Drugs: The neglected influencer of orthodontic treatment and outcome

1Dr Paridhi Gupta, Department of Orthodontics and Dentofacial Orthopaedics, JSS Dental college and hospital, JSS AHER, Mysuru -570015, Karnataka, India
2Dr Bhagyalakshmi A. Department of Orthodontics and Dentofacial Orthopaedics, JSS Dental college and hospital, JSS AHER, Mysuru -570015, Karnataka, India
3Dr Raghunath N., Department of Orthodontics and Dentofacial Orthopaedics, JSS Dental college and hospital, JSS AHER, Mysuru -570015, Karnataka, India

Corresponding Author: Dr Paridhi Gupta, Department of Orthodontics and Dentofacial Orthopaedics, JSS Dental College and hospital, JSS AHER, Mysuru -570015, Karnataka, India

Citation of this Article: Dr Paridhi Gupta, Dr Bhagyalakshmi A., Dr Raghunath N., “Drugs: The neglected influencer of orthodontic treatment and outcome”, IJDSIR- February - 2020, Vol. – 3, Issue -1, P. No. 299 – 305.

Copyright: © 2020, Dr Paridhi Gupta, et al. This is an open access journal and article distributed under the terms of the creative commons attribution noncommercial License. Which allows others to remix, tweak, and build upon the work non commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract
Orthodontic tooth movement works on the principle of remodeling of paradental tissues when mechanical forces are applied. Mechanical, chemical, and cellular events take place within these tissues, which bring about structural alterations and hence movement of tooth. During orthodontic treatment, we often prescribe drugs to manage pain, TMJ problems and tackle some infections throughout the course of treatment. Apart from these drugs patients who consume vitamins, minerals, hormonal supplements and other compounds for the prevention or treatment of various diseases, can have profound effect on orthodontic tooth movement. Some of these drugs may have profound effects on the short and long term outcomes of orthodontic practice. Hence it is necessary to review the mechanism of action and effects of commonly used drugs on tissue remodeling and orthodontic tooth movement.

Introduction
Orthodontic tooth movement works on the principle of remodeling of paradental tissues when mechanical forces are applied. When a force is applied to the crown of a tooth, it is transmitted to the periodontal ligament and alveolar bone through the root. According to the direction of the force, there will be areas of pressure and areas of tension¹.
Figure 1: Biologic pathways during orthodontic tooth movement.

If the tooth is to move there must also be resorption of alveolar bone on the side of force application and deposition on the opposite side. Classical theory of tooth movement dictates that differential pressure induces cellular changes in the periodontal ligament and the alveolar bone.

WHO in 1966 stated that a drug is any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. Drugs are prescribed by doctors for pain during orthodontic treatment or may be consumed by the patient due to other diseases or in the form of supplemental vitamins. Recently the abuse of over-the-counter drugs has increased significantly, making it difficult to elicit accurately the drug history in many patients. Orthodontists, should be aware of the disease process as well as any effects of the drugs on the tooth movement process.

Drugs that can influence the rate of tooth movement can be divided into 6 main categories:

- Non steroidal anti-inflammatory drugs
- Hormones
- Bisphosphonates
- Vitamin D metabolites
- Fluoride
- Anticonvulants
- Alcohol abuse

1. Non steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a group of drugs that have analgesic, antipyretic and anti-inflammatory action. They are most commonly used in orthodontics to control the pain.

a. Analgesics

These drugs relieve pain by acting on peripheral pain receptors or through CNS. They are weak inhibitor of prostaglandin (PG) synthesis. They act by inhibiting COX activity, leading to alteration in vascular and extravascular matrix remodeling, hence reducing the rate of tooth movement. This controls levels of matrix metalloproteinases (MMP9 and MMP2) which 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.

Knop et al reported that PG inhibition by NSAIDs leads to a reduction in osteoclastic activity, Howship lacunae, and blood vessels leading to slower tooth movement.

b. Acetaminophen (Paracetamol)

It is one of the most common antipyretic and analgesic drugs, and it is often also used in combination with other drugs. It does not have significant anti-inflammatory action and hence the mechanism of action differs slightly with that of NSAIDs. It has a weak COX-1 and COX-2 inhibitor. Studies have shown it has no effect on
orthodontic tooth movement and hence can be prescribed to patients undergoing orthodontic treatment.

c. Aspirin
Acetylsalicylic acid and compounds, act by inhibiting COX activity, which converts unsaturated fatty acids in the cell membrane to PGs. Salicylate therapy decreases bone resorption by inhibition of PGs’ synthesis and in-turn decreases differentiation of osteoclasts from their precursors. Therefore, it is recommended that aspirin should not be prescribed to patients undergoing orthodontic tooth movement as it delays the treatment process.

d. COX-2 inhibitors
Selective COX-2 inhibitors do not affect the Prostaglandin E2 (PGE2) synthesis and bring about selective inhibition of COX-2 enzyme inhibiting the production of PG that cause pain and inflammation. Since it does not affect COX-1 enzyme it can be taken during orthodontic tooth movement. Villa PA et al. reported a drug named nabumetone (NSAID group) which reduces root resorption and pain experienced during intrusive orthodontic forces, without affecting the rate of tooth movement 7.

e. Other NSAIDs
Yamasaki et al. found that administration of indomethacin reduced the appearance of osteoclast and bone resorption in rats leading to delayed movement 8. Sandy and Harris reported flurbiprofen, a prostaglandin cyclooxygenase inhibitor brought about significant decrease in the number of osteoclasts in the bone adjacent to the induced tooth movement suggesting NSAIDs can partially inhibit orthodontic tooth movement 9. Mohammed et al. found that tooth movement in rats were inhibited that were given indomethacin. However, they also found that AA861, a leukotriene inhibitor that causes an increase in the production of PGE2, inhibited tooth movement 10.

2. Hormones
Hormones are chemical messengers that are secreted directly into the blood, which carries them to organs and tissues of the body to exert their functions. Hormones can influence not only the rate of tooth movement but root resorption.

a. Estrogen
Estrogen affects bone metabolism especially in women. It reduces bone remodeling and thereby preserving calcium within the bone. It reduces osteoclast mediated bone resorption by acting on various cytokines and directly stimulates the activity of osteoblasts. Hence they reduce the rate of tooth movement 11. Androgens also inhibit bone resorption and modulate the growth of the muscular system in turn affecting the tooth movement. Therefore, prolonged use of oral contraceptives and androgens by athletes can affect their orthodontic treatment.

b. Thyroid hormone
Thyroid hormones are mainly administered as substitutive drugs post thyroidectomy and in patients with hypothyroidism. Administration of thyroxin increases bone resorption and reduces bone density. Bone tissue remodeling is due to activation of interleukin-1 (IL-1B) production and cytokine mediated osteoclastic bone resorption thereby increasing rate of tooth movement. Low dose thyroxin therapy has shown to reduce force induced root resorption this is due to in bone remodeling process and a reinforcement of the protection of the cementum and dentin to force induced osteoclastic resorption 12.

c. Calcitonin
Calcitonin is opposite to that of thyroid in its action. It is a peptide hormone which decreases the reabsorption of renal and intestinal calcium. It reduces bone resorption by inhibiting osteoclasts and decreasing the surface area of ruffled surface on it. Hence, delaying tooth movement.
d. Relaxin

Relaxin is released during child birth, to bring about widening of birth canal and help in parturition. Liu et al. demonstrated that the administration of relaxin accelerated the early tooth movements in rats. Nicozis and his colleagues in 2000 suggested that Relaxin can be used as an adjuvant in orthodontic therapy, to increase stability, 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.

e. Parathyroid hormones (PTH)

This hormone mainly deals in maintaining a balance of calcium and phosphorus in the body. They regulate blood calcium levels but do not have any direct effect on the growth of an individual. PTH affects osteoblasts’ cellular metabolic activity, multiple protease secretion and gene transcriptional activity. It affects the production of Receptor activator of nuclear factor kappa -B legend (RANK-L), which plays a crucial role in osteoclasts formation. Recent studies have demonstrated that rats who were administered PTH systemically or locally show increased rate of movement.

f. Corticosteroids

Corticosteroids are used as anti inflammatory and immunosuppressive agent in treatment of a number of medical conditions. They bring about varied effects on tooth movement depending on the dosage. They act by inhibiting inhibiting osteoblasts and hence decreasing bone formation activity. Corticosteroids acts by preventing the formation of prostaglandins by influencing the arachidonic acid pathway. An endogenous protein, lipocortin formed by steroids acts by blocking the activity of phospholipase A2, thus inhibits the release of arachidonic acid which in return influences the synthesis of prostaglandin, leukotrienes or thromboxanes.

Corticosteroids also act by reducing the release of lymphokines, serotonin and bradykinin at the injured site. They play a vital role in inhibiting the intestinal calcium absorption, which leads to direct inhibition of osteoblastic function, and increase in bone resorption. This causes increased tooth movement but the movement is not stable due to lack of bone.

g. Prostaglandins (PGs)

Prostaglandins are stress mediators during orthodontic tooth movement. They increase cAMP, stimulate bone resorption by increasing the number of osteoclasts and decrease collagen synthesis. A lower concentration of PGE2 has been found to be effective in tooth movement but higher doses cause root resorption. Local injection of PGs have increased tooth movement but can induce hyperalgesia at the same time.

h. Interleukin antagonists

Interleukin antagonists inhibit IL-1 (produced by inflammatory cells like monocytes, macrophages), IL-6 and COX-2. These drugs influence the inflammatory reaction following the application of orthodontic force, thereby decreasing the pace of tooth movement and bone remodeling.

i. TNF-α antagonists

TNF-α antagonists block TNF-α (Tissue necrotic factor) released in inflammatory cytokinins by activated monocytes, macrophages, and T-lymphocytes, which are required for an inflammatory responses post force application. They also decrease rate of tooth movement.

j. Echistatin and RGD peptides (Arginine–Glycine–Aspartic acid)

Local injection in rats of integrin inhibitors like echistatin and RGD peptides to prevent tooth movement, in order to enhance anchorage has been studied recently. Administration of Echistatin has demonstrated decrease in root resorption following orthodontic force.
k. Immunosuppressant drugs (Cyclosporine)
Immunosuppressant drugs are prescribed to patients in order to prevent graft rejection but these drugs can cause some difficulty during orthodontic treatment. Cyclosporine A produces severe gingival hyperplasia, making maintenance of oral hygiene and orthodontic treatment difficult. Gingivectomy to remove the excess gingival growth should be carried out before commencing orthodontic treatment. Removable appliance do not fit properly and are not recommended. Fixed mechanotherapy should be kept for a minimum period 21.

l. Anticancer drugs
Patients who have been on chemotherapy with busulfan/cyclophosphamide are under risk for orthodontic treatment. These drugs damage the precursor cells involved in bone remodeling process, thereby complicating tooth movement 22.

3. Anticonvulsants
They are antiepileptic drugs used for the treatment of epileptic seizures.
Valproic acid has a potential to induce gingival bleeding even with minor trauma making orthodontic maneuvers difficult. Phenytoin induces gingival hyperplasia involving the interdental papilla, making orthodontic treatment and maintaining oral hygiene difficult. If given to a pregnant mother can induce cleft lip and palate. Gabapentin, causes dryness of mouth, making oral hygiene difficult.

4. Vitamin D
The amount of calcium and phosphorus levels are regulated by Vitamin D and its active metabolite, 1,25,2(OH)D3, along with parathyroid hormone and calcitonin.Vitamin D receptors are present on both osteoblasts and osteoclast precursors. Kale and colleagues in 2004, observed that local applications of vitamin D enhanced the rate of tooth movement in rats due to increased bone turnover 23. Stimulation of osteoblasts by vitamin D can help to stabilize orthodontic tooth movement. In 2004, Kawakami suggested that local application of vitamin D intensified the re-establishment of supporting alveolar bone, post orthodontic treatment.

5. Bisphosphonates
They are analogues of pyrophosphate and are commonly used in the treatment of bone disorders such as osteoporosis, bone pain from some types of cancer etc . Studies have demonstrated that topical application of bisphosphonates can inhibit orthodontic tooth movement. They cause inhibition of hydroxyapatite aggregation due to their strong chemical affinity to calcium phosphate. 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. Igarashi et al evaluated the anchorage and retentive effects of bisphosphonates on tooth movements in rats and concluded that it could be useful in enhancing anchorage and retaining teeth 24.

6. Fluoride
Fluoride has an effect on tissue metabolism and is one of the trace element. It has been used in the treatment of metabolic bone disease like osteoporosis as it causes increase in bone mass and mineral density. Treatment with Sodium fluoride has been shown to inhibit the osteoclastic activity and reduce the number of active osteoclasts and hence delay tooth movement 25.

7. Alcohol abuse
Alcohol crosses the placental barrier and can stunt fetal growth or weight, damage neurons, which can result in psychological or behavioral problems, and cause other physical damage (Fetal Alcohol Syndrome or FAS). The three FAS facial features are a smooth philtrum, thin vermilion, and small palpebral fissures. Chronic ingestion
of large amounts on a daily basis may have devastating effects on skeletal system. Circulating ethanol inhibits the vitamin D3 hydroxylation in liver, thus impending calcium homeostasis. Leading to increased PTH synthesis, causing enhanced resorption of mineralized tissues, including root resorption, in order to maintain normal levels of calcium in blood. Davidovitch et al. reported that there was high risk of root resorption in chronic alcoholics undergoing orthodontic treatment.

**Conclusion**

All the drugs have therapeutic effects, as well as side effects, that may influence the cells targeted by orthodontic forces. Drug-consumption history must be an integral part of every orthodontic diagnosis and treatment plan. An orthodontist must be aware of these drugs so that the treatment best suited for a patient is provided in a simpler way.

**References**


