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Systematic review

Does medication administration affect the rate of orthodontic tooth movement and root resorption development in humans? A systematic review

Eleftherios G. Kaklamanos[1], Miltiadis A. Makrygiannakis[2] and Athanasios E. Athanasiou[3]

[1]Hamdan Bin Mohammed College of Dental Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates, [2]Private practice limited to Orthodontics, Athens, Greece, and [3]Department of Dentistry, European University Cyprus, Nicosia, Cyprus

Correspondence to: Eleftherios G. Kaklamanos, Hamdan Bin Mohammed College of Dental Medicine (HBMCDM), Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU), Building 34, Dubai Healthcare City, Dubai, United Arab Emirates. E-mail: eleftherios.kaklamanos@mbru.ac.ae; kaklamanos@yahoo.com

Summary

Background: Recently, the potential impact of different medications on the rate of orthodontic tooth movement and the associated root resorption has been systematically reviewed in animal studies and various effects have been shown. However, animal data cannot be extrapolated to human clinical situations directly.
Objectives: To systematically investigate the most up to date available evidence from controlled human studies regarding the effect of medication administration on the rate of orthodontic tooth movement and associated root resorption development.
Search methods: We searched eight databases (covering also grey literature) without restrictions and we performed hand searching up until October 2018.
Selection criteria: Controlled studies in humans assessing the effect of various medications on the rate of orthodontic tooth movement and root resorption development.
Data collection and analysis: Study selection was followed by data extraction and risk of bias assessment using the ROBINS-I tool for non-randomized and the Cochrane Risk of Bias Tool for randomized studies.
Results: Eight studies, at various risk of bias, were finally identified. With regard to the rate of orthodontic tooth movement, local injections of prostaglandin E1 were found to exert an increasing effect, whereas systemic intake of nabumetone decreased it. Following tenoxicam administration, drinking water with fluoride or local injections of calcitriol (vitamin D metabolite), no significant effects were demonstrated. Concerning root resorption development, nabumetone administration was shown to reduce it, whereas fluoride, overall, was not observed to exert any effect. Only in individuals subjected to heavy orthodontic forces, did fluoride show a protective effect for the period of force application, but not in the longer term during retention.
Conclusions: The aforementioned substances may show varying effects on the rate of orthodontic tooth movement and root resorption development in human subjects. Despite the observed limitations, the orthodontist should be able to identify patients taking pharmaceuticals and consider any implications related to orthodontic treatment.
Registration: PROSPERO (CRD42017078208).

Introduction

Rationale

A careful medical history is always a necessity when planning orthodontic treatment (1). In this context, information on the consumption of any medication is not only meaningful for understanding general health status, but can also be related to possible repercussions on the intricate molecular signalling pathways pertinent to the cellular events leading to tooth movement as well as the root resorption associated with it (2–4). Prescription medication use has risen considerably during the past years, partly affected by a steadily growing demand for treatments aimed at chronic diseases (5–7). Thus, medication consumption is anticipated to be widespread among adults seeking orthodontic therapy (8–9). Interestingly, in school-age children, that make up the great majority of orthodontic patients, the prevalence of specific therapeutic classes use has also been reported to increase (10). Furthermore, the increase in use of over-the-counter drugs makes the procedure of taking an accurate and complete medication record for potential patients even more complicated (11).

Recently, the potential effect of various drugs on the rate of orthodontic tooth movement and the associated root resorption in experimental animals has been systematically reviewed (12–14). On the basis of the retrieved information the rate of tooth movement was shown to increase after the administration of diazepam, vitamin C and pantoprazole. One the contrary substances, such as simvastatin, atorvastatin, calcium, strontium ranelate, propranolol, losartan, famotidine, cetirizine, metformin, indomethacin, ketorolac, and morphine, were shown to decrease it when administered in animals (12, 14). Moreover, root resorption was shown to increase in vitamin C-treated animals, whereas decreases were observed after the administration of alendronate, ibuprofen, growth hormone, low doses of meloxicam, simvastatin, lithium chloride, and strontium ranelate. However, animal data do not permit direct inferences to human clinical scenarios (13). Dosage and route of administration for the medications used in animal studies sometimes differ from those used in usual human clinical settings (15). Consequently, it is not clear which substances may affect significantly everyday clinical practice (12–14).

Objective

The aim of this systematic review was to investigate and evaluate the quality of the most contemporary evidence from controlled human studies, assessing the effect of medication administration on the rate of orthodontic tooth movement and the associated development of root resorption.

Materials and methods

Protocol and registration

The guidelines described in the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) statement (16) were used to develop a protocol that was later registered in PROSPERO (CRD42017078208). Conduct and reporting of the review adhered to The *Cochrane Handbook for Systematic Reviews of Interventions* (17) and the PRISMA statement (18), respectively. As the present article constitutes a systematic review, ethical approval was not required.

Eligibility criteria

The eligibility criteria for the participants, intervention, comparison, outcomes, and study design domains are presented in Supplementary Table 1. We reviewed experimental prospective controlled studies (randomized and non-randomized) involving healthy patients undergoing active tooth movement with orthodontic appliances. The rate of movement and root resorption development had to be investigated after the administration, systemic or local, of medication. Comparisons were made to placebo intervention, no administration or different dosages of the investigated substance. Studies comparing different medications without the presence of a placebo or no administration group, non-comparative studies, reviews, systematic reviews, and meta-analyses were excluded.

Information sources and search strategy

We searched the whole content of eight databases (that included grey literature) until 6 October 2018. The strategies were developed by the first author and were based on the MEDLINE search (Supplementary Table 2). No restrictions were imposed (status or date of publication and language). The reference lists of the included and excluded studies, the retrieved reviews, and other relevant articles were searched also. If additional information was needed, we contacted the corresponding authors.

Study selection

The titles and abstracts of the retrieved records were assessed, independently and in duplicate, for inclusion, by the first two authors using the EndNote™ X9.1.1 software (Clarivate Analytics, Boston, Massachusetts, USA). The same procedure was repeated for the full text of potentially included studies. The last author settled any disagreements and records of the decisions were kept. The extent of agreement between assessors was not calculated with kappa statistics as it is not recommended (17).

Data collection and data items

Data extraction followed the previously described procedure and used special forms, where the following information was recorded: bibliographic information, study design, study eligibility, subjects' characteristics, orthodontic mechanics used, pharmacological intervention details, and assessed outcomes and results.

Risk of bias in individual studies

The ROBINS-I for non-randomized (19) and the Cochrane Risk of Bias Tool for randomized studies (20) were used to assess the risk of bias using the same procedures. Summaries of the risk of bias within a study were produced by adhering to the Higgins *et al.* (17) approach.

Summary measures and synthesis of results

As an adequate amount of information regarding each of the studied medication was not retrieved, quantitative synthesis of results was not carried out although originally planned (17,21,22).

Risk of bias across studies and additional analyses

Although pre-planned, analyses for 'small-study effects' and publication bias, as well as exploratory subgroup analyses were not conducted because we could not identify a sufficient number of studies (17). The GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) was used to appraise the quality of evidence (23).

Results

Study selection

Initially, 7491 records were retrieved (4 found in relevant articles), from which 2490 were duplicates and 4987 were excluded after

considering their title and abstract (Figure 1). Of the remaining 14 articles, six studies were subsequently excluded: one as not relating to the assessment of tooth movement or root resorption (24), one involving comparison of medication with corticotomy (25), two with unclear or inconsistent study design (frequency or duration of medication administration) (26,27), and another two because they lacked quantitative data on the rate of tooth movement and/or resorption development (28,29). Finally, eight studies were considered eligible for inclusion. Five studies investigated the effects of prostaglandin E1 [PGE_1 (alprostadil); rate of movement] (30,31), the non-steroidal anti-inflammatory drugs (NSAIDs) nabumetone (rate of movement/root resoprtion) (32) and tenoxicam (rate of movement) (33), as well as the result of calcitriol (vitamin D metabolite) administration (rate of movement) (34), respectively. Three more articles were derived from the same sample and reported the effects of two different randomly assigned varied orthodontic force levels in individuals exposed to high and low amounts of fluoride intake from birth, with regard to the rate of tooth movement (35) and root resorption development, immediately after the cessation of force application (36) and 3 months later into retention (37).

Study characteristics

Tables 1 and 2 present the characteristics of the studies included. The described experiments lasted from 4 to 16 weeks in total. All of them included male and female patients from 12 to 28 years old. Sample size did not conform to any calculation. Springs or power chains were used to move teeth. The studied movements included maxillary canine retraction and intrusion, and buccal or palatal displacement of first maxillary premolars. The rate of movement was assessed on casts, photographs, or clinically. Root resorption development was evaluated by means of staining of histological sections or microcomputed tomography. None of the included studies assessed medication bioavailability in serum.

Risk of bias within studies

Tables 3 and 4 contain a summary of the risk of bias assessment. All three non-randomized studies (30,31,32) were assessed as being at moderate risk of bias, owing to moderate bias due to confounding and selection of the reported result. With regard to the five randomized studies (33–37), one was assessed to be of low risk of bias (33). The studies on the different fluoride levels in the drinking water and calcitriol were considered to be of unclear risk of bias (34–37).

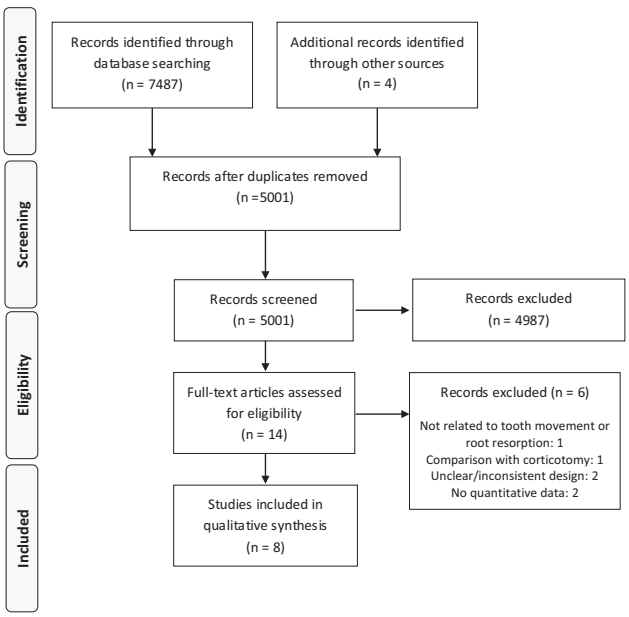

Figure 1. Flow of records through the reviewing process.

Results of individual studies

With regard to the rate of orthodontic tooth movement, local administration of PGE_1 was found to exert an increasing effect, whereas systemic intake of nabumetone decreased it. Following tenoxicam administration, local injections of calcitriol or drinking water with fluoride, no significant effects were demonstrated.

Concerning root resorption, nabumetone administration was shown to reduce it, whereas fluoride, overall, was not found to exert any effect. Only in the group subjected to heavy orthodontic forces, did fluoride show a protective effect during the period of force application, but not in the longer term during the 3 months of retention (Tables 1 and 2).

Risk of bias across studies and additional analyses

Analyses for 'small-study effects', publication bias or subgroup analyses were not possible. Regarding the effect of the investigated medication on the rate of orthodontic tooth movement and root resorption development, the quality of the available evidence (i.e. the confidence that we have that the true effect is more or less similar to the estimated effect) was considered as moderate for the fluoride and tenoxicam studies, mainly because of concerns regarding precision. Concerns regarding the risk of bias led to further downgrading of the quality of evidence for the calcitriol trial, whereas the non-randomized nature of the studies on PGE_1 and nabumetone resulted in the final assessment of the confidence in the observed estimates as very low (Supplementary Tables 3 and 4).

Discussion

Summary of evidence

As numerous, shared signalling pathways, of increased complexity, mediate the cellular events associated with orthodontic tooth movement and the associated root resorption, alterations in bone turnover and density may affect the rate of movement and have an impact on the possibility of undesirable outcomes (4,23). In this sense, pharmaceutical substances that affect these pathways might influence treatment prognosis and potential risks as well. Thus, orthodontic care provided to patients consuming drugs could be supported by relevant evidence-based information. However, direct inference of information derived from animal experiments to human clinical settings cannot be made (12–14).

On the basis of the collected studies, a variable effect on the rate of movement and root resorption was detected. Although the set of retrieved data is limited and the level of confidence in the observed estimates was deemed to be variable and at best as moderate, the orthodontist should identify patients taking pharmaceutical substances and relate possible effects to the planned treatment. Treatment duration might change when a patient is consuming for a long period medication that could possibly lead to a decreased rate of movement. In addition, such patients may present difficulty in closing pre-existing or post-extraction spaces and there would not benefit in asking them to come for adjustments in short time intervals. On the other hand, a closer follow-up could be necessary for patients receiving medications that may accelerate tooth movement. Challenges in anchorage management could also be observed.

Table 1. Characteristics of the studies relevant to the rate of orthodontic tooth movement. ↑, increase; ↓, decrease; C, canine; EG, experimental group that received pharmacological intervention, different than placebo; F, females; FPm, first premolar; HF, heavy force; LF, low force; M, males; M, maxillary; n, no difference in the rate of orthodontic tooth movement relative to control or placebo groups; ns, normal saline; PG, placebo group receiving the vehicle preparation without the active substance; PO, *per os*; RCT, randomized controlled trials; SPm, second premolar; SS, stainless steel;TMA, titanium molybdenium alloy; w, week(s); y, years

Active substance (type of study)	Subjects and tooth movement model (number; gender; age)	Group characteristics* (no; substance; dosage; route; administration)	Assessment of tooth movement	Results**
Nabumetone Villa *et al.*, 2005 (32) Split mouth	25; 13 F and 12 M; 12–25 y 0.017″ × 0.025″ SS spring for intrusion of Mx FPm (113.4g) Force application: 4 w + placebo for the right side followed by 4 w + active substance for the left side	EG: 25 quadrants; nabumetone (2 × 500 mg); PO; daily PG: 25 quadrants; crystalline microcellulose (100 mg/kg); PO; daily Sample size calculation: No Medication administration: 4 w Medication bioavailability assessment: No	Measurements on dental casts Vertical movement of FPm	(2 × 500 mg): ↓
Tenoxicam Arantes *et al.*, 2009 (33) RCT Split mouth	36 (72 quadrants); gender not mentioned; 16-25 y NiTi springs for bilateral C retraction Force application: 4 w	EG1: 24 quadrants; 20 mg before activation, placebo after, 20 mg at 24 h and 48 h; PO EG2: 24 quadrants; placebo before activation, 20 mg after, at 24 h and 48 h; PO PG: 24 quadrants; placebo before activation, after, at 24 h and 48 h; PO Patients were offered paracetamol (750 mg) up to 4 times/day, in case of pain Sample size calculation: No Medication administration: up to 48 h after each activation Medication bioavailability assessment: No	Clinical measurements Distance between the C and SPm	(20 mg + placebo): n (placebo + 20 mg): n
Fluoride Karadeniz *et al.*, 2011 (35) RCT (for force level)	48; 25 F and 23 M; 11.75–20 y Buccally directed force on Mx FPm: 0.016″ TMA (25g LF) or 0.017″ × 0.025″ TMA (225g HF) Force application: 4 w	EG1: 24; LF + 0.05 ppm fluoride; PO; in drinking water EG2: 24; HF + 0.05 ppm fluoride; PO; in drinking water EG3: 24; LF + 2 ppm fluoride; PO; in drinking water EG4: 24; HF + 2 ppm fluoride; PO; in drinking water Sample size calculation: No Medication administration: 4 w Medication bioavailability assessment: No	Measurements on dental casts 2-D movement of FPm (buccal/palatal cusps) 3-D movement of FPm (buccal/palatal cusps)	HF: (0.05 ppm) versus (2 ppm): n LF: (0.05 ppm) versus (2 ppm): n
PGE1 (alprostadil) Patil *et al.*, 2005 (30) Split mouth	14 (28 quadrants); 10 F and 4 M; 13–26 y C retraction with NiTi retraction springs (150g) Force application: 8 w	EG: 14 quadrants; PGE_1 (1g); local administration; at Day 1, 6, and 17 of canine retraction PG: 14 quadrants; 1 ml lignocaine; local administration; at Day 1, 6, and 17 of canine retraction Sample size calculation: No Medication administration: 17 days Medication bioavailability assessment: No	Measurements on occlusograms Distance of the tip of the C in relation to the median palatine rugae	(1 g): ↑
Spielmann *et al.*, 1989 (31) Split mouth	5; 1 F and 4 M; 12–20 y Clear power chain between FPm Force application: 4 w (weekly reactivation)	EG: 5 quadrants; PGE_1 (10 μg); local administration; once per week PG: 5 quadrants; 0.1 ml ns; local administration; once per week Sample size calculation: No Medication administration: 4 w Medication bioavailability assessment: No	Measurements on photographs Palatal movement of the FPm central groove	(10 μg): ↑
Vitamin D (calcitriol) Al-Hasani *et al.*, 2011 (34) RCT (for dosage) Split mouth	15; 17–28 y Canine retraction with 0.018″ base archwire (150g) Force application: 3 w (reactivated weekly)	EG1: 5 quadrants; 15 pg vitamin D; local administration; weekly EG2: 5 quadrants; 25 pg vitamin D; local administration; weekly EG3: 5 quadrants; 40 pg vitamin D; local administration; weekly PG: 15 quadrants 0.2 ml dimethylsulphoxide; local administration; weekly Sample size calculation: No Medication administration: 3 w Medication bioavailability assessment: No	Clinical measurements Distance between the C and SPm	(15 pg): n (25 pg): n (40 pg): n

*Dosages were standardized to mg/kg where possible.

**All results shown represent comparisons with placebo or comparison between different dosages.

Table 2. Characteristics of the studies relevant to root resorption. ↑, increase; ↓, decrease; C, canine; EG, experimental group that received pharmacological intervention, different than placebo; F, females; FPm, first premolars; HF, heavy force; LF, low force; m, months; M, males; Mx, Maxillary; *n*, no difference in the rate of orthodontic tooth movement relative to control or placebo groups; ns, normal saline; PG, placebo group receiving the vehicle preparation without the active substance; PO, *per os*; RCT, randomized controlled trials; SPm, second premolar; SS, stainless steel; TMA, titanium molybdenium alloy; w, week(s); y, years

Active substance (type of study)	Subjects and tooth movement model (number; gender; age)	Group characteristics* (no; substance; dosage; route; administration)	Methodology (area of assessment and measurement)	Results**
Fluoride Karadeniz *et al.*, 2011 (36) RCT (for force level)	48; 25 F and 23 M; 11.75–20 y Buccally directed force on Mx FPm: 0.016″ TMA (25g LF) or 0.017″ × 0.025″ TMA (225g HF) Force application: 4 w	EG1: 24; LF + 0.05 ppm fluoride; PO; in drinking water EG2: 24; HF + 0.05 ppm fluoride; PO; in drinking water EG3: 24; LF + 2 ppm fluoride; PO; in drinking water EG4: 24; HF + 2 ppm fluoride; PO; in drinking water Sample size calculation: No Medication administration: since birth Medication bioavailability assessment: No	Microcomputed tomography (whole root) Volume of resorption lacunae (mm^3)	HF: (0.05 ppm > 2 ppm) LF: (0.05 ppm) versus (2 ppm): n
Karadeniz *et al.*, 2013 (37) RCT (for force level)	Same as Karadeniz *et al.*, 2011 Plus, 12 w of retention on the right side	Same as Karadeniz *et al.*, 2011	Same as Karadeniz *et al.*, 2011	HF: (0.05 ppm) versus (2 ppm): n LF: (0.05 ppm) versus (2 ppm): n
Nabumetone Villa *et al.*, 2005 (32) Split mouth	25; 13 F and 12 M; 12–25 y 0.017″ × 0.025″ SS spring for intrusion of Mx FPm (113.4g) Force application: 4 w + placebo for the right side followed by 4 w + active substance for the left side	EG: 25 quadrants; nabumetone (2 × 500 mg); PO; daily PG: 25 quadrants; crystalline microcellulose (100 mg/kg); PO; daily Sample size calculation: No Medication administration: 4 w Medication bioavailability assessment: No	Histomorphometry (whole root) Depth of tissue lost due to resorption (%) Number of resorption lacunae (n)	(2 × 500 mg): ↓

*Dosages were standardized to mg/kg where possible.
**All results shown represent comparisons with placebo or comparison between different dosages.

Table 3. Summary of risk of bias assessment for non-randomized studies

Domain	Patil *et al.*, 2005 (30)	Spielmann *et al.*, 1989 (31)	Villa *et al.*, 2005 (32)
Bias due to confounding	Moderate	Moderate	Moderate
Bias in selection of participants for the study	Low	Low	Low
Bias in classification of interventions	Low	Low	Low
Bias in measurement of outcomes	Low	Low	Low
Bias in selection of the reported result	Moderate	Moderate	Moderate
Overall	Moderate	Moderate	Moderate

Table 4. Summary of risk of bias assessment for randomized studies

Domain	Al-Hasani *et al.*, 2011 (34)	Arantes *et al.*, 2009 (33)	Karadeniz *et al.*, 2011 (35)	Karadeniz *et al.*, 2011 (36)	Karadeniz *et al.*, 2013 (37)
Sequence generation	Unclear	Low	Unclear	Unclear	Unclear
Allocation concealment	Unclear	Low	Unclear	Unclear	Unclear
Blinding of participants and personnel	Unclear	Low	Low	Low	Low
Blinding of outcome assessment	Unclear	Low	Low	Low	Low
Incomplete outcome data	High	Low	Low	Low	Low
Selective outcome reporting	Low	Low	Unclear	Unclear	Unclear
Other potential threats to validity	Low	Low	Low	Low	Low
Overall	Unclear	Low	Unclear	Unclear	Unclear

During orthodontic tooth movement, various biomolecules are released by the osteocytes. Prostaglandins are considered to be the most significant as they stimulate both osteoclasts and osteoblasts (38, 39). Prostaglandins also elevate metalloproteinases' levels and lead to procollagen production decreases. Procollagen is essential for bone and periodontal ligament remodelling (40). Consequently,

prostaglandin inhibition might have repercussions on tooth movement (41). NSAIDs, which are used widely for their analgesic and anti-inflammatory properties, exert their action on the cyclooxygenases. These enzymes modulate the production of prostaglandins from arachidonic acid and could influence potentially the processes associated with orthodontic tooth movement and root resorption development (42–45).

Local administration of PGE_1 was found to exert an increasing effect on the rate of orthodontic tooth movement by 1–2 mm per month (30,31). Although, this finding is consistent with observations of increased bone resorption in humans (46), the results of the GRADE assessment suggest that the true effect could be markedly different from the estimated effect. With regard to NSAIDs, only information on nabumetone and tenoxicam administration was retrieved. Although nabumetone administration was found to lead, with very low certainty, to clinically small reductions in the speed of tooth movement, tenoxicam administration did not seem to have significant effects; the GRADE assessment suggested that this estimate is probably close to the true effect. Moreover, nabumetone seemed to reduce root resorption in comparison to placebo, but the confidence in the observed effect was also very low. The results regarding the association of NSAIDs with bone formation or resorption have been found to be controversial (47).

Three recent systematic reviews on animal studies have also shown varying effects of NSAIDs on the rate of orthodontic tooth movement and root resorption (12–14). The overall effects on animal bone metabolism have also been variable. Differences in the experimental design, in the dosage used, the route, and the time period of administration, as well as animal species and gender, have been considered as possible sources for this variation (42,48). In small rodents, animal species differ significantly in bone chemical and cellular content, density, and biomechanical properties (49). Moreover, the pharmacokinetic characteristics of NSAIDs might vary among different species (50) or animal genders (51). The hormonal variations in female animals encountered during the oestrous cycle may account for changes in tooth movement through the effects of oestradiol on bone resorption (51).

Local injections of calcitriol, a vitamin D metabolite, were not shown to exert a statistically significant effect on the rate of orthodontic tooth movement, but with a low level of confidence. Vitamin D constitutes a potent modulator of bone metabolism (52), affecting the osteoclasts (53) and increasing the rate of tooth movement in animal subjects (54). Apart from the differences in species and dosages, as well as the variations in study design, also the lack of sample size calculation could account for the observed discrepancy between human and animal studies.

Fluoride is the most widely used agent in preventive dentistry. On the basis of the findings of the present review, drinking water with variable levels of fluoride was not found to have any statistically significant effect on the rate of orthodontic tooth movement; the GRADE assessment again suggested that this estimate is probably close to the true effect. Previous studies on animals have produced contradictory results. Hellsing and Hammarström (55) reported that fluoride subcutaneous administration by means of an osmotic pump in rats resulted in a reduction in the rate of orthodontic tooth movement. Gonzales *et al.* (56), who investigated the effect of administering fluoride in the drinking water of rats from birth, observed also a decrease in the rate of movement and concluded that the longer the fluoridated water was administered to the rats, the lower was the rate of movement. Histomorphological investigations showed also a reduction in the number of osteoclasts on the pressure side of the periodontal ligament (55). The observed discrepancies could be attributed to the extremely high fluoride concentrations used in the aforementioned studies (15 mg/g weight; 45 ppm) (55,56), concentrations that would be toxic for the human body. Apart from the dosage difference, calcium and vitamin D levels, different species, variations in fluoride consumption, and individual characteristics could account for the observed variability (57,58).

Concerning root resorption, overall, fluoride did not demonstrate a statistically significant effect. Only in the group subjected to heavy forces, did fluoride show a protective effect during the 4-week period of force application, but not in the longer term, after 3 months of retention (36,37). Histologically, fluoride has been shown to decrease the number of osteoclasts in bone (55), as well as the number, the area, and depth of the resorption lacunae (59,60). Previous studies on animals have reported inconsistent effects. Foo *et al.* (61) were not able to demonstrate a statistically significant reduction in the average amount of root resorption in rats after fluoride administration. However, others have shown that animals receiving fluoridated water showed a significant decrease in the depth and length of the root resorption lesions (62). The results of Gonzales *et al.* (56) were in accordance with the previous investigation that led to the conclusion that not only did fluoride reduce the depth, volume, and roughness of the resorption craters in the experimental groups, but also the increasing duration of exposure to the drinking water exerted a significant protective effect against root resorption development. Once again, differences in dosages and species, as well as individual susceptibility or resistance, could account for the observed variability (57,58,63).

Strengths and limitations

The present systematic review followed specific guidelines. The strategies for the database search were comprehensive and covered potentially relevant records up to October 2018, without any restrictions on language. By performing all procedures independently and in duplicate, as well as by settling disagreements after consultation with the third author, all possible care was taken to minimize bias to the extent possible.

However, some limitations became evident because of the experimental designs and the characteristics of the data located for the review; these resulted in the quality of evidence to be rated as being, at best, as moderate. Meta-analyses and additional analyses were not possible because of scarcity in relevant information. Also, methodological characteristics lead to unclear or moderate risk of bias assessments. Furthermore, all three studies on fluoride lacked a zero-fluoride intake control group, a fact that constitutes a limitation *per se*. The comparison is made between two groups that both received fluoride *via* drinking water, however, in different concentrations. Among the retrieved information, there were three studies (30,31,34) in which the relevant medication was administered by means of local injection. This route of administration might not be compatible with the everyday consumption of the medication, but could be considered where an attempt is made to manipulate pharmacologically the rate of tooth movement of individual teeth. Medication bioavailability measurements could also be important, but were not performed. In addition, as specific tooth movement mechanics were used the generalizability of results might be curtailed. Finally, power sample calculations were not done in most studies, posing limitations in terms of precision. Consequently, there is a variable degree of certainty regarding the effects of medications in everyday clinical scenarios.

Recommendations for future research

As many orthodontic patients can consume various medications, further research is justified, using standardized methods that contribute to the generalizability of the retrieved results and the reduction of the risk of bias. In order for studies to resemble more closely to clinical scenarios in everyday practice, medication dosage, route, and duration of administration, as well as the type of biomechanics used, should receive appropriate attention. In addition, there should be careful and detailed examination and report of the adverse effects.

Conclusions

On the basis of the collected information, medicinal substances consumed during orthodontic treatment may have different effects on the rate of tooth movement and root resorption development in humans. Although the assessed level of evidence implies that these results should be regarded sometimes cautiously, the possible implications should not be ignored.

Supplementary material

Supplementary data are available at *European Journal of Orthodontics* online.

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Conflict of interest

None declared.

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