anchorage in experimental models, associated with reduced osteoclastogenesis and modulation of inflammatory pathways.

OPG-based approaches have similarly demonstrated inhibition of tooth movement and improved anchorage ratios in experimental models.

The future possibility is therefore not simply to accelerate orthodontics, but to pharmacologically differentiate the biological response of individual teeth.

For example, a drug could theoretically be delivered locally to a molar intended to remain stationary while conventional orthodontic force is applied to another tooth. This concept could become particularly relevant to personalized orthodontic biomechanics.

10. PHARMACOLOGICAL CONTROL OF ORTHODONTIC RELAPSE

Orthodontic relapse remains a clinically important problem after active treatment.

Relapse is associated with remodeling of periodontal and alveolar tissues and continued osteoclast activity.

Local OPG-Fc administration has experimentally reduced post-orthodontic relapse and improved recovery of bone parameters.

Statins have also attracted interest because of their potential anti-inflammatory and osteogenic effects and possible influence on relapse.

However, pharmacological retention remains experimental. Long-term safety, optimal timing, dose, treatment duration and effects on periodontal health must be established before clinical application.

11. EMERGING MOLECULAR TARGETS

The field is moving beyond conventional drugs toward molecular regulation of bone remodeling.

Recent research has identified autophagy-related mechanisms, including ATG7, as potential regulators of orthodontic movement through effects on the RANKL/OPG ratio.

Similarly, microRNAs and other regulatory molecules are being investigated for their roles in osteoblast differentiation and mechanotransduction.

These developments raise the possibility of future therapies based on small-molecule inhibitors, peptides, recombinant proteins, RNA-based therapeutics and gene-regulatory approaches. However, such approaches are substantially further from routine clinical application than conventional pharmacological agents.

12. PROTECTION OF ALVEOLAR BONE DURING ORTHODONTIC MOVEMENT

Pharmacological modulation may also be used to protect tissues rather than merely alter tooth velocity.

Orthodontic movement can contribute to alveolar bone dehiscence in susceptible patients. Recent experimental work has investigated prophylactic local delivery of bone-anabolic agents to reduce alveolar bone defects during orthodontic force application.

This suggests a broader therapeutic framework:

Acceleration → Anchorage → Retention → Tissue protection

Rather than viewing pharmacological intervention only as a method for shortening treatment time, future orthodontic drug-delivery systems may be designed to improve the biological safety of tooth movement.

13. CLINICAL TRANSLATION: CURRENT EVIDENCE VERSUS FUTURE POTENTIAL

Despite extensive experimental research, the clinical evidence remains considerably less mature than the preclinical evidence.

The principal limitations include:

- predominance of animal studies;
- heterogeneous drug doses;
- differences in orthodontic force systems;
- different routes of administration;
- variation in outcome measures;
- short observation periods;
- limited human randomized clinical trials;
- uncertain long-term safety.

Recent systematic reviews emphasize that promising biological effects do not necessarily translate into predictable clinical benefits.

Therefore, pharmacological modulation should currently be regarded as an adjunctive research field rather than a replacement for established orthodontic biomechanics.

14. FUTURE OF TARGETED ORTHODONTIC DRUG DELIVERY

The most promising direction is the development of site-specific, controlled and personalized drug delivery.

An ideal orthodontic delivery system would:

1. Identify the biological target.
2. Deliver the active molecule locally.
3. Maintain therapeutic concentration for a predictable period.
4. Minimize systemic exposure.
5. Be biodegradable or easily removable.
6. Avoid damage to PDL and alveolar bone.
7. Permit repeat administration when necessary.
8. Integrate with conventional orthodontic mechanics.

Future systems may combine biomaterials, nanotechnology and molecular biology to produce responsive delivery systems capable of releasing drugs according to local biological conditions.

For example, a biomaterial could theoretically respond to local inflammatory or enzymatic activity and release an active molecule only during a defined phase of tooth movement.

Such systems could eventually allow orthodontists to customize the biological response of individual teeth.

15. SAFETY AND ETHICAL CONSIDERATIONS

The possibility of pharmacologically accelerating tooth movement must not overshadow the biological risks.

Excessive stimulation of osteoclastogenesis could potentially increase root resorption, alveolar bone loss, periodontal complications, unwanted tooth movement and post-treatment instability.

Similarly, excessive inhibition of bone turnover could delay treatment or impair normal tissue adaptation.

Biological agents such as RANKL also raise safety concerns because their molecular targets participate in systemic bone metabolism.

Consequently, local delivery does not automatically eliminate risk. Systemic absorption, dose-dependent effects and long-term tissue responses must be evaluated in well-designed clinical studies.

16. DISCUSSION

The pharmacological modification of OTM has progressed from observations concerning conventional medications to sophisticated experimental approaches involving molecular targets and engineered delivery systems.

The available evidence supports the biological plausibility of modifying OTM pharmacologically. NSAIDs and antiresorptive drugs may inhibit movement, while agents including vitamin D, prostaglandins, PTH and selected biological molecules may enhance remodeling under specific experimental conditions.

However, the most important development is arguably the emergence of localized drug delivery.

Local delivery changes the therapeutic objective from administering a systemic drug to selectively manipulating the microenvironment around an orthodontically moving tooth.

Experimental evidence with OPG-Fc, EGF-liposomes, simvastatin and RANKL-containing microneedles illustrates different versions of this concept.

The next stage of research should therefore focus on the interaction between pharmacology + drug-delivery technology + orthodontic biomechanics + patient-specific biology.

This integrated approach could potentially transform orthodontic pharmacology from a largely experimental concept into a precision therapeutic modality.

17. CONCLUSION

Pharmacological modulation of orthodontic tooth movement is an expanding interdisciplinary field linking orthodontics, bone biology, pharmacology and drug-delivery technology. Conventional medications such as NSAIDs and bisphosphonates can influence the rate of tooth movement, while agents including vitamin D, prostaglandins, PTH and selected anabolic or osteoclast-modulating molecules have demonstrated potential to enhance or inhibit orthodontic movement.

The major emerging opportunity lies in localized and targeted drug delivery. Liposomes, biomaterial-based systems, sustained-release formulations and microneedle platforms may permit controlled modulation of the local bone-remodeling environment while reducing systemic exposure.

Nevertheless, most advanced approaches remain preclinical. Robust human trials are required to establish optimal dosage, delivery route, treatment timing, efficacy and long-term safety.

The future of orthodontic pharmacology is therefore unlikely to depend on simply prescribing drugs to accelerate tooth movement. Instead, it is likely to involve precision delivery of selected biological agents to specific orthodontic sites, enabling controlled modification of bone remodeling, anchorage, retention and tissue protection.

Such an approach could ultimately provide a new generation of personalized pharmacological adjuncts to conventional orthodontic treatment.

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