Journal of Research in Medical and Dental Science
2021, Volume 9, Issue 7, Page No: 149-161

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Effects of Common Medications on Orthodontic Tooth Movement: A Systematic Literature Review

Eman Ibrahim Al Shayea*

Division of Orthodontics, Department of Pediatric Dentistry and Orthodontics, College of Dentistry, King Saud University, Kingdom of Saudi Arabia

ABSTRACT

Orthodontic treatment is founded on the premise that the application of force on a tooth transmits cellular, chemical, and mechanical occurrences to the tissues nearby. Such coordinated tissue resorption and formation in the surrounding bone and periodontal ligament lead to the movement of the tooth. The impacts of the mechanical forces are usually synergistic, additive, or inhibitory. Accordingly, this study aims at discussing the effects of common medications on the orthodontic tooth movement since the key to any orthodontic treatment is a good medical control. Utilizing electronic databases, a systematic literature review of the topic is performed. The databases used for the electronic searches included Cochrane database, Cinahl, Web of Science, Scopus, PubMed, Science Direct, Trip, Scielo, Lilacs, and Medline. The systematic literature review comprises of five phases that include formulating the study questions, searching for the relevant literature, selecting the literature, briefing the research outcomes, and reporting the findings. A total of 614 relevant peer-reviewed articles were identified. Out of this sample, only 72 articles met the inclusion criteria, and were selected for the review. In conclusion, it is imperative that the orthodontists pay attention to the drug consumption history of every patient, before and during the orthodontic treatment.

Key words: Tooth movement, Orthodontic tooth movement, Drugs effects, Medications, Medicines

HOW TO CITE THIS ARTICLE: Eman Ibrahim Al Shayea, Effects of Common Medications on Orthodontic Tooth Movement: A Systematic Literature Review, J Res Med Dent Sci, 2021, 9(7): 149-161

Corresponding author: Dr. Eman, BDS, M Sc, Cert Ortho
E-mail ✉ :e_shayea@hotmail.com
Received: 14/06/2021
Accepted: 09/07/2021

INTRODUCTION

Orthodontic treatment is founded on the premise that the application of force on a tooth transmits cellular, chemical, and mechanical occurrences to the tissues nearby. Such results in the structural modifications lead to the movement of the tooth [1,2]. The transformations that take place in the investing bone tissue adjacent to the moving tooth are known as bone deposition and resorption. Bone deposition is the process of depositing new bone matrix by the osteoblasts, while bone resorption is the process by which osteoclasts break down the tissue in bones and hence release minerals to the blood. The biological sequence of events that causes the tooth to move following the application of mechanical forces include Extracellular matrix strain and fluid flow, cell strain, cell activation and differentiation, and finally tissue remodelling [3,4]. Acute seditious response categorized by periodontal vasodilatation, migration of leukocytes out of PDL capillaries, and sensations of pain, is usually associated with early phase of orthodontic tooth movement (OTM). Most of the orthodontic patients experience such symptoms.

Notwithstanding, orthodontic practitioners and scientific researchers have not yet comprehended the main conversion mechanism facilitated by the force generated by the moving tooth. In the past few years, however, scientific advances have enabled orthodontists and researchers to explore the role performed by some factors and released inflammatory mediators, such as prostaglandins (PGs), collagenase, calcium, and cyclic adenosine monophosphate (cAMP). Such mediators have significant roles in enhancing tooth movement subjected to orthodontic force [1,2].

The above mentioned biological sequence of events may be a brief summary of recent understanding of complex activities and interactions occurring in the PDL and alveolar bone following the application of mechanical force or action of chemical mediators. The combined effect of mechanical forces and these mediators can be synergistic, preservative, or inhibitory [1,2]. Therefore, the present research was designed in the form of systematic literature review to focus on reviewing, summarizing evidence from existing literatures, and to investigate the effects of commonly used medications on OTM. Hence, the aim is to elucidate, for orthodontists, the influence of each medication on the rate of tooth movement.

MATERIALS AND METHODS

The study is a systematic literature review based on reviewing numerous relevant peer-reviewed articles and journals from electronic databases. Electronic databases including Cochrane database, Cinahl, Web of Science, Scopus, PubMed, ScienceDirect, Trip, Scielo, Lilacs, and Medline were searched from January 1982 to April 2021 to obtain sources with no language or location restrictions. Moreover, terminologies such as "tooth movement," "orthodontic tooth movement, "drugs effects"," and "effects of medications" were used when performing the literature search. The inclusion criteria were set by selecting the studies that fulfill the following:

Studies focused on examining the effects of medications on OTM.

Studies with experimental animal or human clinical investigations with a minimum of one control and experimental group.

Studies with local or systemic administration of well-defined medication or dietary supplements that might have side effects to bone physiology.

Studies that adequately described the administration regimes and dosages, the orthodontic force magnitude, the approach used to examine the rate of tooth movement.

RESULTS

Based on reviewing titles and abstracts and through the computerized literature search and review of reference lists, a total of 423 articles were identified. Following the screening of these articles, 306 articles were excluded as they failed to meet the inclusion criteria. In addition, articles for which the full text was impossible to obtain, along with articles in other language than English with no translation were excluded from the study. Moreover, six duplicates were identified, and therefore were removed them from the study. This made only 72 pertinent peer-reviewed articles that met the inclusion criteria and hence were included in the present review for further analysis. The illustration in Figure 1 displays the results of the methodical literature review evaluation.

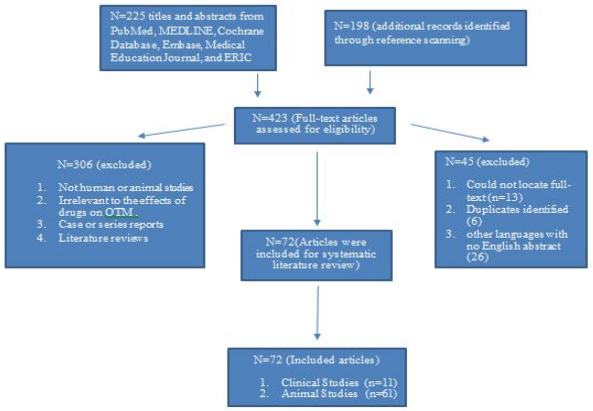

Figure 1: Literature review and retrieval flow diagram.

Furthermore, a summarized published data of the studies included in the review are presented in Table 1. The table shows the literatures' year of publication, type of drug used in the study, sample size and type, dose and method of drug administration, methods of force application, and the authors' conclusions. All the drugs reviewed have therapeutic effects, as well as, side effects that may influence the cells targeted by orthodontic forces, and hence the outcome of mechanotherapy. These drugs included different analgesics, different hormones, Immunosuppressant and immunomodulatory drugs, **anticancer drug, anticonvulsants,** Bisphosphonates (BPNs), Vitamin D, and fluorides. Most of the studies are experimental animal studies which constitute 84.7% of the total studies, while the clinical studies represented 15.3% of the total studies. The table shows that the majority of the studies were published between 1996 and 2014 (75%).

DISCUSSION

This systematic literature review was conducted to focus on reviewing, summarizing evidence from existing literatures, and to investigate the impacts of commonly used medications on OTM. Furthermore, the review identifies the various effects of dosages used for each medication by identifying the approach used for drug administration, the amount and the methods of force applied during drug administration, and the techniques used to examine the OTM. Although the orthodontic diagnosis and treatment are founded on the clinical evaluation and the investigation of diagnosis records, it is usually essential for any orthodontist to perform a comprehensive medical history and make such an inquiry a major part of every orthodontic diagnosis [1,5,6].

Over the years, there has been a significant expansion in medication prescriptions. This expansion has been primarily caused by the increase in the demand for medications that are effective in targeting chronic illnesses and those related to age. Also, the trend has been significantly influenced by other factors such as medical advertisements and health insurance entities [7-9]. In spite of the increase in the consumption of such medications, researchers have asserted that the demand for orthodontic treatment is expanding among children and adolescents. For instance, in the United States, 7% of children and teenagers aged 6 to 17 years are using prescribed medication for behavioural and psychological difficulties [10-12]. Clearly, the wide use of over-the-counter drugs causes various complications among patients using them excessively. These over-the-counter drugs have certain pharmaceutical substances that may have effects on tissue remodelling, tissue homeostasis, and hence orthodontic tooth movement [13,14].

Analgesics are medications used by patients as pain reliever. It is divided into Nonsteroid anti-inflammatory drugs "NSAIDs", and non- NSAIDs which lacks anti-inflammatory properties such as "Acetaminophen". These

analgesics are the commonly used medications in orthodontics for the purpose of controlling pain following force application on the teeth. According to the chemical composition, NSAIDs is subdivided into different groups such as Salicylates, Arylalkanoic acids (diclofenac), Arylpropionic acids (Profens), Oxicams and Coxibs. Several researches demonstrated their effects and action mechanisms by inhibition of Cycloxygenase activity "COX", leading to suppress the production of all prostanoids; such as PGs, that have a significant role in bone resorption during orthodontic therapy, and hence causing a reduction in the rate of OTM [15]. The effects of a conventional NSAID "Diclofenac", and a specific COX-2 inhibitor, "Rofecoxib" on the inhibition of OTM in rats was investigated and the studies revealed that both rofecoxib and diclofenac significantly inhibited dental movement, partially in the case of rofecoxib and totally in the case of diclofenac [16-18]. Sodagar et al reported the effect of celecoxib, a highly-selective COX-2 inhibitor, on OTM in rats. They found that bone resorption and tooth movement were inhibited by this kind of NSAID [19].

Sari et al., 2004 in clinical study compared the effects of Acetylsalicylic acid with those of Rofecoxib on PGE2. The study found that the inhibition effect of acetylsalicylic acid on PGE2 was greater than Rofecoxib, which highlights the suitability of using Rofecoxib as an analgesic to control pain without affecting the result of orthodontic treatment [20]. Same result was found in a recent study done on rats by Kirschneck et al., 2020. They found that Etoricoxib is a suitable analgesic during OTM, as it has been reported not to affect tooth movement [21]. Furthermore, several studies were conducted to evaluate the effect of different analgesics on OTM in the animals and humans. It was found that the use of Ibuprofen, and aspirin inhibit PGE2 synthesis, which in turn alters tooth movement. On the other hand, Acetaminophen had no effect on PGE2 synthesis, and was considered safe to be prescribed during orthodontic treatment without the risk of affecting the pace of tooth movement [22-24]. Similarly, Tenoxicam is shown to effectively control the pain experienced by orthodontic patients without any effects of on the OTM [25,26].

Two clinical trials evaluated the effect of injecting Prostaglandin E1 (PGE1) on the moving tooth in human patients. They portrayed a substantial advance of tooth movement in the injected side compared to the control side. They identified great differences with upsurge in tooth movement associated with the stimulation of the nearby tissues and bones. Injecting PGE1 at the site of OTM appears to be effective in stimulating the transformation of the alveolar bone and in increasing its vascularity [27,28]. Other animal experiments, as well, have shown that local application of PGE2 increases the speed of OTM [29-34].

The hormones medications reviewed in this study, which affect OTM, include calcitonin, parathyroid hormone, estrogens, insulin, thyroid hormones, relaxin, corticosteroids, immuno-suppressant and immunomodulatory drugs, anticancer drugs, and interleukin antagonists. Thyroid hormones (T3, T4) are hormones produced and released by the thyroid gland. They are responsible for regulation of metabolism. It was found that the administration of Thyroxin leads to increased bone remodeling, and hence increases the speed of OTM. Therefore, clinicians should always ensure that they prescribe low dosages of thyroid hormone medications among orthodontic patients [35,36]. In contrast, Calcitonin is another hormone secreted by the thyroid, which acts to reduce blood calcium opposing the effects of parathyroid hormone (PTH). It inactivates osteoclasts and hence inhibits bone resorption. It also stimulates the bone forming activity of osteoblasts [15], and hence minimizes post-orthodontic relapse, as recently reported in different animal studies [37,38]. Parathyroid hormone (PTH) is a hormone secreted by the parathyroid glands that regulates the serum calcium concentration through its effects on bone, kidney, and intestine. Animal studies on rats have shown that local or systemic injection of PTH accelerated OTM and significantly increased osteoclast activity [39-41]. Such research findings elucidate that orthodontists should be careful when treating patients using the PTH medication.

Estrogen is a substantial sex hormone that regulates bone remodelling in females. It also prevents the production of numerous cytokines that help in the bone resorption. Moreover, estrogens prevent the osteoblasts response to PTH. Most of the previous studies evaluating the indirect effect of estrogens on OTM are experimental studies. They have shown that estrogen is similar to calcitonin, in the way it minimizes the pace of teeth movement [42-49]. Among the human studies, one clinical case report of a postmenopausal orthodontic patient concluded that the estrogens used to treat osteoporosis might have delayed OTM [50]. In addition, more rapid tooth movement was observed in female orthodontic patients during the menstrual period than in the ovulation period [51,52]. As such, the effects of estrogen levels on OTM can be taken into consideration when orthodontists select the timing for recall visits, as well as if the patient is under any oral contraceptive pills, as it contains estrogens, which inhibits tooth movement.

Relaxin is an ovarian hormone, and commonly known as a pregnancy hormone. It stimulates osteoclast and osteoblast activities. Studies conducted on animals showed that the administration of human relaxin may accelerate the early stages of orthodontic tooth movement, and prevent relapse in orthodontic practice [53-56]. In 2011, Mcgorray conducted a randomized clinical trial to compare relaxin and a placebo with regard to tooth movement and stability in human subjects. He found that no differences in tooth movement over 8 weeks of treatment or relapse at 4 weeks post treatment were detected between groups. He attributed that to the small dosage used in the experiment [57].

Insulin is a hormone made in pancreas and regulates blood sugar levels. Injections of insulin can help treat both types of diabetes. Two experimental studies reported the effects of insulin injection on OTM. The first study evaluated the effects of induced diabetes type 1 on osteoclast recruitment and activity and, consequently, on

orthodontic tooth movement in mice. This was compared with another group that was treated with insulin after diabetes induction. They found that OTM in the diabetic mice were faster, and the treatment with insulin resulted in slower OTM similar to normoglycemic rats [58]. Another study by Villarino et al., 2011 evaluated the effect of diabetes and Insulin injection on rats. The results showed that bone response to orthodontic forces in insulin-treated diabetic subjects does not differ significantly from that observed in healthy subjects [59].

Corticosteroids are prescribed as anti-inflammatory and immunosuppressive medications. They act by preventing the formation of prostaglandins, and inhibiting the intestinal calcium absorption, which leads to direct inhibition of osteoblastic function, and an increase in bone resorption. Most of studies on animals reported that the tooth movement rate increased in the chronic group that require long term corticosteroid therapy. Whereas, in acute corticosteroid ingestion, the studies reported suppressed bone turnover. This finding indicates that the orthodontic force level should be reduced and maintained more frequently in patients with chronic corticosteroid ingestion, and postponed orthodontic treatment in patients on acute steroid treatment until a time the patient is free of the drug [60,61]. Immunosuppressant and immunomodulatory are medications that work to lower the body's ability to reject a transplanted organ, and they include drugs such as glucocorticoids, cyclosporine, tacrolimus, and sirolimus. Other immunosuppressant drugs are often used to treat autoimmune disorders such as rheumatoid arthritis, psoriasis, and lupus. All these medications that work to prevent organ rejection following transplantation have been reported as having effects on bone mineral homeostasis and consequently influence OTM. In addition, the immunosuppressant drug is associated with various unwanted effects, such as gingival overgrowth, making orthodontic treatment and maintenance of oral hygiene difficult [62]. Further, the Interleukin antagonists (IL-1RA) is a protein in humans secreted by various types of cells including immune cells, epithelial cells, and adipocytes, and it is a natural inhibitor of the pro-inflammatory effect of IL1β. The inflammatory response following orthodontic loading characterized by the release of such inflammatory mediators on periodontal tissues that is directly involved in bone resorption. This was confirmed by a study on mice treated with IL-1RA which showed diminished OTM and decreased numbers of osteoclasts. The finding suggested that IL-1RA downregulates OTM, probably by its anti-inflammatory actions [63].

A TNF inhibitor is a pharmaceutical drug that suppresses the physiologic response to tumor necrosis factor (TNF), which is part of the inflammatory response. TNF-α antagonists are being used to treat moderate to severe diseases in patients having contraindications, not responding, or when side effects were developed to conventional systemic treatments. It was found that TNF-α plays an important role, directly or via chemokine release, in osteoclast recruitment and activation [64]. Furthermore, recent study explained the role of TNF-α in inducing sclerostin expression in osteocytes on the compression side during OTM. TNF-α enhances sclerostin expression in osteocytes; then, sclerostin increases the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) by osteocytes. Hence, the study concluded that osteoclast formation was enhanced by TNF-α through increased sclerostin expression in osteocytes on the compression side during OTM [65]. Moreover, local injection of integrin inhibitors, like echistatin and RGD peptides, on rats significantly decreased root resorption surface areas and reduced the number of root resorption lacunae in orthodontically treated teeth, as well as useful to limit or prevent OTM of specific teeth in case of enhancing anchorage [66,67].

Anticancer drug, also called **antineoplastic drug**, is effective in the treatment of malignant, or cancerous disease. A significant increase in the overall rate of childhood cancers was reported in recent decades [68]. No experimental or clinical studies were found on the effect of the anticancer drugs on the rate of OTM. However, these drugs are known to inhibit cell division and proliferation, not only destroy cancer cells but also destroy normal cells. So, they have consequences for growth, dental development, craniofacial growth, bone remodeling process, and hence complicating OTM [69]. One recent study compared the stability of orthodontic treatment in cancer survivors who had been treated with cytotoxic drugs with a generally healthy control group. The authors concluded that previous treatment with cytotoxic drug significantly decreases the stability of orthodontic treatment among cancer survivors, particularly within first year following the end of the treatment [70].

Anticonvulsants, also known as antiepileptic drugs, are a diverse group of pharmacological agents used in the treatment of epileptic seizures. It has been reported in experimental study that Valproic acid and carbamazepine can decrease bone density which may induce accelerated OTM in rats [71]. Nevertheless, Phenytoin did not show any statistically significant effects on the rate of OTM [72], the gingival enlargement that may occur after prolonged use of phenytoin making orthodontic treatment and maintenance of oral hygiene difficult [73].

Bisphosphonates (BPNs) are drugs that prevent the loss of bone density, used to treat osteoporosis and similar diseases. Previous animal studies have reported the local and systemic effect of BPNs on OTM, which decreases bone resorption, inhibit OTM, and hence delay the orthodontic treatment [74-85]. These findings were further confirmed by the results obtained from case reports, case series, and retrospective cohort studies of orthodontic patients under bisphosphonate medication that exerted forces on teeth led to longer treatment duration, incomplete space closure, poor root parallelism, poor incisor alignment, and wide PDL with tooth mobility in some cases. Therefore, these drugs would be helpful if orthodontic anchorage control was needed during orthodontic treatment [50,86-90].

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects. One of the most important compounds in this group in humans, is vitamin D3 (also known as cholecalciferol) [91]. Animal studies showed that local injection of vitamin D3 increased the number of osteoclasts, and accelerated OTM [92-95]. Moreover, same findings were found in single randomized clinical trial where the patients treated with different doses of vitamin D3. It was found that locally injected calcitriol, in dose dependent pattern, is clinical and cost effective in increasing OTM among humans [96].

The last medication considered in this review was fluorides. The main function of this medication is the mineralization of bones and teeth. Fluoride has an effect on tissue metabolism, and it increases bone mass and mineral density. It has been found in experimental study on rats that treatment with sodium fluoride during orthodontic treatment inhibits the osteoclastic activity and reduces the number of active osteoclasts, leading to minimizing OTM, and hence lengthening the orthodontic treatment [97,98]. On the other hand, the effect of fluoride on OTM were studied in humans to determine whether high and low fluoride concentrations in drinking water affected the early stages of tooth movement, when heavy and light orthodontic force were applied. The average rate of tooth movement was found to be greater in high fluoride intake patients under both light and heavy orthodontic force application [99].

Table 1: Summarized published data of the studies included in the systematic review.

Drug Used	Study	Sample Type	Sample Size and Method	Outcomes
diclofenac (Voltaren) Vs COX-2 inhibitor (rofecoxib)	De Carlos et al. [16]	Animal (Rats)	42 male Wistar rats, 3 groups with 50-g coil spring and(2 rofecoxib injections of 1 mg/kg wt., (2 diclofenac injections of 10 mg/kg wt, 0.9% saline-solution injections. 3 groups with 100-g coil appliance and the same pharmacological treatment.	Both rofecoxib and diclofenac significantly inhibited dental movement. partially in rofecoxib and totally in diclofenac
Rofecoxib, Celecoxib, Parecoxib	De Carlos et al. [17]	Animal (Rats)	28 male Wistar rats in 4 groups, injected with Rofecoxib 0.5 mg/kg, 8 mg/kg with Celecoxib, 25 mg/kg with Parecoxib, & 0.9% saline	Celecoxib and Parecoxib, but not Rofecoxib, appropriate for pain relief while avoiding interference during tooth movement.
potassium diclofenac Vs	Knop et al., [18]	Animal (Rats)	90 male Wistar rats, 3 groups (0.9% saline in control, 5 mg/kg potassium diclofenac, 2 mg/kg dexamethasone dissodium phosphate)	potassium diclofenac inhibits bone resorption during the initial period of OTM
Celecoxib	Sodagar et al. [19]	Animal (Rats)	28 male Wistar rats in 4 groups with orthodontic appliance(no injections, celecoxib injections (0.3 mg in 0.1 ml saline solution),normal saline injections (0.1 ml saline solution), and needle penetration without injecting any solution.	Celecoxib decreases OTM and osteoclast count.
Acetylsalicylic acid and Rofecoxib	Sari et al. [20]	Human	36 extraction patients, 3 groups (control, 500 mg Acetylsalicylic acid, and 25 mg rofecoxib)	The inhibition effect of aspirin on PGE(2) was more than that of rofecoxib.
Etoricoxib	Kirschneck et al. [21]	Animal (Rats)	40 male Fischer344 rats, 4 gps with orthodontic appliance. (control, 7.8mg/kg/day etoricoxib for three, seven days/ week and 13.1mg/kg/day (high dose) for seven days/week,	No OTM effect. So, Etoricoxib is a suitable analgesic during OTM
Ibuprofen, and Acetaminophen	Shetty et al. [22]	Human	42 patients. 3 gps, 400 mg ibuprofen 3 times/day/2 days, 500 mg acetaminophen 3 times/ day, control gp	Ibuprofen inhibits PGE2 synthesis > acetaminophen.
Aspirin, acetaminophen, and ibuprofen	Arias et al. [23]	Animal (Rats)	36 male Wistar rats, 4 gps with ortho. Appliance. 100 mg/kg acetylsalicylic acid, or 30 mg/kg ibuprofen, or 200 mg/kg acetaminophen	Aspirin and ibuprofen diminish the number of osteoclasts, thereby reducing orthodontic tooth movement.No effects with acetaminophen
acetaminophen	Roche et al. [24]	Animal (rabbits)	14 rabits,2 gps. springs were ligated. Control (received water) & experimental (1000 mgs of acetaminophen daily)	No effect on the rate of OTM

Tenoxicam	Arantes et al. [25]	Human	36 patients.3 gps (control: placebo)(20 mg tablet before and placebo after), (opposite to gp.2)	Pain control with no effect on OTM
Prostaglandin E1	Yamasaki et al. [27]	Human	3 Phases, injection of PGE1 (submucosal)max. 1st premolar, distal of canine for 2nd &3rd phases in experimental sides over 2 wks, 10 days, respectively.	More rapid tooth movement in experimental side with no side effects.
	Patil et al. [28]	Human	15 patients, 3 gps. (control, 1g PGE1, 1g lignocaine), canine retraction	More rapid tooth movement in experimental side with no side effects.
PGE1&2	Yamasaki et al. [29]	Animal (monkeys)	Two female monkeys with IM injection of Ketalar (0.2 ml/kg). combined with orthodontic tooth movement	More rapid tooth movement in experimental side with no side effects.
PGE2	Leiker et al. [30]	Animal (Rats)	132 rats.2 periods gps(2,4wks), four subgroups(PGE2 injections, i.e., 0.1, 1.0, 5.0 and 10.0 micrograms.), closed springs were ligated.	More rapid tooth movement in experimental side with no side effects.
PGE1	Sekhavat et al. [31]	Animal (Rats)	64 rats, contro, and experimental groups received 2.5, 5.0, 10.0, 25.0, 50.0, and 100.0 microg/kg misoprostol every 24 hours for 2 weeks. Springs were ligated	oral misoprostol enhances OTM with minimal root resorption.
PGE2	Seifi et al. [32]	Animal (Rats)	24 rats,3gps(control with saline, 0.1 ml of 1 mg/ml PGE2, intraperitoneal injection of 200 mg/kg Ca (10%) in addition to the PGE2.), ligated springs	PGE2 significantly increasing OTM
PGE2	Kale et al. [33]	Animal (Rats)	32 rats,4gps(control, 20-microL 3-days injection of dimethyl sulfoxide, 20-microL 3-days injection of dimethyl sulfoxide, single inj. of 0.1 mL of 0.1 microg PGE2)	PGE2 significantly increasing OTM.
PGI2	Gurton et al. [34]	Animal (Rats)	150 rats,5gps,applyortho force(PGI2 analog,PGI2 inhibitor,TxA2 analog,TxA2 inhibitor))in 3 different concentrations dissolved in 0.9%saline	PGI2 increased osteoclasts number, osteoclastic bone resorption, and rate of OTM
Thyroxin	Shirazi et al. [35]	Animal (Rats)	50 rats,5gps(normal(no intervention),control(saline inj.), thyroxin groups(with ligated springs & 5, 10 and 20/ microgram/kg i.p./day L-thyroxin	administration of 20/ microgram/kg i.p./day L-thyroxin increased bone remodeling, and OTM
	Seifi et al. [36]	Animal (Rats)	64 rats,8gps with ortho app. (control, 20µg/kg thyroxine traperitoneally, 0.1 ml of 1 mg/ml PGE2 (SM), 10% (200 mg/kg) calcium gluconate, PGE2 (SM) & 10% calcium intraperitoneally, Thyroxine (intraperitoneally) &PGE2(SM), 20µg/kg thyroxine with calcium, PGE2 (SM) with calcium and thyroxine.	Thyroxine &PGE2 would decrease the root resorption and increase the rate of OTM.
Calcitonin (CT)	Guan et al. [37]	Animal (Rats)	80 rats,5gps(-ve controls, +ve control with saline, 3 doses of injected CT 0.2 IU, 1 IU or 5 IU/kg/day),springs were ligated	CT diminishs undesired tooth movement via enhancing anchorage or preventing relapse.
Calcitonin (CT)	Alnajar, et al. [38]	Animal (Rats)	36 rats with ortho.app. 3 gps(control with saline,1 inj. CT (20 IU/Kg), 3 inj CT (20 IU/Kg).	3 doses of CT may minimize the relapse ratio
PTH	Soma et al. [39,40]	Animal (Rats)	rats were treated with SC of vehicle or hPTH(1-84) at 1-10 micrograms/100 g of body weight/day with ortho. App.	Continuous administration of PTH is applicable to accelerate OTM

	Lee et al. [41]	Animal (Rats)	30 rats,3gps(sham-operated, OVX and ovariectomized rats injected with PTH), and springs were ligated	Application of PTH did not promote OTM in OVX rat, decrease in relapse tendency.
Estrogen	Yamashiro et al. [42]	Animal (Rats)	6 wk-old female rats received a bilateral ovariectomy (OVX), ortho movement	Estrogen deficiency increased OTM
	Haruyama et al. [43]		10 wk-old female rats received repeated orthodontic force during estrous cycle.	Estrogen deficiency increased OTM
	Arslan et al. [44]		42 female rats(control & ovariectomized rats),ortho force was applied after 2 mon	Estrogen deficiency increased OTM
	Sirisoontorn et al. [45]		10 female rats(control,rat with OVX),springs were ligated after month, tomography was taken	Estrogen deficiency increased TM
	Sirisoontorn et al. [46]		15 rats(ovariectomy, ovariectomy + zoledronic acid, and control), springs were applied	Zoledronic acid inhibits OTM in OVX rats.
	Seifi et al. [48]		10 OVX female,10 orchiectomized male rats(experimental), (same for control),ortho. springs	Hormones influence the rate of OTM
	Tan et al. [49]		4 gps (Control,1-time force-loading, 5-times force-loading, sham) in different estrous stage.	The largest amount of OTM in the estrus gp
	Celebi et al. [47]	Animal (Cats)	18 female cats,3gps(150 IU (eCG)estrous, anestrous, and OVX), springs were applied.	OTM in the estrous group was low.
	Wang et al. [51]	Human	Twelve women(6 menstrual, 6 ovulation period group),springs were ligated, GCF samples were collected.	More OTM during the menstrual period than in the ovulation period
	Yang et al. [52]			
Relaxin	Liu et al. [53]	Animal (Rats)	3gps(control with saline, minipumps inj.,SC inj of relaxin),ortho app was placed, Ceph Rx.	Relaxin accelerates the early stages of OTM ,modulates the collagen metabolism. Therefore, useful to prevent orthodontic relapse following orthodontic treatment.
	Stewart et al. [54]	Animal (dogs)	24dogs, second incisors were orthodontically rotated, 3gps(control with placebo, relaxin gingival inj., gingival fiberotomies)	Relaxin accelerates the early stages of OTM, modulates the collagen metabolism. Therefore, useful to prevent orthodontic relapse following orthodontic treatment.
	Madan et al. [55]	Animal (Rats)	96 rats, ortho. App.,2gps(control, relaxin inj.), ceph Rx	Relaxin accelerates the early stages of OTM, modulates the collagen metabolism. Therefore, useful to prevent orthodontic relapse following orthodontic treatment.
	Hirate et al. [56]	Animal (Rats)	Springs were applied, 500 ng/ml relaxin for 1wk, tomography and immunofluorescence stain.	Relaxin accelerates the early stages of OTM, modulates the collagen metabolism. Therefore, useful to prevent orthodontic relapse following orthodontic treatment.
	Mcgorray et al. [57]	Human	39 patiens(control with 0.2ml of placebo, 0.2ml relaxin inj), series of max. aligners, PVS imp.	No difference in OTM& Relapse was observed
Insulin	Braga et al. [58]	Animal (mice)	Rats,3gps(control, induced diabetes type 1, insulin inj. after diabetes induction),ortho app. Was placed	Tremanet with insulin resulted in slower OTM similar to normoglycemic mice and rats

	Villarino et al. [59]	Animal (Rats)	3gps (experimental ortho., experimental diabetes and orthodontics, and experimental diabetes with insulin and experimental orthodontics. Orthodontic forces were applied	Treatment with insulin resulted in slower OTM similar to normoglycemic mice and rats
Corticosteroids	Kalia et al. [60]	Animal (Rats)	64 male rats,3 gps (control,Acute,chronic) 8 mg/kg/day corticosteroid treatment. App. applied	OTM increased in the chronic corticosteroid therapy & suppressed in acute ingestion.
	Verna et al. [61]			
IL-1RA	Salla et al. [63]	Animal (mice)	Ortho app. in C57BL6 mice treated with vehicle or IL-1Ra (10 mg/kg/day).	decreased OTM and decreased# of osteoclasts
TNF receptor type1	Andrade et al. [64]		Ortho. app. was placed in wild-mice&p55-deficient mice. Levels of TNF-alpha and 2 chemokines were evaluated in periodontal tissues.	TNFR-1 plays a significant role in OTM associated with changes in chemokine levels.
	Ohori et al. [65]	Animal (mice)	3gps(wild-type, TNFR-1, deficient (TNFRsKO) mice),analysis of primary osteocytes, which were isolated from DMP1-Topaz mice by sorting the Topaz variant of GFP-positive cells	TNF-α may stimulate sclerostin expression in osteocytes and enhance OTM.
echistatin and RGD peptides	Talic et al. [66]	Animal (Rats)	14 rats with elastic bands were placed, 2gps(0.8 microg/kg/min echistatin IV for 8 hours & controls with saline), microscopy was used	Echistatin significantly decreased root resorption, hence decreased OTM
	Dolce et al. [67]	Animal (Rats)	local administration of echistatin orRGD, using ELVAX to integrin inhibitors adjacent to teeth	Echistatin significantly decreased root resorption, hence eased OTM
Anticancer drug	Mitus-Kenig et al. [70]	Human	104 patients,2gps(cancer survivors,control). w-PAR,ICON indices were assessed before treatment, after the treatment, and at the 3-year follow-up	cytotoxic drug decreases the stability of OTM among the cancer survivors
Anticonvulsants	Akhoundi et al. [71]	Animal (Rats)	2gps (control&Exp.)carbamazepine and valproic acid infusion, Bone densitometry on ceph	Decreases the bone density&accelerated OTM.
	Pithon et al. [72]	Animal(rabbits)	22,3gps(normal,control,phenobarbital)with ortho.device was placed. clinical & Rx analysis	No difference on the rate of OTM
BPNs	Adachi et al. [74]	Animal (Rats)	Expansion spring under (topical administration of risedronate, 0.9% NaCl control)	decreases bone resorption, inhibit OTM, & enhancing anchorage
	Igarashi et al. [75]		Expansion spring under (systemic administration of AHBuBP, 0.5 mg P/kg control)	decreases bone resorption, inhibit OTM, & enhancing anchorage
	Igarashi et al. [76]		Expansion spring under topical administration of risedronate,7 days,3wks evaluation	prevents root resorption of teeth during OTM
	Alatli et al. [77]		single injection of 1-hydroxyethylidene-1, 1-bisphosphonate, ortho force was applied	Inhibits the formation of acellular cementum.
	Kim et al. [78]		Band was inserted, BPN was administered 1 day before band removal, relapse was studied	decreases the relapse in moved rat molars
	Liu et al. [79]		Expansion spring under Local injection of Clodronate inj. (left), control (right)	Significant reduction in OTM
BPNs	Keles et al. [80]	Animal (mice)	Inhibition of tooth movement by osteoprotegerin (OPG) vs.	OPG could have clinical utility in preventing undesired tooth movement.

			pamidronate under conditions of constant orthodontic force	
	Fujimura et al. [81]		Spring was ligated, 2 microg/20 microl Bisphosphonate was injected daily into a local site	Inhibiting effect on OTM
	Karras et al. [82]	Animal (Rats)	2gps with spring was ligated (control, alendronate sodium 7 mg/kg of body weigh/wk)	Inhibiting effect on OTM
	Choi et al. [83]		54 rats,3gps with ortho. force(2.5 mmol/L clodronate, 10 mmol/L clodronate, and control)	Inhibiting effect on OTM
	Kaipatur et al. [84]		4 gps with spring was ligated (alendronate,and vehicle during concurrent OTM, 3 months pretx with alendronate or vehicle inj., BPN tx was discontinued before OTM)	Inhibiting effect on OTM.
	Venkataramana et al. [85]	Animal(rabbits)	20,2gps(control, BP-1.5mg/kg Pamidronate was given intra-peritonially,1st, 7th,14th day	Inhibiting effect on OTM.
Vitamin D3	Collins, et al. [92]	Animal (Cats)	Vitamin D metabolite 1,25-dihydroxycholecalciferol inj. into the PDL.spring was ligated	Increased the number of osteoclasts, and accelerated OTM
	Takano-Yamamoto et al.	Animal (Rats)	60 rats,2gps(20 microL of 1,25(OH)2D3 (10(-10) and 10(-8) mol/L) was injected locally,right, saline,left in in young and mature rats), ortho force	Increased the number of osteoclasts, and accelerated OTM
	Kale et al. [94]	Animal (Rats)	32 rats,4gps(control,20-microL inj. of dimethyl sulfoxide on (0,3,6days),20 microL of 10(-10) mol/L 1,25-DHCC on (0,3,6 days),0.1 mL of 0.1 microg PGE2 only on day 0)	increased the number of osteoclasts, and accelerated OTM
	Kawakami et al. [95]	Animal (Rats)	Ortho elastics (1,25(OH)2D3,10(-10) M inj locally,once every 3 days)	Increased the number of osteoclasts, and accelerated OTM
Calcitriol	Al-Hasani et al. [96]	Human	15 patients,3gps(15,25,40µg of calciriol, 0.2 ml of vehicle in control side.) three times for every subject at 3 visits	In dose dependent manner it can be a cost-effective way to accelerate OTM
Fluorides	Hellsing& Hammarström. [97]	Animal (Rats)	3gps female rats (non-pregnant, pregnant, and non-pregnant NaF-supplied.),fixed ortho. App. Rx was taken	Velocity of OTM is influenced by hormones as well as trace elements.
	Gonzales et al. [98]		50 rats,5gps with springs were applied(-ve control(nothing received),+ve control(no sodium fluoride but had tooth movement),3gps (received 45 ppm sodium fluoride from birth to 2, 4, and 12 wks, respectively.)	Inhibits osteoclastic activity and reduces the number of active osteoclasts, leading to minimizing OTM
	Karadeniz et al. [99]	Human	48 patiens (2 ppm high fluoride-heavy force, 0.05 ppm low fluoride-heavy force, high fluoride-light force, low fluoride-light force), ortho springs were applied.	Fluoride and heavy forces both increase OTM

CONCLUSION

Orthodontic tooth movement results from a remarkably complicated cascade of events including mechanical and biochemical factors, level of activity of bone cells, modeling and remodeling of the alveolar process in response to mechanical loading. By understanding the effects of common medications on the molecules that enhance or reduce homeostasis in tissues adjacent to the moving tooth subjected to orthodontic forces, orthodontists will imperatively pay more attention to the medical and drug consumption history of each patient before and during orthodontic treatment. The present review showed experimental and few clinical evidences for the effects of many prescriptions and over-the-counter drugs on OTM. Some of these drugs are Promoter drugs for OTM such as Acitominophin, Tenoxicam, PGE1, thyroid and PTH, relaxin, chronic corticosteroids

ingestion, TNF inhibitors, anticonvulsants, and Vitamin D3. On the other hand, other drugs have inhibitory effects of tooth movement such as most of the NSAIDs, Calcitonin, Estrogen, Insulin, BPNs, acute Corticosteroids ingestion, IL-1RA, and Integrin inhibitors. Therefore, these suppressor drugs may be effective as an adjunctive orthodontic approach to lessen undesired tooth movement through enhancing anchorage or preventing relapse after OTM. In addition, some drugs like Phenytoin and immunosuppressant drugs might be involved in unwanted orthodontic side effects, such as gingival overgrowth, making orthodontic treatment and maintenance of oral hygiene difficult. Finally, it has become clear that further well-designed human studies are needed to be able to draw an effective conclusion on the effects of various medications on OTM.

ACKNOWLEDGMENTS

This research project was supported by a grant from the "Research Center of the Female Scientific and Medical Colleges", Deanship of Scientific Research, King Saud University. Also, I am grateful to my husband "Professor Abdullah Alhammadi" for his helpful advice and valuable contribution during the preparation of this research.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work. This work has not been published previously and is not under consideration by another journal.

REFERENCES

1. Diravidamani K, Sivalingam S, Agarwal V. Drugs influencing orthodontic tooth movement: An overall review. J Pharm Bioallied Sci 2012; 4:299-303.
2. Krishnan V, Vijayaraghavan N, Manoharan M, et al. The effects of drug intake by patients on orthodontic tooth movement. Semin Orthod 2012; 18:278-285.
3. Qiao H, Gao Y, Huang Q, et al. The central nucleus of the amygdala lesion attenuates orthodontic pain during experimental tooth movement in rats. Brain Behav 2019; 10.
4. Henneman S, Von den Hoff JW, Maltha JC. Mechanobiology of tooth movement. Eur J Orthod 2008; 30:299-e306.
5. Miller C. AAOM clinical practice statement: Subject: medical history. Oral Surg Oral Med Oral Pathol Oral Radiol 2016; 121:618-9.
6. Greenwood M. Essentials of medical history-taking in dental patients. Dent Update 2015; 42:308-10, 313-15.
7. Piette JD, Rosland AM, Silveira MJ, et al. Medication cost problems among chronically ill adults in the US: Did the financial crisis make a bad situation even worse? Patient Prefer Adherence 2011; 5:187-94.
8. Vyas M, Panesar A. Pharmaceutical marketing communication strategies and its influence on physician prescription preference. Int J Multidisciplinary Res 2019; 9:288–99.
9. Kesselheim AS, Huybrechts KF, Choudhry NK, et al. Prescription drug insurance coverage and patient health outcomes: A systematic review. Am J Public Health 2015; 105:e17-30.
10. Werneck EC, Mattos FS, Da Silva MG, et alEvaluation of the increase in orthodontic treatment demand in adults. Brazilian Dent Sci 2012; 15:47-52.
11. Samsonyanová L, Broukal Z. A systematic review of individual motivational factors in orthodontic treatment: Facial attractiveness as the main motivational factor in orthodontic treatment. Int J Dent 2014; 2014:938274.
12. Howie LD, Pastor PN, Lukacs SL. Use of medication prescribed for emotional or behavioral difficulties among children aged 6-17 years in the United States, 2011-2012. NCHS Data Brief 2014; 148:1-8.
13. Kebodeaux CD. Prescription and over-the-counter medication record integration: A holistic patient-centered approach. J Am Pharm Assoc 2019; 59:S13–7.
14. Bartzela T, Türp JC, Motschall E, et al. Medication effects on the rate of orthodontic tooth movement: A systematic literature review. Am J Orthod Dentofacial Orthop 2009; 135:16-26.
15. Tyrovola JB, Spyropoulos MN. Effects of drugs and systemic factors on orthodontic treatment. Quintessence Int 2001; 32:365-71.
16. De Carlos F, Cobo J, Diaz-Esnal B, et al. Orthodontic tooth movement after inhibition of cyclooxygenase-2. Am J Orthod Dentofacial Orthop 2006; 129:402-406.
17. De Carlos F, Cobo J, Perillan C, et al. Orthodontic tooth movement after different coxib therapies. Eur J Orthod 2007; 29:596-9.
18. Knop LA, Shintcovsk RL, Retamoso LB, et al. Non-steroidal and steroidal anti-inflammatory use in the context of orthodontic movement. Eur J Orthod 2012; 34:531-5.
19. Sodagar A, Etezadi T, Motahhary P, et al. The effect of celecoxib on orthodontic tooth movement and root resorption in rat. J Dent 2013; 10:303-11.
20. Sari E, Olmez H, Gürton AU. Comparison of some effects of acetylsalicylic acid and rofecoxib during orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2004; 125:310-5.
21. Kirschneck C, Wolf F, Cieplik F, et al. Impact of NSAID etoricoxib on side effects of orthodontic tooth movement. Ann Anat 2020; 232:151585.
22. Shetty N, Patil AK, Ganeshkar SV, et al. Comparison of the effects of ibuprofen and acetaminophen on PGE2 levels in the GCF during orthodontic tooth movement: A human study Prog Orthod 2013; 14:6.
23. Arias OR, Marquez-Orozco MC. Aspirin, acetaminophen, and ibuprofen: Their effects on orthodontic tooth movement. Am J Orthod Dentofac Orthop 2006; 130:364-70.
24. Roche JJ, Cisneros GJ, Acs G. the effect of acetaminophen on tooth movement in rabbits. Angle Orthod 1997; 67:231-236.

25. Arantes GM, Arantes VM, Ashmawi HA, et al. Tenoxicam controls pain without altering orthodontic movement of maxillary canines. Orthod Craniofac Res 2009; 12:14-9.
26. Juneja P, Shivaprakash G, Kambalyal PB. An overview of the role of drugs and systemic factors on orthodontic tooth movement. J Indian Orthodont Society 2008; 42:36-47.
27. Yamasaki K, Shibata Y, Imai S, et al. Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. Am J Orthod 1984; 85:508-18.
28. Patil AK, Keluskar KM, Gaitonde SD. The clinical application of prostaglandin E1 on orthodontic tooth movement. J Indian Orthod Soc 2005; 38:91-98.
29. Yamasaki K, Shibata Y, Fukuhara T. The effect of prostaglandins on experimental tooth movement in monkeys (Macaca fuscata). J Dent Res 1982; 61:1444-6.
30. Leiker BJ, Nanda RS, Currier GF, et al. The effects of exogenous prostaglandins on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop 1995; 108:380-388.
31. Sekhavat AR, Mousavizadeh K, Pakshir HR, et al. Effect of misoprostol, a prostaglandin E1 analog, on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop 2002; 122:542-7.
32. Seifi M, Eslami B, Saffar AS. The effect of prostaglandin E2 and calcium gluconate on orthodontic tooth movement and root resorption in rats. Eur J Orthod 2003; 25:199-204.
33. Kale S, Kocadereli I, Atilla P, et al. Comparison of the effects of 1,25 dihydroxy-cholecalciferol and prostaglandin E2 on orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2004; 125:607-14.
34. Gurton AU, Akin E, Sagdic D, et al. Effects of PGI2 and TxA2 analogs and inhibitors in orthodontic tooth movement. Angle Orthod 2004; 74:526-32.
35. Shirazi M, Dehpour AR, Jafari F. The effect of thyroid hormone on orthodontic tooth movement in rats. J Clin Pediatr Dent 1999; 23:259-64.
36. Seifi M, Hamedi R, Khavandegar Z. The effect of thyroid hormone, prostaglandin E2, and calcium gluconate on orthodontic tooth movement and root resorption in rats. J Dent 2015; 16:35-42.
37. Guan L, Lin S, Yan W, et al. Effects of calcitonin on orthodontic tooth movement and associated root resorption in rats. Acta Odontol Scand 2017; 75:595-602.
38. Alnajar HA, Al Groosh DH. The effects of calcitonin on post-orthodontic relapse in rats. Clin Exp Dent Res 2020; 1-9.
39. Soma S, Iwamoto M, Higuchi Y, et al. Effects of continuous infusion of PTH on experimental tooth movement in rats. J Bone Miner Res 1999; 14:546-54.
40. Soma S, Matsumoto S, Higuchi Y, et al. Local and chronic application of PTH accelerates tooth movement in rats. J Dent Res 2000; 79:1717-24.
41. Lee HS, Heo HA, Park SH, et al. Influence of human parathyroid hormone during orthodontic tooth movement and relapse in the osteoporotic rat model: A preliminary study. Orthod Craniofac Res 2018; 21:125–131.
42. Yamashiro T, Takano-Yamamoto T. Influences of ovariectomy on experimental tooth movement in the rat. J Dent Res 2001; 80:1858-61.
43. Haruyama N, Igarashi K, Saeki S, et al. Estrous-cycle-dependent variation in orthodontic tooth movement. J Dent Res 2002; 81:406-10.
44. Arslan SG, Arslan H, Ketani A, et al. Effects of estrogen deficiency on tooth movement after force application: an experimental study in ovariectomized rats. Acta Odontol Scand 2007; 65:319–23.
45. Sirisoontorn I, Hotokezaka H, Hashimoto M, et al. Tooth movement and root resorption; the effect of ovariectomy on orthodontic force application in rats. Angle Orthod. 2011; 81:570-7.
46. Sirisoontorn I, Hotokezaka H, Hashimoto M, et al. Orthodontic tooth movement and root resorption in ovariectomized rats treated by systemic administration of zoledronic acid. Am J Orthod Dentofacial Orthop 2012; 141:563-73.
47. Celebi AA, Demirer S, Catalbas B, et al. Effect of ovarian activity on orthodontic tooth movement and gingival crevicular fluid levels of interleukin-1β and prostaglandin E(2) in cats. Angle Orthod 2013; 83:70-5.
48. Seifi M, Ezzati B, Saedi S, et al. The effect of ovariectomy and orchiectomy on orthodontic tooth movement and root resorption in wistar rats. J Dent 2015; 16:302-9.
49. Tan Z, Zhao Q, Chen Y. The mutual effects between orthodontic tooth movement and estrous cycle or estrogen1. Biological Rhythm Research 2010; 41:75–81.
50. Schwartz JE. Some drugs affect tooth movement. Am J Orthod Dentofacial Orthop 2005; 127:644.
51. Wang B, Yang X, Zhou J, et al. Orthodontic tooth movement at different stages of adolescent female menstrual cycle. J Clin Rehabilitative Tissue Eng Res 2014; 18:2332–2337.
52. Yang X, Dai H, Wang B, et al. Preliminary study on the best-exerted force chance in the female menstrual cycle. West China J Stomatol 2014; 32:252-5.
53. Liu ZJ, King GJ, Gu GM, et al. Does human relaxin accelerate orthodontic tooth movement in rats? Ann Acad Sci 2005; 1041:388-94.
54. Stewart DR, Sherick P, Kramer S, et al. Use of relaxin in orthodontics. Ann Acad Sci 2005; 1041:379-87.
55. Madan MS, Liu ZJ, Gu GM, et al. Effects of human relaxin on orthodontic tooth movement and

periodontal ligaments in rats. Am J Orthod Dentofacial Orthop 2007; 131:8.e1-10.

56. Hirate Y, Yamaguchi M, Kasai K. Effects of relaxin on relapse and periodontal tissue remodeling after experimental tooth movement in rats. Connect Tissue Res 2012; 53:207–19.
57. McGorray SP, Dolce C, Kramer S, et al. A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability. Am J Orthod Dentofacial Orthop 2012; 141:196-203.
58. Braga SM, Taddei SR, Andrade I, et al. Effect of diabetes on orthodontic tooth movement in a mouse model. Eur J Oral Sci 2011; 119:7-14.
59. Villarino ME, Lewicki M, Ubios AM. Bone response to orthodontic forces in diabetic Wistar rats. Am J Orthod Dentofacial Orthop 2011; 139:S76–82.
60. Kalia S, Melsen B, Verma C. Tissue reaction to orthodontic tooth movement in acute and chronic corticosteroid treatment. Orthod Craniofac Res 2004; 7:26-34.
61. Verna C, Hartig LE, Kalia S, et al. Influence of steroid drugs on orthodontically induced root resorption. Orthod Craniofac Res 2006; 9:57–62.
62. Anjusha B, Seema G. Immunosuppressant drugs: Role in periodontium. J Scientific Dent 2016; 6:60-66.
63. Salla JT, Taddei SR, Queiroz-Junior CM, et al. The effect of IL-1 receptor antagonist on orthodontic tooth movement in mice. Arch Oral Biol 2012; 57:519-24.
64. Andrade I, Silva TA, Silva GA, et al. The role of tumor necrosis factor receptor type 1 in orthodontic tooth movement. J Dent Res 2007; 86:1089-94.
65. Ohori F, Kitaura H, Marahleh A, et al. Effect of TNF-α-induced sclerostin on osteocytes during orthodontic tooth movement. J Immunol Res 2019; 2019:9716758.
66. Talic NF, Evans C, Zaki AM. Inhibition of orthodontically induced root resorption with echistatin, an RGD-containing peptide. Am J Orthod Dentofacial Orthop 2006; 129:252-60.
67. Dolce C, Vakani A, Archer L, et al. Effects of echistatin and an RGD peptide on orthodontic tooth movement. J Dent Res 2003; 82:682-6.
68. Reedijk AMJ, Kremer LC, Visser O, et al. Increasing incidence of cancer and stage migration towards advanced disease in children and young adolescents in the Netherlands, 1990-2017. Eur J Cancer 2020; 134:115-126.
69. Krishnan V, Davidovitch Z. The effect of drugs on orthodontic tooth movement. Orthod Craniofac Res 2006; 9:163-71.
70. Mitus-Kenig M, Derwich M, Czochrowska E, et al. Cancer survivors present significantly lower long-term stability of orthodontic treatment: a prospective case-control study. Eur J Orthod 2021; 12.
71. Akhoundi MSA, Sheikhzadeh S, Mirhashemi A, et al. Decreased bone density induced by antiepileptic drugs can cause accelerated orthodontic tooth movement in male Wistar rats. Int Orthod 2018; 16:73-81.
72. Pithon MM, de Oliveira Ruellas AC. Clinical and radiographic evaluation of phenobarbital (Gardenal®) influence on orthodontic movement: A study in rabbits. Rev Dent Press Ortodon Ortop Facial 2008; 13:34-42.
73. Karsten J, Hellsing E. Effect of phenytoin on periodontal tissues exposed to orthodontic force-an experimental study in rats. Br J Orthod 1997; 24:209-15.
74. Adachi H, Igarashi K, Mitani H, et al. Effects of topical administration of a bisphosphonate (risedronate) on orthodontic tooth movements in rats. J Dent Res 1994; 73:1478-86.
75. Igarashi K, Mitani H, Adachi H, et al. Anchorage and retentive effects of a bisphosphonate (AHBuBP) on tooth movements in rats. Am J Orthod Dentofacial Orthop 1994; 106:279-89.
76. Igarashi K, Adachi H, Mitani H, et al. Inhibitory effect of the topical administration of a bisphosphonate (risedronate) on root resorption incident to orthodontic tooth movement in rats. J Dent Res 1996; 75:1644-9.
77. Alatli I, Hellsing E, Hammarström L. Orthodontically induced root resorption in rat molars after 1-hydroxyethylidene-1,1-bisphosphonate injection. Acta Odontol Scand 1996; 54:102-108.
78. Kim TW, Yoshida Y, Yokoya K, et al. An ultrastructural study of the effects of bisphosphonate administration on osteoclastic bone resorption during relapse of experimentally moved rat molars. Am J Orthod Dentofac Orthop 1999; 115:645-53.
79. Liu L, Igarashi K, Haruyama N, et al. Effects of local administration of clodronate on orthodontic tooth movement and root resorption in rats. Eur J Orthod 2004; 26:469-73.
80. Keles A, Grunes B, Difuria C, et al. Inhibition of tooth movement by osteoprotegerin vs. pamidronate under conditions of constant orthodontic force. Eur J Oral Sci 2007; 115:131-6.
81. Fujimura Y, Kitaura H, Yoshimatsu M, et al. Influence of bisphosphonates on orthodontic tooth movement in mice. Eur J Orthod 2009; 31:572-7.
82. Karras JC, Miller JR, Hodges JS, et al. Effect of alendronate on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop 2009; 136:843-7.
83. Choi J, Baek SH, Lee JI, et al. Effects of clodronate on early alveolar bone remodeling and root resorption related to orthodontic forces: A histomorphometric analysis. Am J Orthod Dentofacial Orthop 2010; 138:548.e1-8.
84. Kaipatur NR, Wu Y, Adeeb S, et al. Impact of bisphosphonate drug burden in alveolar bone during orthodontic tooth movement in a rat model: a pilot study. Am J Orthod Dentofacial Orthop 2013; 144:557-67.

85. Venkataramana V, Chidambaram S, Reddy BV, et al. Impact of bisphosphonate on orthodontic tooth movement and osteoclastic count: An animal study. J Int Oral Health 2014; 6:1-8.
86. Krieger E, d'Hoedt B, Scheller H, et al. Orthodontic treatment of patients medicated with bisphosphonates-a clinical case report. J Orofac Orthop 2013; 74:28-39.
87. Lotwala RB, Greenlee GM, Ott SM, et al. Bisphosphonates as a risk factor for adverse orthodontic outcomes: a retrospective cohort study. Am J Orthod Dentofacial Orthop 2012; 142:625–634.e623.
88. Rinchuse DJ, Rinchuse DJ, Sosovicka MF, et al. Orthodontic treatment of patients using bisphosphonates: a report of 2 cases. Am J Orthod Dentofacial Orthop 2007; 131:321-6.
89. Zahrowski JJ. Optimizing orthodontic treatment in patients taking bisphosphonates for osteoporosis. Am J Orthod Dentofacial Orthop 2009; 135:361–74.
90. www.nihcm.org
91. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 2014; 21:319–29.
92. Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. Am J Orthod 1988; 94:278–84.
93. Takano-Yamamoto T, Kawakami M, Yamashiro T. Effect of age on the rate of tooth movement in combination with local use of 1,25(OH)2D3 and mechanical force in the rat. J Dent Res 1992; 71:1487-92.
94. Kale S, Kocadereli I, Atila P, et al. Comparison of the effects of 1,25 –dehydroxycholecalciferol and prostaglandin E2 on orthodontic tooth movement. Am J Orthod 2004; 125:607-14.
95. Kawakami M, Takamo-Yamamoto T. Local injection of 1,25-dihydroxyvitamin D3 enhanced bone formation for tooth stabilization after experimental tooth movements in rats. J of Bone and Mineral Metabolism 2004; 22:541-6.
96. Al-Hasani N, Glares G, Albustani A, et al. Clinical efficacy of locally injected calcitriol in orthodontic tooth movement. Int J Pharm Pharm Sci 2011; 3:139-43.
97. Hellsing E, Hammarström L. The effects of pregnancy and fluoride on orthodontic tooth movements in rats. Eur J Orthod 1991; 13:223-30.
98. Gonzales C, Hotokezaka H, Karadeniz EI, et al. Effects of fluoride intake on orthodontic tooth movement and orthodontically induced root resorption. Am J Orthod Dentofacial Orthop 2011; 139:196-205.
99. Karadeniz EI, Gonzales C, Elekdag-Turk S, et al. The effect of fluoride on orthodontic tooth movement in humans. A two- and three-dimensional evaluation. Aust Orthod J 2011; 27:94-101.