

AI and Conventional Techniques used for Drugs and Orthodontic Tooth Movement

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Abstract Artificial Intelligence (AI) is emerging as a transformative force in both drug development and orthodontics. This paper provides an overview of key AI techniques employed in these fields. In drug development, AI is accelerating discovery, development, and delivery through generative models, predictive modeling, image analysis, and natural language processing. Orthodontics benefits from AI through image analysis, treatment planning, and patient experience enhancement. Common AI techniques in both domains include machine learning, deep learning, natural language processing, and computer vision. By leveraging these technologies, researchers and clinicians can achieve significant advancements in drug discovery, treatment efficacy, and patient care.



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1. INTRODUCTION

Conventional orthodontic treatment with fixed appliances is likely to last for 20 to 24 months. The duration of orthodontic treatment is one of the major concerns that patients complain about, most-especially the adult patient [1]. One of the first questions asked by new orthodontic patients is: How long will I need to wear my braces? About duration of treatment. Unfortunately, long orthodontic treatment time poses several disadvantages like higher predisposition to dental caries, gingival recession and root resorption, in addition to the demotivation for the patient to complete their treatment. Therefore, there is a demand to find a more suitable and convenient methods to accelerate the rate of tooth movement with the least possible disadvantages.

The World Health Organization (1966) defined drug as any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. During orthodontic treatment, drugs are prescribed to manage pain from force application to biological tissues, manage temporomandibular joint (TMJ) problems and tackle some infection throughout the course of treatment [2].

Apart from these drugs, orthodontists increasingly see patients that use medication for prevention or treatment of various diseases on a regular basis. In the USA, the National Drug Early Warning System (NDEWS) reports data and trends showing that prescription drug abuse explodes. Among prescription medication users, about half used concurrently over-the-counter medications and/or dietary supplements. Orthodontists should be aware of that, as it may result in

increase or decrease in the rate of orthodontic tooth movement (OTM) or other unwanted side effects that should be discussed with the patients [3]. Any pharmacologic agent or supplement consumed by a patient can reach the periodontal tissues through circulation and thus interacts with and influence a cell's response to orthodontic forces [4].

Orthodontic tooth movement is triggered by the prolonged application of controlled mechanical forces activating various cell signaling pathways ultimately leading to stimulation of periodontal ligament metabolism resulting in localized bone resorption and deposition [5]. Inflammatory mediators, neurotransmitters, and growth factors, in addition to numerous other cytokines such as Interleukin-1 (IL-1), play a vital role in orthodontic tooth movement. The main mediators involved in this complex process are hormones and systemic factors, growth factors, cytokines, colony stimulating factors, prostaglandins.

In a study done in Iraq concerning orthodontist's and patient's perception about the time of orthodontic treatment and their willingness to undergo and pay for various acceleration techniques and procedures. The study concluded most orthodontists were willing to pay up to 40% of treatment income for the acceleration procedure, while the payment of patients was up to 20%. Both orthodontists and patients were interested in techniques that can decrease the treatment duration. Noninvasive accelerating procedures were more preferable by orthodontists and patients than invasive surgical procedures [6].



Orthodontic tooth movement has been defined as a result of a biologic response to interference in the physiologic equilibrium of the dentofacial complex by an externally applied force [7]. To achieve OTM, mechanical forces are applied on teeth. This initially causes fluid movement within the PDL space and distortion of the PDL components (cells, extracellular matrix, and nerve terminals), setting into motion the process of release of a multitude of molecules (neurotransmitters, cytokines, growth factors, arachidonic acid metabolites, etc.) which initiate alveolar bone remodeling [8]. One of the immediate responses of the PDL at sites of compression is also the rise in the level of matrix metalloproteinases (MMPs) which are produced by activated fibroblasts. MMPs either degrade collagen fibers (MMP-1 and MMP-8) or eliminate the degraded collagen (MMP-9 and MMP-2) to allow tooth movement [9]. The degradation of collagen is thought to enhance osteoclast activation, osteoclast migration and adhesion to bone.

Prostaglandin E2 (PGE2) is the most widely researched PG with respect to OTM. PGE2 is produced mainly by PDL fibroblasts and osteoblasts [10] by the action of the inducible enzyme COX-2 (cyclooxygenase 2), and subsequently by a specific synthase enzyme (PGE synthase). The newly formed PGE2 has different effects depending on the type of transmembrane receptor to which it binds. PGE2 can drive RANKL expression in osteoblasts (by binding to the Prostaglandin E Receptor 2 (EP2) or EP4 receptors), which subsequently leads to osteoclast activation [11] or drive bone mineralization by osteoblasts when binding to the EP1 receptor addition, PGE2 has been shown to aid osteoclast formation or lead to transient osteoclast inhibition when added to osteoclasts *in vitro*. The displacement of tooth per unit time and is usually measured in mm per an hour, day, week or a month. Clinical studies show OTM rates between 0.55 and 2.44 mm per month when using full fixed appliances and NiTi wires for initial alignment.

2. THEORIES OF ORTHODONTICS TOOTH MOVEMENT

2.1. Pressure tension theory

The histological research about tooth movement by **Schwarz** led him to hypothesize that a tooth moves in the periodontal space by generating a “pressure side” and a “tension side”. This hypothesis explained that, on the pressure side, the Periodontal

Ligament (PDL) displays disorganization and diminution of fiber production. Here, cell replication decreases seemingly due to vascular constriction. On the tension side, stimulation produced by stretching of PDL fiber bundles results in an increase in cell replication and this enhanced proliferative activity leads eventually to an increase in fiber production. The concept taken further, by correlating the tissue response to the magnitude of the applied force with the capillary bed blood pressure. So, the study concluded that the forces delivered as part of orthodontic treatment should not exceed the capillary bed blood pressure (20-26 g/cm² of root surface). If one exceeds this pressure, compression could cause tissue necrosis through “suffocation of the strangulated periodontium.” Application of even greater force levels will result in physical contact between teeth and bone, yielding resorption in areas of pressure and undermining resorption or hyalinization in adjacent marrow spaces.

2.2. BLOOD FLOW THEORY: According to this theory tooth movement occurs as a result of alteration in fluid dynamics in the periodontal ligament. **Bein**, has been credited for proposing the fluid dynamic or the blood flow theory.

2.3. Piezoelectric/bone bending/bioelectric theory:

Piezoelectricity is a phenomenon observed in many crystalline materials, the deformation of crystal structure produces a flow of electric current as electrons are displaced from one part of the crystallite to another [7].

2.4. Mechano-chemical theory

According to this theory, application of physical stress to bone changes solubility of hydroxylapatite crystals, which results in remodeling of bone

2.5. Molecular Concept of Orthodontics Tooth Movement:

A necessary prerequisite for selecting, designing and testing suitable molecules to influence OTM is a detailed knowledge of the role of the different cellular and molecular components driving the biological process of OTM. An outline of the main cellular and molecular components of OTM is shown in (Figure 1).

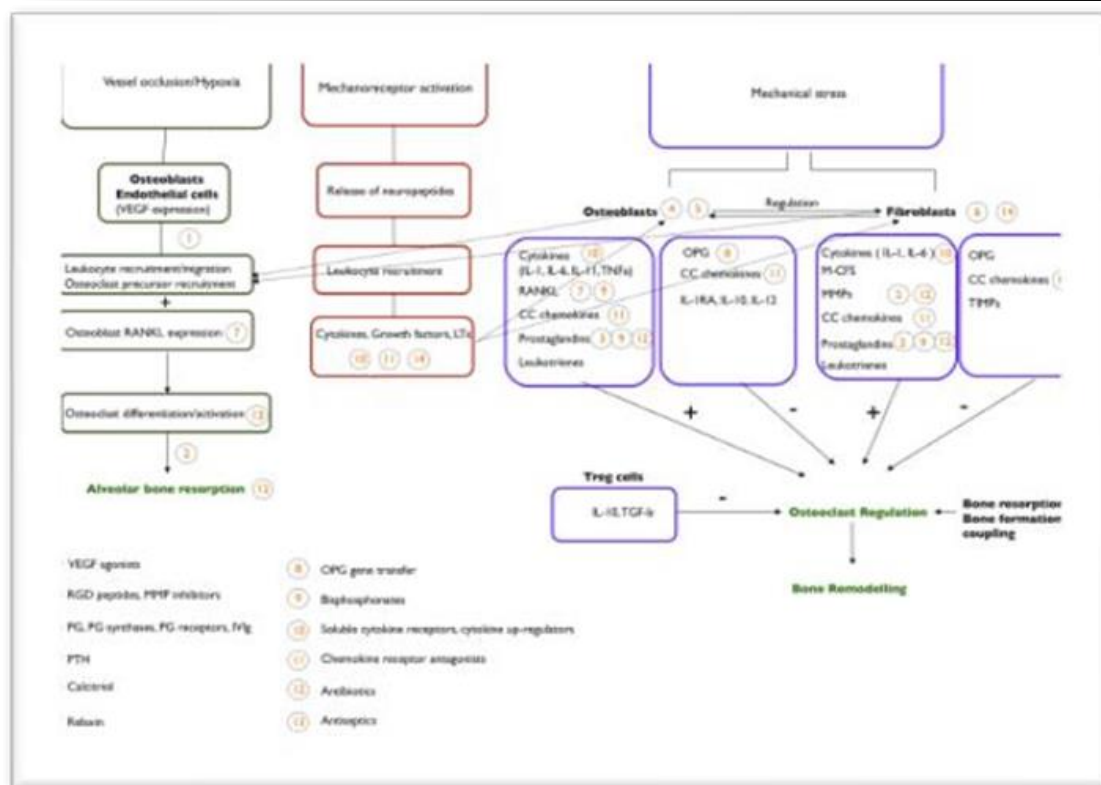


Figure1: An outline of the cellular and molecular mechanism behind the process of OTM.

Potential pharmacological agents that could be used to affect OTM and their site of action are indicated (Krishnan and Davidovitch, 2006). THERE ARE MANY FACTORS WHICH ARE AFFECTING THE RATE OF TOOTH MOVEMENT [12], INCLUDE: (1) Force: Magnitude or Duration, (2) Age, (3) Occlusal interlock, (4) Genetic and Individual variation and (5) Drug and systemic factor.

3. THE SEARCH FOR PHARMACOLOGICAL AGENTS TO CONTROL ORTHODONTIC TOOTH MOVEMENT

In the last decades an increasing number of pharmacological agents have been explored aiming at the identification of suitable pharmacological means of accelerating or inhibiting OTM. Experimental evidence is mainly based on in vitro and animal studies, and a limited number of case-control clinical studies.

3.1. List of Drugs That Affect Tooth Movement

Drugs that affect tooth movement can be divided into drugs that increasing the rate of tooth movement and drugs that decrease the rate of tooth movement as seen below in **Table 1**.

Table 1: Drugs that influence tooth movement (Daniel et al., 2018)

Drugs increasing rate of tooth movement	Drugs decreasing rate of tooth movement
Arachidonic Acid Metabolites	Analgesics
Vitamin D	Fluorides
PTH	Bis-phosphonates
Thyroid hormone	Estrogen
Corticosteroids	Calcitonin
Relaxin	Antibiotics
Growth hormone	
Nicotine	
No effect on tooth movement-Acetaminophen	

4. PHARMACOLOGICAL ACCELERATION OF Vitamin D ORTHODONTIC TOOTH MOVEMENT

A weekly intraligamental injection of a 1,25,2(OH)D3 solution produced a significantly increased amount of orthodontic tooth movement after a 21 -day experimental period, when compared with the control group. On histological level there was an increased rate of recruitment and activation of mononuclear osteoclasts resulting in greater bone resorption of the alveolus on the pressure side of the periodontal ligament than in control teeth [13].

A comparison between local injection of vitamin D and PGEs on two different groups of rats was also investigated. It was found that there is no significant difference in acceleration between the two groups. However, the number of osteoblasts on the pressure side which was injected by vitamin D was greater than on the PGE2 side. This indicates that vitamin D may be more effective in bone turnover [14].

1,25,2(OH)D3 acts directly on the nucleus of the circulating monocytes and osteoprogenitor cells, which have specific receptors for it. Cells in the early stages of the resorption cycle before they fuse and become classic multinucleated osteoclasts. Vitamin D and its active metabolite, 1,25,2(OH)D3, together with parathyroid hormone (PTH) and calcitonin, regulate the amount of calcium and phosphorus levels. Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts.

5. THYROID HORMONES

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. Thyroxine administration led to increased bone remodeling, increased bone resorptive activity and reduced bone density. Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production induced by thyroid hormones at low concentrations, cytokine stimulated osteoclast formation and osteoclastic bone resorption [15].

The thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication. Low dosage and short-term thyroxine administration are reported to lower the frequency of “force-induced” root resorption. Decrease in resorption may be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to “force-induced” osteoclastic resorption.

5.1. Parathyroid Hormone

By local administration PTH analogues both osteoblast and osteoclast activities are stimulated. The receptors of parathyroid hormone are only expressed on the cell membrane of osteoblasts. After the binding of parathyroid hormone molecules to their receptors, the osteoblasts are stimulated to produce more insulin-like growth factor –1 (IGF-I) via a cyclic

adenosine monophosphate (cAMP)-dependent mechanism, which functions as an autocrine/paracrine factor and activates its adaptor molecule insulin- receptor substrate-1 in osteoblast precursors in bone marrow, and causes osteoblast proliferation, differentiation, and function. On the other hand, osteoblasts stimulated by parathyroid hormone molecules also express more RANKL on the cell membrane, which binds to RANK on the cell membrane of osteoclastic precursors through cell- to-cell contact and stimulates osteoclast proliferation, differentiation, and activation [16].

RANKL/osteoprotegerin and IGF-1 are essential molecules for the effect of parathyroid hormone on bone metabolism. RANKL/osteoprotegerin mediates osteoclastogenesis, whereas IGF-1 mediates osteoblastogenesis. the expression levels of both RANKL and IGF-1 increased, indicating that intermittent parathyroid hormones stimulated both osteoclastogenesis and osteoblastogenesis. The biphasic effect of intermittent parathyroid hormone administration resulted in an increased bone turnover rate; this accelerated tooth movement.

Unlike other osteoporosis-treating medicines (eg, bisphosphonates), parathyroid hormone has a more balanced effect on bone metabolism, stimulating both osteoblastic and osteoclastic activities.

5.2. Corticosteroids

Glucocorticoids enhance the responsiveness of osteoblasts to PTH by increasing the expression of PTH receptors in these cells. As the bone-resorbing actions of PTH require the presence of osteoblasts, an increase in PTH receptors in osteoblasts by glucocorticoids. Evidence indicates that the main effect of corticosteroid on bone tissue is direct inhibition of osteoblastic function and thus decreases total bone formation. Decrease in bone formation is due to elevated PTH levels caused by inhibition of intestinal calcium absorption which is induced by corticosteroids.

Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in a treated patient, they decrease the stability of tooth movement and stability of orthodontic treatment in general. When they are used for longer periods of time, the main side effect is osteoporosis. It has been demonstrated in animal models with this type of osteoporosis that the rate of active tooth movement is greater, but tooth movement is less stable since little bone is present and there is no indication of bone formation. A more extensive retention may be required.

5.3. Relaxin

Relaxin has been known as a pregnancy hormone. It is released just before child birth to loosen the public symphysis, so that

the relaxed suture will allow widening of the birth canal for parturition showed that the administration of Relaxin might accelerate the early stages of orthodontic tooth movements in rats. [17] used gingival injections of Relaxin to relieve rotational memory in the connective tissues of maxillary lateral incisors that had been orthodontically rotated. suggested that Relaxin might be used as an adjuvant to orthodontic therapy, during or after tooth movement, for promotion of stability, for rapid remodeling of gingival tissue during extraction space closure, for orthopedic expansion in non – growing patients, by reducing the tension of the stretched soft tissue envelope, particularly the expanded palatal mucosa, after orthognathic surgery.

5.4. Nicotine

During orthodontic tooth movement in the presence of nicotine at a dosage corresponding to that of an average European smoker, an exponentiation of orthodontic root resorption and accelerated orthodontic tooth movement are to be expected in addition to the previously observed increase in periodontal bone loss. Although the achieved acceleration of tooth movement would be desirable for treatment purposes to reduce total treatment time and associated orthodontic treatment risks, the observed severe side effects indicate the need to properly inform orthodontic patients about the risks and the necessity of nicotine abstinence during orthodontic treatment, which should only be started after complete cessation of nicotine consumption. Since tobacco smoke, however, consists of many more pharmacologically active components than nicotine itself, our effects observed in an animal model at a particular nicotine dosage should be clinically translatable to direct nicotine intake, for example, via a nicotine patch, but need not necessarily be generalizable to smokers or tobacco-consuming patients in general or to other dosages of nicotine intake [17].

5.5. Arachidonic Acid Metabolites

Among the arachidonic acid metabolites, PGE2 is by far the most widely tested substance in terms of its capacity to modify OTM. Evidence, mainly derived from animal studies, points toward a positive effect of PGE2 with respect to enhancing bone resorption and accelerating tooth movement. The few available clinical studies are of low quality and involve repeated injections of PGE2 and follow- up times of a maximum of 60 days [18]. The mode of application of PGE2 is a major limitation as it involves repeated injection (due its short half-life) in combination with an anaesthetic solution to alleviate the hyperalgesia caused by injection of PGE2. Potential adverse effects (e.g., root resorption) linked to long-term administration of PGE2, as required in the context of orthodontic treatment, are possible given its mode of action but have not been evaluated so far.

Specific synthases are involved in the pathway of the synthesis of each type of prostaglandins (e.g., PGE and Prostaglandin D (PGD) synthases) and many of them have been cloned and could provide drug targets for the regulation of the synthesis of specific prostaglandins, such as PGE2 in the case of OTM. In addition, it is possible that other PGs such as PGI2 may be involved in bone resorption providing further targets for drugs. Another obvious group of drug target are the identified receptors of specific prostaglandins (such as the receptors EP1, EP2, or EP4 of prostaglandin PGE2) and the design of selective agonists can provide pharmacological methods of modifying OTM through these receptors.

Intravenous immunoglobulin (IVIg) preparations are polyspecific and polyclonal immunoglobulin therapeutic preparations used as a replacement therapy in immunodeficient patients [19]. These IVIg preparations were shown to induce COX-2 mediated PGE2 synthesis and cytokine production. It is possible that local administration of these IVIg preparations could be used to modulate bone modeling through PEG2 induction and bypass some of the limitations of PEG2 injections.

5.6. Growth Hormone

Orthodontic tooth movements appeared to up-regulate Growth Hormone receptor (GHR) and IGF-1R immunoreactivity. The number of IGF1- and IGF-1R- cells

increase significantly on the tension side and decrease on the compression side. These

data indicate a close relationship between the mechanical loading of the PDL and the autocrine/paracrine expression of the components of the IGF system as an early step in the mechanotransduction process leading in the long term to an organized remodeling of the alveolar bone. Orthodontic forces applied for 9 days on the maxillary first molar in rats increase root resorption with an increase in IGF system components, including IGF-1R, IGF2, and IGF binding proteins (IGFBPs), observed in pressure areas and resorption gap. These results suggest an involvement of the IGF system in the resorption-repair sequence, which is a known bone coupling process. Conversely, IGF1, IGF-1R, and PCNA (Proliferating Cell Nuclear Antigen) are less expressed in PDL cells of hypofunctional groups than in controls. These results suggest that occlusal stimuli via orthodontic tooth movements induce cell proliferation of PDL cells by increasing IGF1 and IGF-1R expression. Interestingly, this overexpression of IGF1 may be enhanced in maxillary alveolar bone when occlusal stimuli are associated with physical activity. Of note, recent studies also showed that effects of intermittent PTH on the stability of orthodontic retention are improved by IGF1 [20].

Bone remodeling necessary for orthodontic tooth movements involves active osteoclasts, which are positive for tartrate-resistant acid phosphatase (TRAP) activity and which may also be regulated by GH via GHR. Orthodontic tooth movements appeared to upregulate GHR expression along rat alveolar bone, root surfaces, and PDL. TRAP and GHR-positive cells were increased in the compression side along the alveolar bone, root surface, and in the PDL space in rats treated with orthodontic appliances for tooth movements.

5.7. Interaction of Various Stimulators to Produce Tooth Movement

Conly stimulating factor (M-CSF) acts directly on osteoclast precursor cells to control their proliferation and differentiation. Stimulators of bone resorption such as 1,25(OH)₂ vitamin D₃, parathyroid hormone, and interleukin-1 increase osteoclast formation by stimulating the expression of RANKL by osteoblasts/stromal cells, as shown in Fig. (2).

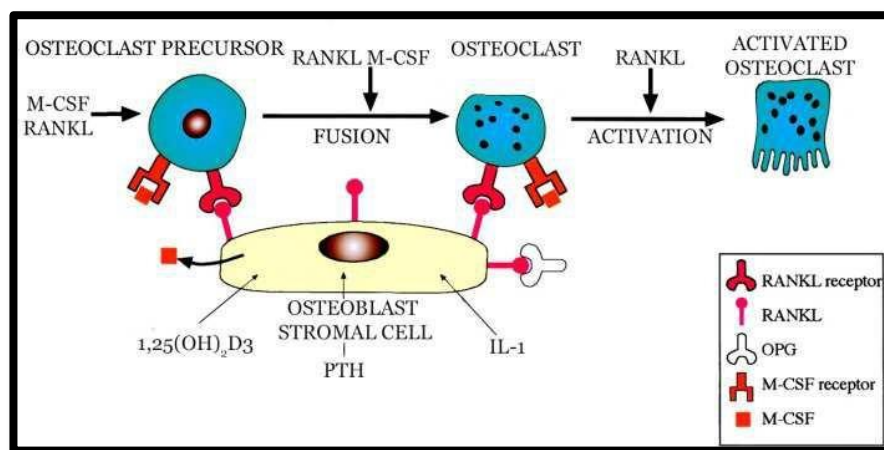


Figure 2: Schematic Diagram showing the mechanism of activation of osteoclast (Meikle, 2006)

6. PHARMACOLOGICAL DECELERATION OF ORTHODONTIC TOOTH MOVEMENT

6.1 Fluorides

Fluoride is one of the trace elements having an effect on tissue metabolism. Fluoride increases bone mass and mineral density, and because of these skeletal actions, it has been used in the treatment of metabolic bone disease, osteoporosis. Even a very active caries treatment with sodium fluoride during orthodontic treatment may delay orthodontic tooth movement and increase the time of orthodontic treatment. Sodium fluoride has been shown to inhibit the osteoclastic activity and reduce the number of active osteoclasts. On the cellular level it has been shown to stimulate bone formation and, recently, it was discovered that the osteoclastic activity in rats is inhibited [21].

6.2. Analgesics

Analgesic is a drug that selectively relieves pain by acting on the Central Nervous System or peripheral pain mechanisms, without significantly altering consciousness. Nonsteroid anti-inflammatory drugs (NSAIDs) do not affect the tenderness induced by direct application of PGs, but block the pain-sensitizing mechanism induced by bradykinins, tumor necrosis factors (TNFs), interleukins (ILs), etc. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG

medicated sensitization of nerve endings. NSAIDs are a relatively weak inhibitor of PG synthesis and anti-inflammatory action may be exerted by reduced generation of

superoxide by neutrophils, and TNF release, free radical scavenging, and inhibition of metalloprotease activity in cartilage [15].

6.3. NSAIDs

Most commonly used medications in orthodontics are for control of pain following mechanical force application to tooth. Inhibition of the inflammatory reaction produced by PGs slows the tooth movement. Recent research demonstrated the molecular mechanisms behind the inhibition of tooth movement by NSAIDs. The levels of matrix metalloproteinases (MMP9 and MMP2) were found to be increased, along with elevated collagenase activity, followed by a reduction in procollagen synthesis which is essential for bone and periodontal remodeling. The whole process is controlled by inhibition of cyclooxygenase (COX) activity, leading to altered vascular and extravascular matrix remodeling, causing a reduction in the pace of the tooth movement [22].

6.4. Aspirin

Acetylsalicylic acid and the related compounds, and their action result from inhibition of COX activity, which converts unsaturated fatty acids in the cell membrane to PGs. Clinical

experience shows that orthodontic tooth movement is very slow in patients undergoing long-term acetylsalicylic therapy. Salicylate therapy decreases bone resorption by inhibition of PG's synthesis and may affect differentiation of osteoclasts from their precursors. Therefore, it is recommended that patients undergoing orthodontic treatment should not be advised to take aspirin and related compounds for longer period during orthodontic treatment.

6.5. COX-2 inhibitors

An interesting recent development is seen in prescriptions of a specific COX-2 inhibitor, a drug with no effect on PGE2 synthesis. The drug selectively blocks the COX-2 enzyme and impedes the production of PGs that cause pain and swelling. Because it selectively blocks COX-2 enzyme and not COX-1 enzyme, it was suggested that the drug can be safely employed during orthodontic mechanotherapy, without

causing negative effects on tooth movement. This drug is no more prescribed due to risk of cardiovascular events. A recent study reported that nabumetone, belonging to NSAID group, reduces the amount of root resorption along with control of pain from intrusive orthodontic forces, without affecting the pace of tooth movement.

6.6. Other NSAIDs

Yamasaki administered indomethacin to rats and inserted a piece of elastic between their molar teeth. The appearance of osteoclasts in the interradicular septum of bone of the first molar was found to be inhibited by the indomethacin. They also found imidazole, which is a specific inhibitor of thromboxane A2 synthesis but does not stop the synthesis of other prostaglandins, to have a similar effect. **Sandy and Harris** found that flurbiprofen inhibited the appearance of osteoclasts, but had no significant effect on tooth movement in rabbits. **Chumbley and Tuncay** found that indomethacin reduced orthodontic tooth movement in cats by half and also asserted that tooth movement is inhibited in patients taking NSAIDs. **Mohammed [23]** found significant inhibition of tooth movement in rats that were given indomethacin. However, they also found that a leukotriene inhibitor (AA861) that causes an increase in the production of PGE2, inhibited tooth movement.

6.7. Tramadol

Tramadol hydrochloride is a mu (μ)-opioid receptor agonist, it may affect bone metabolism and, consequently, OTM. Although the affinity of this drug for μ -opioid receptors is 400 times less than that of morphine, its major metabolite, *O*-desmethyltramadol, shows a remarkable affinity for μ -opioid receptors (10 times less than morphine and may have a role in the reduced OTM in this study), while the inhibitory effect of tramadol hydrochloride's major metabolite (*O*-

desmethyltramadol) on the function of substance *P* receptors can be a possible explanation. Substance *P* is one of the initial triggers of the biomechanical cascade that includes activation of

different periodontal ligament cells. This neurotransmitter is involved in the remodeling of PDL and alveolar bone during OTM [24].

The effects of tramadol on OTM depend on the dosage used. At therapeutic doses, it has no effect on OTM, whereas higher doses reduce OTM. Additional studies are required to clarify the exact underlying processes.

6.8. Bisphosphonates

Pharmacological site of action is in the osteoclast, which removes the outer ruffled border, inactivates function, and decreases the lifespan of the cell. Also, it inhibits formation of actin ring in the cytoskeleton of osteoclasts. There is some evidence that this drug group might also inhibit osteoclast precursors and osteoblast communication with osteoclasts [25].

Bisphosphonates (BPNs) have strong chemical affinity to the solid-phase surface of calcium phosphate; this causes inhibition of hydroxyapatite aggregation, dissolution, and crystal formation. Bisphosphonates cause a rise in intracellular calcium levels in osteoclastic-like cell line, reduction of osteoclastic activity, prevention of osteoclastic development from hematopoietic precursors, and production of an osteoclast inhibitory factor.

Studies have shown that BPNs can inhibit orthodontic tooth movement and delay the orthodontic treatment. Histologic examination showed that in the experimental animal's fewer osteoclasts appeared on the alveolar bone surface, and both bone resorption and root resorption were inhibited. Topical application of BPNs could be helpful in anchoring and retaining teeth under orthodontic treatment.

6.9. Estrogens

Estrogen is known to inhibit osteoclasts both directly and indirectly. It inhibits the production of various cytokines which are involved in bone resorption by stimulating osteoclast formation and osteoclast bone resorption. It has been shown that estrogens

decrease the velocity of tooth movement. Oral contraceptives, taken for long periods of time, can influence the rate of tooth movement. Androgens also inhibit bone resorption, modulate the growth of the muscular system, and may affect the length and results of the orthodontic treatment. Orthodontic therapy should be planned according to the menstrual cycle since tooth movement, under the application of force, is faster during low estrogen levels. Hypothesis were stated that orthodontic force

after each ovulation may promote tooth movement, thereby shortening the course of orthodontic treatment.

6.10. Calcitonin

Calcitonin inhibits bone resorption by direct action on osteoclasts, decreasing their ruffled surface which forms contact with resorptive pit. It also stimulates the activity of osteoblasts. Because of its physiological role, it is considered to inhibit the tooth movement; consequently, delay in orthodontic treatment can be expected.

6.11. Antibiotics/Antiseptics

Chemically modified tetracyclines (CMTs) are derivatives of the tetracycline groups of antibiotics that lack antimicrobial activity and the adverse effects associated with the conventional tetracyclines. Their ability to inhibit MMPs and pro inflammatory cytokines and their apoptotic effects on osteoclasts initially rendered them attractive therapeutic agents for the management of chronic periodontitis. The CMTs have been shown to modify the COX-2 enzyme leading to inhibition of PGE2 production and represent also potent inhibitors of MMPs. These properties make CMTs a potentially useful pharmacological agent to inhibit tooth movement in order to control anchorage or enhance tooth stability after orthodontic treatment.

Initial animal studies [26] showed that oral administration of CMT-3 (now known as COL-3) reduced the rate of tooth movement in rats in a concentration- dependent manner. The exact mechanism of action remains to be elucidated. Animal studies showed that a modified version of enoxacin (bis-enoxacin) with enhanced binding to bone selectively inhibited osteoclasts resulting in inhibition of tooth movement in rats after 28 days.

There is also some evidence from in vitro experiments that the well-known antiseptic Cetyl Pyridinium Chloride (CPC) inhibits RANKL-induced osteoclast formation from bone marrow derived macrophages possibly by suppressing a key event in the RANKL induced intracellular signaling pathway or by interfering with M-CFS signaling (Zheng *et al.*, 2013).

6.12. Drugs with No Effects on Orthodontics Tooth Movement

Orthodontists need to prescribe drugs to manage pain and discomfort resulting from orthodontic treatment, for that reason Acetaminophen (paracetamol) Rofecoxib, Tenoxicam and Relaxin are drug of choice for the patients, because of their ability to reduce pain intensity without alteration in tooth movement because these drugs have no effect on PGE2 synthesis [27].

Tooth movement is a complex process controlled by the nature of the mechanical stimuli, by a multitude of signaling pathways and influenced by the individual's genetic make-up. Naturally, the huge majority of available *in vivo* experimental evidence derives from animal studies. These have major limitations which include:

1. The inherently different biology in animals which prevents complete inference of the effects and the side effects of the pharmacological agents in humans.
2. The inability to calculate from animal experiments suitable dosages for clinical testing, as systemic application of the drug is often used in these models and may not result in effective or comparable (species difference) drug concentrations at the site of orthodontic intervention.
3. The generally small sample sizes used and different ages of animals used, which makes reliable conclusions even in the animal studies impossible to be reached
4. The lack of longer-term animal studies, which would enable examination of the effects of an agent on tooth movement over a time period and also allow observation of side-effects [28].

When clinical human studies are conducted, there are obvious problems related to ethical and practical issues: (1) recruitment of sufficient patient numbers, (2) evaluation of the effect of individual variation, (3) need for initial dose-response studies including measurements to assess the levels of the therapeutic agent at the sites of interest and measurements of the tissue-level outcomes. The huge majority of the above-mentioned studies have employed a systemic administration or local injection of the pharmacological agents. There is multitude of problems associated with these approaches. A systemic administration does not ensure a constant delivery of an ideal dose of the agent in the PDL. As it is not clear how circulating values correspond to the gingival dose and how they fluctuate in time, mainly due to degradation of the agent, in many cases a dose tested in the experimental set-up could have been insufficient to obtain the desired biologic effect. A more important problem is the potential of systemic administration to provoke undesirable systemic effects, especially when pharmacological agents lacking specificity are used. The mere evaluation of side effects is doubtful in the current experimental protocols as either the test periods are too short or the experimental protocol has not included specific methods to evaluate such effects.

7. LIMITATION OF THE AVAILABLE STUDIES:

8. Discussion and Comments

Understanding the pharmacology and the way it affects tooth movement, will aid the orthodontist in knowing the specific consideration for each case from the rate of OTM to root resorption. However, pharmacology hasn't come far enough to formulate a drug that can accelerate OTM without subsequent side effects.

Orthodontist will not prescribe medication to the patient to accelerate OTM, since it is not a part of the treatment routine, adding to that lack of scientific evidence or a protocol of drug administration during orthodontic treatment. However, if an orthodontist decides to administer drugs for acceleration of orthodontic treatment or pain control it is based on personal opinions, and that would be a weak issue.

One of the promising techniques to accelerate tooth movement, is a non- pharmacological, which is the application of cyclic loading (vibration) of 0.25 N (25 g) at the frequency of 30 Hz, as an adjunct to treatment with a fixed orthodontic appliance, significantly increases the rate of orthodontic tooth movement. Which can be used until pharmacology advances allows for better intervening measures.

As more and more chemical analogues are being used in the form of new drugs to avoid resistance, today's clinicians should mandatorily update his knowledge on the clinical efficacy of the new drugs as well as the beneficial and harmful effects on human tissues. It is always advisable for a dentist or an orthodontist to confirm with the family physician or the concerned physician for fitness of the patients who undergo orthodontics involving tooth movement. Orthodontists should assume that many patients are taking prescription or over-the-counter medications regularly. The orthodontist must identify these patients by carefully questioning them about their medication history and their consumption of food supplements and it should consider a part of every orthodontic diagnosis.

9. SUGGESTIONS AND LIMITATION OF THE STUDIES

Limitation:

1. The Need For The Design Of Specific Pharmacological Agents

Targeting key processes in the bone remodeling mechanism without other undesirable local side effects precludes a detailed knowledge of the cellular events involved. The selection of appropriate targets for the drugs and the design of novel drugs or suitable analogs of naturally occurring molecules with high specificity, is key for clinically successful strategies. The pharmacological agents also need to demonstrate high potency and efficacy in order to achieve clinically significant differences. The cost implications of the process of designing, testing and eventually obtaining approval for the clinical

application of a potential therapeutic agents need to be carefully considered and kept to the minimum to decrease the eventual cost to the patient.

1. Development of suitable vehicles of drug delivery and mode of administration

Suitable drug delivery materials need to be developed to provide the appropriate mode of release of pharmacological agents in their active form, that is, at the desired rate and amount for a long period of time (reflecting the duration of orthodontic treatment or retention time). Sustained and low-grade prostaglandin release through a suitable delivery system could, for example, be used to induce and sustain further endogenous PG production (through a known amplifying mechanism). This can be used to prolong the effects of short periods of stress in OTM. Establishment of other studies to:

2. Involve reviewing other up to date types of drugs that can accelerate or decelerate the course of tooth movement.
3. Involve reviewing drugs that can affect on root resorption (Increasing or decreasing it).
4. Conduct a questionnaire for orthodontist about their drugs prescription protocols of pain control during the orthodontics treatment.
5. Involve reviewing of new technologies that can accelerate the tooth movement.

10. Theoretical Foundations of AI and Classical Methods in Drugs and Orthodontics

10.1. Classical Methods

- **Drug Development:** Primarily based on empirical observations and biochemical principles. Drug discovery relied on random screening or rational drug design based on known target structures. Drug development involved extensive clinical trials to assess efficacy and safety.
- **Orthodontics:** Based on biomechanical principles of tooth movement and growth. Diagnosis was primarily observational, and treatment planning relied on clinical experience and static models.

10.2. AI Techniques

- **Machine Learning:** Underpins many AI applications. It involves algorithms that learn from data without explicit programming. In drug development, this includes predicting molecular

properties, identifying drug targets, and optimizing drug design. In orthodontics, it's used for image analysis, treatment planning, and patient-specific treatment predictions [29-40].

- **Deep Learning:** A subset of machine learning using artificial neural networks. It excels in pattern recognition and is applied in image analysis for both drug development (e.g., protein structure prediction) and orthodontics (e.g., cephalometric analysis) [41-71].
- **Natural Language Processing (NLP):** Extracts information from text data. In drug development, it's used for literature mining and information extraction. In orthodontics, it can be applied for patient records analysis and clinical guideline extraction [72-78].
- **Computer Vision:** Deals with processing and understanding visual information. In drug development, it's used for image-based drug screening and analysis. In orthodontics, it's essential for image analysis, including cephalometric analysis and 3D image processing [79-95].

10.3. Convergence of AI and Classical Methods

While AI offers powerful tools, it often complements rather than replaces classical methods. For example:

- **Hybrid Approaches:** Combining AI with traditional methods can improve accuracy and efficiency. In drug development, AI-generated molecules can be validated using biochemical assays. In orthodontics, AI-based treatment plans can be refined based on clinician expertise.
- **Data-Driven Refinement:** AI can enhance classical models by providing data-driven insights. For example, AI can identify new patterns in clinical data that can inform the development of new drugs or orthodontic techniques.
- **Knowledge Integration:** AI can integrate knowledge from various sources, including classical research, clinical data, and public databases, to create more comprehensive models.

In essence, AI is not a replacement for traditional methods but a powerful tool to augment and enhance them. By understanding the theoretical foundations of both AI and classical approaches, researchers can effectively combine their strengths to drive innovation in drug development and orthodontics. Table 2. Gives the Comparison of AI and Classical Methods in Drugs and Orthodontics.

Table 2. Comparison of AI and Classical Methods in Drugs and Orthodontics

Aspect	Classical Methods	AI Techniques	Advantages of AI
Drug Discovery	Relied heavily on high-throughput screening of large compound libraries	Utilizes generative models to design novel drug candidates, accelerates target identification through predictive modeling, and employs protein structure prediction for precise drug design	Increased efficiency and success rates
Drug Development	Involved extensive and time-consuming clinical trials with often unpredictable outcomes	Optimizes clinical trials through patient stratification, predicts drug efficacy and toxicity, and enables personalized medicine based on individual patient data	Faster and more targeted drug development
Diagnosis (Orthodontics)	Primarily based on physical examination, dental casts, and cephalometric radiographs, which can be subjective and time-consuming	Employs image analysis for accurate and automated cephalometric analysis, dental image analysis for early detection of anomalies, and 3D image analysis for comprehensive treatment planning	Enhanced accuracy, efficiency, and automation
Treatment Planning (Orthodontics)	Involved manual construction of treatment plans, often leading to variations in treatment outcomes	Utilizes predictive modeling to simulate tooth movement and optimize treatment plans	More precise, efficient, and predictable treatment outcomes

11. Spectral Methods in Drugs and Orthodontics: A Focus on Wavelet Transform

Spectral methods, particularly the wavelet transform, have shown promise in various fields, including signal processing, image analysis, and data compression. Their application in

domains like drugs and orthodontics is relatively nascent but holds significant potential. Unlike Fourier transforms, which break down a signal into a sum of sine and cosine functions, wavelet transforms analyze signals using wavelets - functions that oscillate and decay rapidly [96-110]. This allows for better

localization in both time and frequency, making them suitable for analyzing signals with transient features.

11.1. Application in Drugs

- **Drug Discovery:**
 - **Molecular Spectroscopy:** Wavelet transforms can be used to analyze spectral data from techniques like infrared and Raman spectroscopy to identify molecular structures and functional groups.
 - **Drug Release Profiles:** Studying drug release patterns over time can be enhanced using wavelet transforms to extract relevant features and predict release kinetics.
- **Pharmacokinetics:**
 - **Signal Processing:** Wavelet transforms can be applied to process pharmacokinetic data, such as drug concentration-time curves, to extract relevant information about absorption, distribution, metabolism, and excretion.

11.2. Application in Orthodontics

- **Image Analysis:**
 - **Cephalometric Analysis:** Wavelet transforms can be used to extract features from cephalometric radiographs, aiding in growth assessment and treatment planning.
 - **Dental Image Analysis:** Analyzing dental images using wavelets can help detect anomalies, such as caries or periodontal disease, with improved accuracy.
- **Tooth Movement Analysis:**
 - **Force Analysis:** Wavelet transforms can be used to analyze force patterns applied to teeth during orthodontic treatment, helping to optimize treatment plans.
 - **Image Registration:** Registering dental images over time can benefit from wavelet-

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based techniques for accurate comparison and assessment of tooth movement.

11.3. Challenges and Future Directions

While wavelet transforms offer promising applications, several challenges need to be addressed:

- **Data Quality:** The quality of input data is crucial for accurate wavelet analysis. Noise reduction and preprocessing techniques are essential.
- **Computational Efficiency:** Wavelet transforms can be computationally intensive, especially for large datasets. Efficient algorithms and hardware acceleration are required.
- **Feature Extraction:** Identifying the most relevant wavelet features for specific applications is challenging and requires domain expertise.

Future research should focus on developing advanced wavelet-based techniques tailored to the specific needs of drug development and orthodontics. Combining wavelets with other signal processing and machine learning methods could lead to even more powerful tools for these fields.

12. CONCLUSION

The integration of AI in drug development and orthodontics holds immense potential for improving human health. By harnessing the power of machine learning, deep learning, and other AI techniques, researchers and clinicians can expedite drug discovery, optimize treatment plans, and enhance patient outcomes. As AI continues to evolve, its applications in these fields will undoubtedly expand, leading to groundbreaking innovations and improved healthcare delivery. Future research should focus on developing robust AI models, ensuring data privacy and security, and exploring ethical considerations associated with AI-driven healthcare. Overall Comparison Both drug development and orthodontics benefit significantly from the integration of AI. AI techniques offer substantial advantages in terms of speed, accuracy, and efficiency compared to classical methods. By automating routine tasks, providing data-driven insights, and enabling predictive modeling, AI is transforming these fields and improving patient outcomes

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