

# Effectiveness of biologic methods of inhibiting orthodontic tooth movement in animal studies

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**Introduction:** A number of biologic methods leading to decreased rates of orthodontic tooth movement (OTM) can be found in the recent literature. The aim of this systematic review was to provide an overview of biologic methods and their effects on OTM inhibition. **Methods:** An electronic search was performed up to January 2016. Two researchers independently selected the studies (kappa index, 0.8) using the selection criteria established in the PRISMA statement. The methodologic quality of the articles was assessed objectively according to the Methodological Index for Non-Randomized Studies scale. **Results:** We retrieved 861 articles in the initial electronic search, and 57 were finally analyzed. Three biologic techniques were identified as reducing the rate of OTM: chemical methods, low-level laser therapy, and gene therapy. When the experimental objective was to slow down OTM, pharmacologic modulation was the most frequently described method (53 articles). Rats were the most frequent model (38 of 57 articles), followed by mice (9 of 57), rabbits (4 of 57), guinea pigs (2 of 57), dogs (2 of 57), cats (1 of 57), and monkeys (1 of 57). The sample sizes seldom exceeded 25 subjects per group (6 of 57 articles). The application protocols, quality, and effectiveness of the different biologic methods in reducing OTM varied widely. **Conclusions:** OTM inhibition was experimentally tested with various biologic methods that were notably effective at bench scale, although their clinical applicability to humans was rarely tested further. Rigorous randomized clinical trials are therefore needed to allow the orthodontist to improve the effect of translating them from bench to clinic. (Am J Orthod Dentofacial Orthop 2016;150:33-48)

**A**bsolute control over tooth movement is a key factor in orthodontics.<sup>1-7</sup> One main remaining limitation of past and current orthodontic treatments is the inability to completely prevent the unexpected movement of certain teeth; this is frequently defined as loss of anchorage during treatment or relapse during the retention phase.<sup>7</sup> At present, auxiliary devices such as temporary anchorage devices are used to provide additional biomechanical resistance and help prevent undesirable tooth

movement. Similarly, in recent decades, a number of biologic methods have emerged that can decrease the rate of orthodontic tooth movement (OTM) or even inhibit it completely<sup>4-7</sup> by interfering with osteoclast cell activity during the bone remodeling on which OTM depends.<sup>2-4</sup>

In this respect, chemical methods, including hormones, drugs, and various synthetic molecules, have been used from the earliest to the most recent studies on OTM. Bisphosphonates<sup>3,4</sup> (inhibitors of bone resorption) and prostaglandin inhibitors, such as ibuprofen<sup>2</sup> and acetylsalicylic acid,<sup>1</sup> have been widely studied because of their activity in slowing OTM. Apart from the administration of specific drugs, other methods proposed in the literature to reduce the rate of OTM include processes that modify the biologic substrate, such as low-level laser therapy<sup>5,6</sup> or gene therapy.<sup>7</sup> The doses, protocols, and hypotheses are as varied as the studies themselves; this makes it difficult for the clinician to establish useful comparisons between studies and their relevance, if any, to the clinical field.

The purposes of this review were (1) to compile, analyze, and summarize the data available in the literature regarding experimental studies in animals that used biologic methods against a control group that resulted in a decreased rate of OTM or its inhibition;

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(2) to compare the different methods and their outcomes; and (3) to give the clinician a clear overview of the scientific evidence available in the literature with a quality analysis of the methodologies used in the articles reviewed, thus facilitating research for professionals with an interest in this area. The main specific questions asked in this review were the following: Which experimental biologic methods have a decreasing or inhibitory effect on OTM? How efficient are these methods?

## MATERIAL AND METHODS

### Protocol

The structure of the review protocol was developed before the start of the study, and the reporting of findings followed the PRISMA guidelines ([www.prisma-statement.org](http://www.prisma-statement.org)). Because the experimental studies on which this systematic review was based were on animals, our protocol could not be registered in the PROSPERO database.

### Information resources

A search was made of the MedLine (Entrez PubMed, [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), SCOPUS ([www.scopus.com](http://www.scopus.com)), and Web of Science ([www.isiknowledge.com](http://www.isiknowledge.com)) databases to find possible studies matching our established selection criteria, including all articles published up to January 21, 2016. We searched for gray literature by exploring the OpenGrey database, European Association for Grey Literature Exploitation, also up to January 21, 2016, without applying language restrictions.

### Search strategy

Our search strategy used the medical subject heading term “tooth movement” crossed with “inhibition,” “inhibit,” or “decrease” and excluded the terms “relapse” or “increase” or “enhance” or “promotion.” [Supplementary Table 1](#) summarizes the full search strategy, including animal search filters, in all databases used.<sup>8</sup> Some main orthodontic journals not indexed in the Journal Citation Report index were also hand searched to identify potential studies not found in the electronic search ([Supplementary Table 1](#)).

### Eligibility

Articles selected for this study fulfilled the following criteria for inclusion, according to the PICOS format.

1. Population: animals; any experimental study or clinical investigation that included at least 1 experimental group with a minimum of 5 animals or samples per group.

2. Intervention: biologic methods of decreasing or inhibiting tooth movement using orthodontic or orthopedic devices to apply forces.
3. Comparison: control group without a biologic method.
4. Outcome: rate of OTM deceleration or inhibition.
5. Study design: experimental controlled trials.

Excluded from the selection were case reports, case series, descriptive studies, review articles, opinion articles, letters, and articles that did not correspond to the objectives of this review or did not have an adequate description of the technique or the administration dose.

### Study selection

Eligibility was assessed by 2 observers (M.C-P. and R.M.Y-V.) acting independently. Articles were initially selected on the basis of the title and abstract, with the complete article reviewed whenever there was doubt about whether it should be included. Disagreements were resolved by consensus or by a third experienced reviewer who was requested to arbitrate (A.I-L.). After the 2 reviewers had separately applied the inclusion and exclusion criteria to each article, concordance between them was measured using the kappa index.

### Data collection and analysis

Data were extracted by 1 observer (M.C-P.). A data extraction sheet was developed and piloted. Conflicts during data collection were resolved by discussion with a second (R.M.Y-V.) or a third experienced observer (A.I-L.). Data were extracted for the following items: author and year, study design, sample (size, species, age, and sex), a brief description of the methods, applied force, total treatment or experimentation time, decrease in the rate of OTM, and clinical applicability.

### Methodologic quality and risk of bias of individual studies

The methodologic quality of the selected articles was assessed using the Methodological Index for Non-Randomized Studies (MINORS).<sup>9</sup> The 12 variables analyzed were clearly stated: aim, inclusion of consecutive patients, prospective collection of data, end points appropriate to the aim of the study, unbiased assessment of the study end point, follow-up period appropriate to the aim of the study, loss to follow-up less than 5%, prospective calculation of the study size, adequate control group, contemporary groups, baseline equivalence of the groups, and adequate statistical analysis. After this analysis, every item scored 0 when not reported, 1 when it was reported but inadequate, and 2 when it

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