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Systematic review

Does common prescription medication affect the rate of orthodontic tooth movement? A systematic review

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Summary

Background: As the taking of any medication may theoretically affect the complex pathways responsible for periodontal tissue homeostasis and the events leading to orthodontic tooth movement, it is considered important for the orthodontist to be able to identify prospective patients' history and patterns of pharmaceutical consumption.
Objective: To systematically investigate and appraise the quality of the available evidence regarding the effect of commonly prescribed medications on the rate of orthodontic tooth movement.
Search methods: Search without restrictions in eight databases and hand searching until June 2017.
Selection criteria: Controlled studies investigating the effect of commonly prescribed medications with emphasis on the rate of orthodontic tooth movement.
Data collection and analysis: Following study retrieval and selection, relevant data was extracted and the risk of bias was assessed using the SYRCLE's Risk of Bias Tool.
Results: Twenty-seven animal studies, involving various pharmacologic and orthodontic interventions, were finally identified. Most studies were assessed to be at unclear or high risk of bias. The rate of orthodontic tooth movement was shown to increase after the administration of diazepam, Vitamin C and pantoprazole, while simvastatin, atorvastatin, calcium compounds, strontium ranelate, propranolol, losartan, famotidine, cetirizine, and metformin decreased the rate of orthodontic tooth movement. No interference with the rate of orthodontic tooth movement was reported for phenytoin, phenobarbital and zinc compounds, whereas, inconsistent or conflicting effects were noted after the administration of L-thyroxine, lithium compounds, fluoxetine and insulin. The quality of the available evidence was considered at best as low.
Conclusions: Commonly prescribed medications may exhibit variable effects on the rate of orthodontic tooth movement. Although the quality of evidence was considered at best as low, raising reservations about the strength of the relevant recommendations, the clinician should be capable of identifying patients taking medications and should take into consideration the possible implications related to the proposed treatment.
Registration: PROSPERO (CRD42015029130)

Introduction

Rationale

Despite the fact that orthodontic diagnosis and treatment planning are mainly based on clinical examination and diagnostic records assessment, a careful medical history is still necessary (1). Particular information on any medication taken is not only significant in providing a proper background to the patient's overall health status. It is also important in order to relate to any possible effects on the complex molecular signalling pathways responsible for periodontal tissue homeostasis and the transduction of mechanical stress to the cascade of biochemical events resulting in orthodontic tooth movement (2, 3). Thus, it is considered important for the clinician to be able to identify prospective patients' history and patterns of pharmaceutical consumption (4).

Prescription medication use has recently expanded significantly, partly influenced by a continuously increasing demand for treatments targeting aging-related and chronic diseases (5–7). Furthermore, this trend has been affected by other parameters such as expanded coverage through health insurance schemes and direct-to-consumer advertising (6–9). The noted increases in pharmaceutical consumption are not only relevant to the increased numbers of adult patients seeking orthodontic therapy and now reported to comprise more than a quarter of the orthodontic population (10, 11) but also to the younger as well as older school-aged children that constitute the vast majority of patients under orthodontic treatment (12). In the USA, for example, approximately 7 per cent of children aged between 6 and 17 years have been reported to use prescribed medication for emotional or behavioural difficulties (13). In addition, the extensive use of over-the-counter medications further complicates the task of retrieving an accurate medication record for many prospective patients (14).

During the last years, the possible influence of different pharmaceutical substances on tissue homeostasis and the events leading to orthodontic tooth movement have been reviewed and various changes in the metabolic state interfering with bone remodelling have been noted (15–19). However, despite the general interest in the aspects of orthodontic treatment related to its duration (20), most publications have not focused explicitly on the influence on the rate of orthodontic tooth movement itself (21).

Objective

The objective of the present review was to systematically investigate and appraise the quality of the available evidence regarding the effect of commonly prescribed systemic medication on the rate of orthodontic tooth movement.

Materials and methods

Protocol and registration

The present review was based on a specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (22) and registered in PROSPERO (CRD42015029130). Furthermore, conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (23) and the PRISMA statement (24), respectively.

Eligibility criteria

The eligibility criteria were based on the Participants, Intervention, Comparison Outcomes and Study design (PICOS) acronym, and controlled studies involving subjects undergoing active orthodontic tooth movement were reviewed. The studies had to investigate the rate of tooth movement after the systemic administration of medication from the therapeutic categories most frequently prescribed in humans (25, 26) compared to no intervention or placebo intervention. Non-comparative studies (case reports and case series), systematic reviews, and meta-analyses were excluded (Supplementary Table 1).

Information sources and search strategy

In total, eight databases were searched up until June 2017. One author (EGK) developed detailed search strategies for each database. These were based on the strategy developed for MEDLINE but revised appropriately for each database to take into account the differences in controlled vocabulary and syntax rules (Supplementary Table 2).

No restrictions were placed on the language, date, or status of publication. In addition, efforts to obtain additional studies were made and the reference lists in reviews, included or excluded studies, as well as other related articles were searched. The authors of studies were to be contacted in order to provide additional data if needed.

Study selection

Two authors (MAM and EGK) electronically assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. Subsequently, they obtained and assessed, again independently, the full report of records considered by either reviewer to meet the inclusion criteria. Disagreements were resolved by discussion or consultation with the third author (AEA).

Data collection and data items

The same two authors performed data extraction independently, and any disagreements were again resolved by discussion or consultation with the third author. Predetermined and pre-piloted data collection forms were used to record the following information: bibliographic details of the study; details on study design and verification of study eligibility; characteristics of the subjects and the mechanisms effecting orthodontic tooth movement; details on the intervention and outcome measurement characteristics and results.

Risk of bias in individual studies

Two authors (MAM and EGK) assessed the risk of bias in individual studies, independently and in duplicate. The ROBINS-I tool was to be used to assess the risk of bias in the case of studies involving humans (27) and the SYRCLE's risk of bias tool in the case of animal studies (28). The risk of bias within a study was assessed in summary according to Higgins and Green (23). Any disagreements were resolved by discussion or consultation with the third author (AEA).

Summary measures and synthesis of results

If deemed possible, the rate of orthodontic tooth movement after the administration of each specific active substance was planned to be expressed as the Weighted Mean Difference (WMD) together with a 95% Confidence Interval (CI) (29).

The random effects method for meta-analysis was to be used to combine data (30, 31), since they were expected to differ across studies due to diversity in terms of subject groups, procedures and follow-up. To identify the presence and extent of between-study

heterogeneity, an overlap of the 95% CI for the results of individual studies was to be inspected graphically and the I^2 statistic was to be calculated (23).

All analyses were done with Comprehensive Meta-analysis software 2.2.046 (©2007 Biostat Inc.). Significance (a) was set at 0.05, except for the 0.10 used for the heterogeneity tests (32).

Risk of bias across studies and additional analyses

If a sufficient number of studies were identified, analyses were planned for 'small-study effects' and publication bias (23). If deemed possible, exploratory subgroup analyses were planned according to intervention characteristics. In addition, the quality of evidence was assessed based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (33).

Results

Study selection

The flow of records through the reviewing process is shown in Figure 1. We initially identified 3805 references, and excluded 730 as duplicates and 3033 more on the basis of their title and abstract. From the 42 records that remained and were assessed for eligibility, 15 studies were excluded, either because they did not investigate the rate of orthodontic tooth movement or used medication not prescribed for humans. Finally, 27 full-text study reports were included in the systematic review (34–60).

Study characteristics

The characteristics of the studies included in the present systematic review are presented in Table 1 and Supplementary Table 3. The papers were published between 1986 and 2017 and investigated animal subjects regarding the rate of orthodontic tooth movement after the administration of specific pharmaceutical substances. The length of the experimental period varied from 6 to 60 days. In the majority of these studies, the animal species used for the investigation were rats and mice, however, other species were used as well, such as cats and rabbits. Orthodontic tooth movement was usually induced by placing coil springs between incisors and molars. Other models included fixed lingual appliance used for buccal movement of upper first molars and springs that exerted reciprocal lateral forces over the incisors. Orthodontic tooth movement was usually measured clinically with calipers or feeler gauges. Other methods included measurements on histological sections, clinical photos, impressions and radiographs.

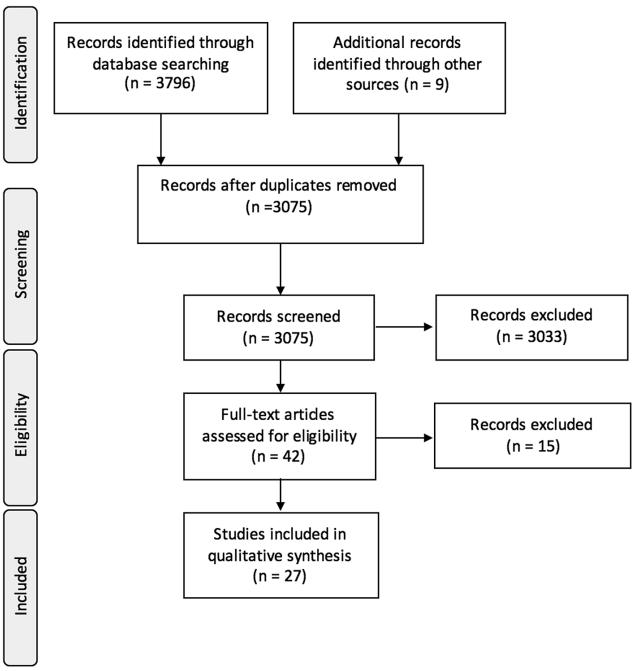

Figure 1. Flow of records through the reviewing process.

The retrieved papers included the study of active substances from the following therapeutic categories (25, 26): Angiotensin converting enzyme (ACE) inhibitors (51); anticonvulsants (44, 52); antidepressants (43, 50, 54); antidiabetic agents (35, 37, 59); antihistamines (46, 47, 58); antihyperlipidemic agents (42, 49); anxiolytics, sedatives and hypnotics (38); beta-adrenergic blocking agents (41); minerals and electrolytes (34, 39, 40, 45, 55, 60); proton pump inhibitors (56); thyroid hormones (36, 53, 55, 57) and vitamins (48).

Risk of bias within studies

Table 2 presents the summary findings of the risk of bias assessment for the included studies. One study was considered as being of low risk of bias (41), 19 of unclear risk of bias (34–36, 38, 39, 42, 43, 45, 48–55, 57, 59, 60) and seven of high risk of bias (37, 40, 44, 46, 47, 56, 58).

In general, most studies included were considered to present unclear risk of bias regarding the domains of random sequence generation, allocation concealment and blinding of the outcome assessors because of insufficient information to form a definite judgement on the risk of bias. Nevertheless, the majority of them used groups similar at baseline, in respect to gender, age and weight of the subjects and consequently were found to be of low risk of bias in the respective domain. There was no information regarding whether animals were randomly housed, as well as whether caregivers and investigators were blinded on the intervention each animal received, resulting in an unclear risk of bias for the majority of the studies. With regards to the random selection of animals for outcome assessment and the existence of incomplete data, the risk of bias was rated as low for almost half of them as the data from all the subjects were analysed, while it was unclear for the remaining studies as there was insufficient information to draw a definite conclusion. Moreover, the review authors did not assume that bias was introduced by selective outcome reporting. Finally, it was impossible to determine if the studies were free of any additional problems that could increase the risk of bias.

Results of individual studies

The results of the studies included in the present review are presented on Supplementary Table 4. Because of the lack of extensive data regarding each specific active substance, as well as differences in the methodology used and the interventions employed, quantitative data synthesis was not possible (23).

Based on the retrieved data, the rate of orthodontic tooth movement was shown to increase after the administration of the anxiolytic diazepam (38) and Vitamin C (48). In addition, the rate of movement was greater after prolonged administration of the proton pump inhibitor pantoprazole (56).

On the other hand, it was noted that the antihyperlipidemic agents, simvastatin and atorvastatin (42, 49), as well as the calcium compounds investigated (40, 55) and strontium ranelate (45) decreased the rate of tooth movement. The same was observed after

Table 1. General characteristics of the studies included in the systematic review (25, 26). ACE: Angiotensin Converting Enzyme; d: days; FM: first molars; I: incisors; IP: intraperitoneal; m: months; Md: mandibular; Mx: Maxillary; PBS: phosphate-buffered saline; w: weeks.

Therapeutic category	Active substance	Study	Subject characteristics [no; species; gender; age; weight]	Tooth movement model
ACE inhibitors	Losartan	Moura *et al.*, 2016 (51)	40 C57BL6/J mice; 10 w old	NiTi coil spring between Mxright FM and both Mx [35 g]
Anticonvulsants	Phenytoin	Karsten and Hellsing, 1997 (44)	20 Sprague-Dawley rats; female; 3–5 m; 250 g on average	Fixed expansion lingual appliance for buccal movement of the Mx FM [Australian light wire; 150 mN]
	Phenobarbital	Pithon and Ruellas, 2008 (52)	20 New Zealand rabbits; 11 male/11 female; 10–14 m; 3 kg on average	Closed coil spring between mandibular FMs and Is [80 cN]
Antidepressants	Fluoxetine	Franzon Frigotto *et al.*, 2015 (43)	48 Wistar rats; male; 9 w; 300–350 g	NiTi closed coil spring between Mx right FM and I [30 cN]
		Mirhashemi *et al.*, 2015 (50)	30 Wistar rats; male; 200–250 g	NiTi closed coil spring between Mx left central I and the FM [60 g at 2 mm activation]
		Rafiei *et al.*, 2015 (54)	30 rats; male; 8–10 w	NiTi closed coil spring between the Mx left FM and central I [50 g]
Antidiabetic agents	Insulin	Arita *et al.*, 2016 (35)	30 Sprague-Dawley rats; male; 10 w; 350–390 g [20 of them made diabetic by streptozotocin; 60 mg/kg; IP]	Closed coil spring between Mx left FM and mini-screw implanted into the anterior palatal bone [10 g]
		Braga *et al.*, 2011 (37)	60 C57BL6/J mice; male; 10 w [35 made diabetic by streptozotocin; 120 mg/kg; IP]	NiTi coil spring between Mx right FM and Is [35 g]
	Metformin	Sun *et al.*, 2017 (59)	30 Wistar rats; male; 7 w; 200 g on average [20 diabetic: high-fat diet/4 w, then IP streptozotocin 35 mg/kg]	Coil spring between Mx right FM and Is [0.5 N]
Antihistamines	Cetirizine	Kriznar *et al.*, 2008 (46)	27 Wistar rats; male; 300–340 g	Superelastic closed coil spring between Mx FM and Is [25 cN]
		Meh *et al.*, 2011 (47)	32 Wistar rats; male; 13–14 w; 320–340 g	Superelastic closed coil spring between Mx left FM and Is [25 cN]
	Famotidine	Sprogar *et al.*, 2008 (58)	27 Wistar rats; male; 320–330 g	Super-elastic closed spring between Mx left FM and Is [25 cN]
Antihyperlipidemic agents	Atorvastatin	MirHashemi *et al.*, 2013 (49)	24 Sprague-Dawley rats; male; adults; 220 ± 20 g	NiTi closed coil spring between Mx left FM and central Is [60 g]
	Simvastatin	Esfahani *et al.*, 2013 (42)	32 rats; male; 8–10 w; 200–250 g	NiTi closed coil spring between Mx FM and central I [0.5 N]
Anxiolytics, sedatives and hypnotics	Diazepam	Burrow *et al.*, 1986 (38)	16 Mongel cats; 12–18 m	Closed coil between right Mx and Mdcanine and third premolar [80 g]
Beta-adrenergic blocking agents	Propranolol	de Oliveira *et al.*, 2014 (41)	15 Wistar rats; male; 3 m; 200–250 g	NiTi closed coil spring between Mx left FM and Is [0.49 N]
Minerals and electrolytes	Calcium carbonate	De Albuquerque Taddei *et al.*, 2014 (40)	15 C57BL6/J mice; male; 8 w	NiTi coil spring between Mx right FM and Is [0.35 N]
	Calcium gluconate	Seifi *et al.*, 2015 (55)	16 Wistar rats; male; 6–8 w; 230–300 g	NiTi closed coil spring between Mx right FM and I [60 g]
	Lithium carbonate	Da Silva Kagy *et al.*, 2016 (39)	128 Wistar rats; male; 9 w; 300–350 g	NiTi closed spring and SS tying wire between Mx right FM and I [30 cN]
	Lithium chloride	Wang *et al.*, 2014 (60)	10 Sprague-Dawley rats; male; 8 w; 200 ± 10 g	NiTi closed coil springs between the MxFM and I [50 g]
	Strontium ranelate	Kirschneck *et al.*, 2014 (45)	48 Wistar rats; male; 40 d (after acclimatization); 196 g in average	Closed coil spring between MxFM and Is [0.25 N]
	Zinc	Akhoundi *et al.*, 2016 (34)	44 Wistar rats; male; 200–250 g	NiTi closed coil springs between Mx left FM and Is [60 g]

Table 1. *Continued*

Therapeutic category	Active substance	Study	Subject characteristics [no; species; gender; age; weight]	Tooth movement model
Proton pump inhibitors	Pantoprazole	Shirazi *et al.*, 2014 (56)	72 Sprague-Dawley rats; male; 9 w; 200–250 g	NiTi closed coil springs between the Mx right FM and Is [60 g]
Thyroid hormones	L-Thyroxine	Baysal *et al.*, 2010 (36)	14 Wistar rats; male; 50–60 d; 132.53 ± 12.65 g	Closed coil spring between MxFM and Is [50g]
		Poumpros *et al.*, 1994 (53)	32 albino Sprague-Dawley rats; male; 42 d; 140 g	Spring between the right and left Mx Is with [50 g]
		Seifi *et al.*, 2015 (55)	16 Wistar rats; male; 6–8 w; 230–300 g	NiTi closed coil spring between Mx right FM and I [60 g]
		Shirazi *et al.*, 1999 (57)	40 albino Sprague-Dawley rats; male; 240–280 g	NiTi closed coil spring between Mx left FM and I [60 g]
Vitamins	Vitamin C	Miresmaeili *et al.*, 2015 (48)	36 Wistar rats; male; 36 w; 225 ± 32 g	Pre-activated open springs bonded on Mx Is [30 g opening force]

the administration of low doses of the beta-blocker propranolol (41), as well as for the ACE inhibitor losartan (51), and the histamine H_2-receptor antagonist famotidine after sustained force application (58). Furthermore, a decrease in the amount of movement was noted for high doses of the histamine H_1-receptor antagonist cetirizine only immediately after force application, whereas lower doses had similar effect after the third week into the experiment (46, 47). Finally, the antidiabetic agent metformin was shown to result in a decrease and subsequent normalization in the high rate of orthodontic tooth movement observed in the control diabetic subjects (59).

No interference with the rate of orthodontic tooth movement was shown by the anticonvulsants phenytoin and phenobarbital (44, 52). The same was also noted for zinc compounds (34).

Finally, inconsistent or conflicting effects regarding the rate of orthodontic tooth movement were noted after the administration of L-thyroxine (36, 53, 55, 57), lithium compounds (39, 60) and the antidepressant fluoxetine (43, 50, 54). The administration of insulin also showed conflicting results; however, regardless of these results, the rate of orthodontic tooth movement was normalized and became comparable to normoglycemic subjects (35, 37).

Risk of bias across studies and additional analyses

It was not possible to conduct analyses for 'small-study effects', publication bias or subgroup analyses. Overall, regarding the effect of the investigated medication on the rate of orthodontic tooth movement the quality of available evidence was considered at best as low (Supplementary Table 5).

Discussion

Summary of evidence

Overall, based on the information provided from the animal studies eligible for inclusion in the present review following well-established guidelines, commonly prescribed medications may exhibit variable effects on the rate of orthodontic tooth movement. Although the quality of evidence was considered at best as low, providing a cautionary perspective on the strength of the relevant recommendations, the clinician should be capable of identifying the patients taking medications and should take into consideration the possible implications related to the proposed treatment.

The small number of medications investigated reflects the scarcity of relevant research. The consequent lack of extensive data for the most commonly prescribed pharmaceutical categories is rather surprising, bearing in mind the fact that prescription and over-the-counter medication use has recently expanded significantly, not only in adults, but also in school aged children (5, 6, 7, 13, 14). As any medication taken may present possible effects on the signalling pathways related to orthodontic tooth movement (2, 3), it is considered important for the clinician to be able to identify prospective patients' medicinal consumption, not only to elaborate on prognosis, treatment planning and biomechanics, but also to avoid risks and complications (4). Thus, relevant, evidence-based information would be beneficial in supporting the care provided in these cases.

The rate of orthodontic tooth movement was shown to increase after the administration of diazepam (38) and Vitamin C (48). Although an explanation for the accelerating effect of diazepam could not be established, either based on the increasing effect on cAMP or its muscle relaxant properties from this publication, the anticholinergic effects of the substance relating to xerostomia and the concomitant risk of decalcification need to be taken into consideration

Table 2. Summary of risk of bias assessment.

Study	Signalling questions										
	1	2	3	4	5	6	7	8	9	10	Summary
Akhoundi *et al*., 2016 (34)	Unclear	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Arita *et al*., 2016 (35)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	low	Unclear	Unclear
Baysal *et al*., 2010 (36)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Braga *et al*., 2011 (37)	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Burrow *et al*., 1986 (38)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	low	Unclear	Unclear
Da Silva Kagy *et al*., 2016 (39)	Unclear	Low	Unclear	High	High	Unclear	Low	Unclear	Low	Unclear	Unclear
De Albuquerque Taddei *et al*., 2014 (40)	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
de Oliveira *et al*., 2014 (41)	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low
Esfahani *et al*., 2013 (42)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Franzon Frigotto *et al*., 2015 (43)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Karsten and Hellsing, 1997 (44)	High	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	High
Kirschneck *et al*., 2014 (45)	Unclear	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
Kriznar *et al*., 2008 (46)	High	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	High
Meh *et al*., 2011 (47)	High	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Miresmaeili *et al*., 2015 (48)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
MirHashemi *et al*., 2013 (49)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Mirhashemi *et al*., 2015 (50)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Moura *et al*., 2016 (51)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Pithon and Ruellas, 2008 (52)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Poumpros *et al*., 1994 (53)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Rafiei *et al*., 2015 (54)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Seifi *et al*., 2015 (55)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Shirazi *et al*., 1999 (57)	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Shirazi *et al*., 2014 (56)	High	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	High
Sprogar *et al*., 2008 (58)	High	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	High
Sun *et al*., 2017 (59)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
Wang *et al*., 2014 (60)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear

1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation adequately concealed?; 4: Were the animals randomly housed during the experiment?; 5: Were the caregivers and investigators blinded to the intervention that each animal received?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study apparently free of other problems that could result in high risk of bias?

(61, 62). Although Vitamin C is essential for bone formation, during resorption ascorbic acid firstly stimulates osteoclast formation, but subsequently limits osteoclast lifespan (63), thus, resulting in the overall bone preservative effect observed *in vivo* (64). The absence of dietary ascorbic acid results in impairment of collagen synthesis and scurvy, increased risk of periodontitis, as well as almost complete cessation of osteogenesis and disorganization of the periodontal ligament (65–67). Rapid orthodontic tooth movement relapse has also been observed in ascorbic acid deficient guinea pigs (68).

Moreover, orthodontic tooth movement rate was found to be greater after 6 or more weeks administration of the proton pump inhibitor pantoprazole (56). Proton pump inhibitors are mainly used for reduction of gastric acid secretion and have been associated with osteoporosis (69). However, conclusive confirmation regarding the pathogenetic mechanisms are still lacking, as studies on the effects of the increase of gastric pH on calcium absorption are conflicting and investigations on bone metabolism cannot currently give plausible explanations for the associated biochemical mechanisms (70–74).

Contrary to the effects of the abovementioned substances, the rate of orthodontic tooth movement was decreased after the administration of statins (42, 49), as well as minerals, such as various calcium compounds (40, 55) and strontium ranelate (45).

Initial evidence from animal investigations suggested that statins increase the rate of bone formation (75, 76). Later studies have shown that they may exert a more anabolic effect than catabolic effect in usual doses, while in lower dosages the opposite might be observed (77–81). In addition, it has been suggested that hydrophilic statins, like atorvastatin, may not influence bone turnover as much lipophilic statins like simvastatin (82–88).

Calcium levels may be related to the recruitment of osteoclasts, their differentiation and activation, their functioning and, thus, bone remodelling. De Albuquerque Taddei *et al.* (40) showed that dietary calcium supplements reduce the number of osteoclasts and decrease alveolar bone resorption. Strontium ranelate has also been shown to alter bone metabolism by attaching to the calcium-sensitive receptors in osteoblasts and osteoclasts (89), and subsequently decreasing the differentiation, proliferation and the activity of osteoclasts, thus reducing bone resorption (90, 91). At the same time, strontium ranelate enhances bone formation by instigating preosteoblast replication (91, 92).

A decrease in the rate of orthodontic tooth movement was also observed after the administration of medications used to treat conditions of the cardiovascular system, such as low doses of the beta-blocker propranolol (41) and the ACE inhibitor losartan (51). Low doses of propranolol have been previously shown to diminish bone resorption by inhibiting RANKL-mediated osteoclast differentiation and resorptive activity, together with cytokine expression (93, 94). Evidence from animal studies has suggested that excessive activation of the renin-angiotensin system upregulates bone resorption by the osteoclasts and induces osteoporosis (95, 96), whereas in clinical studies on the effects of ACE inhibitors, increases in bone density

and reductions in the risk of fractures were observed (97, 98). In the context of orthodontic tooth movement, mRNA levels of various markers of osteoclastic activity were reduced by losartan administration (51). At the same time, the expression of substances characteristic of osteoblastic function, as well as down regulators of bone resorption increased (51).

Histamine receptor antagonists were also shown to diminish the rate of orthodontic tooth movement. A decrease in the amount of movement was noted for high doses of the antihistamine cetirizine, but only immediately after force application, whereas lower doses had similar effect only after the third week of observation (46, 47). The administration of the H_2-receptor antagonist famotidine (58) also influenced the rate of tooth movement after the fifth week of the experiment. It has been shown that excessive histamine levels stimulate bone resorptive processes and that in conditions involving the continuous release of histamine, like systemic mastocytosis, osteoporosis is frequently observed (99, 100). Moreover, studies in ovariectomized animals have shown that the administration of both H_1 and H_2-receptor antagonists is associated with a decrease in the activity of osteoclasts (101, 102).

A decrease in the amount of tooth movement was also noted was the antidiabetic agent metformin (59). Diabetes mellitus has been shown to negatively affect bone remodelling (103). Metformin has been reported to upregulate osteoprotegerin and RANKL in osteoblasts, decrease osteoclastogenesis and act protectively against bone loss in rats subjected to ovariectomy (104, 105). Furthermore, stimulation of osteoblastic differentiation has been noted (106). The observed normalization of the rate of orthodontic tooth movement by metformin was attributed to actions involving the RANK/RANKL and kinase signalling pathways (59).

No interference with the rate of orthodontic tooth movement was observable after the administration of anticonvulsants, such as phenytoin for 6 weeks (44) and phenobarbital for 2 weeks (52). However, there is a growing body of evidence that the chronic use of anticonvulsant medication is associated with an increased risk of osteoporosis (107). Although osteoporosis might result in an increase in the rate of orthodontic tooth movement, it has been also suggested that the gingival enlargement observed after prolonged phenytoin use might lead to the physical obstruction of space closure (62). The gingival enlargement has been attributed to fibroblast proliferation or the creation of a localized folate deficiency possibly causing a decrease in active collagenase (44, 62). No difference between treated and control groups was also noted for the zinc compounds (34). However, it has been observed that Zn may alter bone metabolism by stimulating the activity of osteoblasts and decreasing bone resorption by the osteoclasts, in addition to preventing osteoporosis in animal models (108–110). In addition, it has been suggested that the bone effects of zinc are dependent on the duration of its administration, raising the possibility that the effects normalize over time (111). It has also been observed that zinc supplementation may be effective only where there is a pre-existing deficiency (112).

Although thyroid hormones are essential for normal bone maturation and resorption (15), an unequivocal effect on orthodontic tooth movement could not be established (36, 53, 55, 57). The same applies to lithium compounds administration regarding the orthodontic tooth movement model (39, 60), in accordance with conflicting observations in animals and humans (113–117). Similarly, varying results on the rate of orthodontic tooth movement were observed after the administration of fluoxetine, a selective serotonin re-uptake inhibitor (43, 50, 54). Several components of the serotonergic system, such as 5-HT receptors and 5-HTT transporters, are expressed in osteoclasts and osteoblasts (118, 119) and fluoxetine has been shown to have an anti-inflammatory effect (54). As far as insulin is concerned, despite the conflicting observations of either increase or decrease in the rate of orthodontic tooth movement in comparison to the diabetic animals, both retrieved studies showed a normalization in the values of the normoglycemic groups (35, 37).

Overall, the quality of evidence included in the retrieved studies, based on the GRADE approach (33), was considered at best as low. However, even from this set of animal data, clinicians might get an insight into the relevant clinical considerations related to treatment in patients taking prescription or over-the-counter medications. It is possible that the estimation of the duration of treatment should be modified when a patient is taking medication possibly increasing or decreasing the rate of tooth movement. In terms of mechanotherapy, it must be considered that patients receiving systemic medication that increases tooth movement may present increased needs for anchorage preparation, while patients where movement is pharmacologically hindered might exhibit difficulty in closing pre-existing or post-extraction spaces. Furthermore, appointments might need to be more frequent for patients in the first category in order to check and control the progress of the treatment. On the other hand, it is also possible that there would not be any benefit in having shorter time intervals between the appointments where the patient is receiving medication that may decelerate the tooth movement.

Strengths and limitations

Despite the fact that during the last years, the possible influence of different pharmaceutical substances on the events leading to orthodontic tooth movement have been reviewed, most publications have not focused specifically on the general effect on the rate of orthodontic tooth movement, or have followed a classic review approach (15–19, 21, 120, 121). The strengths of the present review include the use of a methodology following well-established guidelines. The search strategy employed was exhaustive, covering electronic, manual, and grey literature material up to June 2017, and comprehensive including every available study, irrespective of language, date and status of publication. Every effort was made to reduce to the extent possible bias in the methodology employed. Screening, verification of eligibility, abstraction of information, assessment of risk of bias and the quality of evidence were performed in duplicate, and any disagreement was resolved by discussion or consultation with the third co-author until a final consensus was achieved.

There are also some limitations to the present review, arising mainly from the nature and the characteristics of the included studies per se and the data retrieved during the review process, which resulted in an assessment of the level of available evidence being, at best, low. The scarcity of relevant evidence based information precluded meta-analytic procedures and the conduct of additional analyses, although these were included in the respective protocol. Most studies were considered to be of unclear or high risk of bias because of methodological characteristics. Moreover, in most of the retrieved studies there was insufficient data on blinding and reliability of the measurement methods of tooth movement employed, leading to relevant ratings during risk of bias assessment. This relative uncertainty was compounded by inconsistent or conflicting effects in the rate of orthodontic tooth movement being observed after the administration of some substances like L-thyroxine, lithium compounds, fluoxetine and insulin. The effect of L-thyroxine administration on root resorption was also conflicting.

Furthermore, it has to be acknowledged that the data retrieved in the present systematic review relate to animal studies and cannot

be directly extrapolated to humans. In addition, the results were derived after the administration of substances for short periods of time and not extended periods as it might be usual with prescribed medications. This was further complicated by the fact that the substances were administrated in dosages usually different from those used in routine human clinical settings (26) and by routes of administration with possibly different effects on pharmacokinetics and bio-availability (122). Additionally, the investigation of specific biomechanical systems of induced orthodontic tooth movement further curtailed generalizing the retrieved information to human clinical scenarios. Moreover, the assessed investigations, with the exception of the studies on diabetic subjects, involved the administration of various substances in otherwise healthy animals. In the reality of the normal clinical situation, patient's overall health status may relate to the complex pathways responsible for periodontal tissue homeostasis and orthodontic tooth movement (2, 3). In addition to the scarcity of relevant research, most included studies did not include power sample calculations, posing another limitation relating to the precision of the retrieved results. Thus, it remains, to a degree, unclear which type of medication may have a clinically significant effect in the outcomes investigated in everyday clinical scenarios.

Recommendations for future research

Since both prescription and over-the-counter medication use have recently expanded significantly among all age groups, further well-designed experimental studies and, if possible, clinical studies on the effects of different substances on orthodontic tooth movement could be useful. It is highly desirable that study designs become standardized (123) and possible sources of risk of bias receive the appropriate attention (28). Parameters like the period, the dosage and the route of administration, as well as the characteristics of the employed biomechanical systems, should be carefully selected so as to simulate, as closely as is feasible, scenarios in clinical practice in humans.

Conclusions

Commonly prescribed medications may exhibit variable effects on the rate of orthodontic tooth movement. Although the quality of evidence was considered at best as low, providing a qualification to the strength of the relevant recommendations, clinicians should be capable of identifying the patients taking medications and should take into consideration the possible implications related to the proposed treatment.

Supplementary material

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Conflict of Interest

None to declare.

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