DOI: 10.4274/TurkJOrthod.2023.2022.149

TURKISH JOURNAL OF
ORTHODONTICS

Systematic Review

Effect of Lithium on Orthodontic Tooth Movement: a Systematic Review of Animal Studies

Amit Wadke[1], Karthik Kommuri[2], Sandeep Talluri[1], Mythili Kalladka[1], Goutham Kalladka[3], Junad Khan[1]

[1]Orofacial Pain and TMJ Disorders, Eastman Institute for Oral Health, University of Rochester, NY, USA
[2]Orthodontics and Craniofacial Orthopedics, Eastman Institute for Oral Health, University of Rochester, NY, USA
[3]Dayananda Sagar College of Dental Sciences, Department of Orthodontics, Karnataka, India

Cite this article as: Wadke A, Kommuri K, Talluri S, Kalladka M, Kalladka G, Khan J. The Effect of Lithium on Orthodontic Tooth Movement: a Systematic Review of Animal Studies. *Turk J Orthod.* 2024; 37(1): 63-71

Main Points

- Lithium can decrease the rate of orthodontic tooth movement.
- Lithium may increase bone density and volume and reduce root resorption.
- Lithium enhances alveolar bone formation during orthodontic retention phase.

ABSTRACT

Objective: This study aimed to systematically review the effect of lithium on orthodontic tooth movement (OTM).

Methods: The focus question was "does lithium have an effect on OTM?" A systematic search was conducted using indexed databases and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. The quality assessment of the selected studies was performed according to the systematic review center for laboratory animal experimentation.

Results: Five of the initially identified 656 articles fulfilled the eligibility criteria and were selected for this review. The studies reported that lithium administration lowered the rate of OTM by inducing a reduction in the number of osteoclasts and possibly inhibiting osteoclastogenesis. These studies further showed an increase in bone density and bone volume by promoting the Wnt/ß-catenin signaling pathway and osteoblastogenesis. It was also noted that lithium reduced orthodontically induced root resorption during experimental OTM. Further, standardized studies are warranted to understand the impact of lithium in OTM. Overall, the risk of bias for 3 studies was very high, high in 1 study, and moderate in 1 study.

Conclusion: On an experimental level in animals, lithium decreased the rate of OTM during the active treatment phase by increasing bone density and bone volume and reducing root resorption. In addition, lithium may enhance alveolar bone formation during orthodontic retention. Clinically, this may impact the orthodontic treatment duration in patients receiving lithium, and further studies are needed to understand the true impact of lithium on OTM.

Keywords: Lithium, orthodontic tooth movement, systematic review

INTRODUCTION

Orthodontic tooth movement (OTM) is a complex process involving the application of mechanical force followed by a biological response as well as genetic and environmental interactions. OTM encompasses the dynamic process of alveolar bone remodeling in response to controlled orthodontic forces through bone deposition and bone resorption on the tension and pressure sides, respectively. The tooth displacement following OTM varies according to the magnitude, frequency, and duration of the applied force and the biological response of the

Corresponding author: Amit Wadke, **e-mail:** Amit_Wadke@urmc.rochester.edu
Received: September 30, 2022 **Accepted:** March 15, 2023 **Publication Date:** March 28, 2024

periodontal ligament and bone.[1,2] The carefully orchestrated biological responses, such as osteoblastogenesis and osteoclastogenesis, in response to controlled orthodontic forces may also be affected by a plethora of genetic, environmental, local, and systemic factors, including medications.[3,4]

The majority of mental illnesses are diagnosed in adolescences, young adults or adults <50 years.[5] The symptoms of several disorders may fluctuate over time, and management may be lifelong.[5] Bipolar disorders (BDs) are one of the most common mental illnesses affecting adolescents and adults. According to the World Health Organization, approximately 40 million people globally suffer from BD. The prevalence in Turkey was 0.84% during 2006-2019. However, the population has also increased from 69 million to approximately 83 million in the same period as that reported by the World Bank. Lithium is one of the oldest and first-line medications used for the management of BD and is often considered a gold standard in the management of BD. Lithium salts have been used since the early 19th century for the management of manic episodes of BD.[6,7] Lithium salts have also been used in the management of a variety of psychiatric conditions, including obsessive compulsive disorders, hyperactivity disorders in adolescents, attention deficit disorders in children, and unipolar depression in adults. Lithium salts are occasionally used in the management of refractory cases of schizophrenia, certain impulse control disorders, and prophylaxis of certain trigeminal autonomic cephalalgias.[6,8-12] Vestergaard et al.[13] reported that the risk of fracture in Colles and spines among children were lower following lithium consumption. Studies have shown that lithium can increase bone density and bone volume by promoting the Wnt/ß-catenin signaling pathway in mice. The Wnt/ß-catenin signaling pathway not only promotes the production of osteoblasts and osteoblastogenesis but also inhibits the production of osteoclasts and osteoclastogenesis processes, effectively reducing bone resorption.[14] Studies dwelling into the role of lithium in OTM have varied results. Some studies have suggested that lithium may reduce orthodontically induced root resorption[3,15] while others reported it may promote alveolar bone formation.[16] Chronic use of lithium has also been suggested to lower rate of tooth movement.[17,18] Hashimoto et al.[14] reported a negative correlation between bone morphometric measurements and OTM, particularly trabecular bone structure in rats that had undergone ovariectomy procedures.

Because lithium is administered on a long-term basis and significant portion of the population opts for orthodontic treatment in various age groups, the aim of the present systematic review was to assess the influence of lithium on OTM. Due to a lack of clinical studies, pre-clinical animal studies were evaluated with the anticipation of future translation studies.

METHODS

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19]

A meta-analysis was not performed because of the high heterogeneity of the included studies.

Questions

The addressed focused question was "does lithium affect orthodontic tooth movement?"

Patients, Interventions, Control, Outcome (PICO)

Population (P): subjects who underwent orthodontic treatment; Interventions (I): effect of lithium therapy on OTM; Control (C): orthodontic treatment without adjunct lithium administration; and Outcome (O): tooth movement.

Study Eligibility

The eligibility criteria were based on PICO, and controlled studies involving animals and human subjects undergoing active OTM were reviewed. Non-comparative studies (letters to the editor, commentaries, historic reviews, case reports and case series), systematic reviews, and meta-analyses were excluded from this review.

Search Protocol and Study Selection

An electronic search was performed based on the "Preferred Reporting Items for Systematic Review and Meta-Analysis" (PRISMA) guidelines by two authors (AW and KK). A search without time or language restrictions was conducted up to June 2021 in PubMed (National Library of Medicine), Cochrane Library, EMBASE, MEDLINE (OVID), Scopus, Google Scholar, and Web of Science databases. The search was performed using a combination of the following MeSH terms with Boolean operators (AND, OR): 1) orthodontic therapy; 2) orthodontic treatment; 3) OTM; 4) tooth movement techniques; 5) orthodontics; 6) orthodontic brackets; 7) orthodontic appliances; 8) lithium; 9) lithium salts. Two authors (AW and KK) electronically assessed the retrieved records for eligibility independently. The authors were not blinded to the identity of the authors, their institution, or the results of the research. Subsequently, the full report of records considered by each reviewer to meet the eligibility criteria was obtained and assessed a second time independently, with any disagreements resolved by consultation with the sixth author (JK) (Table 1).

Risk of Bias (ROB) Assessment

The systematic review center for laboratory animal experimentation[20] was used to assess ROB in the included studies by author ST. A total of nine questions were used to assess ROB, and based on the results, the overall ROB was evaluated as low, moderate, high, and very high. The following questions were addressed: 1) sequence generation, 2) baseline characteristics, 3) allocation concealment, 4) random housing,

Table 1. Search criteria

	Keywords	MeSH
Lithium	Lithium, Lithium Salts, Lithium compounds, Lithium Chloride, Lithium Carbonate, Lithium acetate, Lithium Sulfate, Lithium Citrate, Lithium Orotate, Lithium Gluconate, Lithium bromide, Lithium Chloride, Lithium iodide, Lithium Fluoride	Lithium (MeSH Term)
Orthodontic tooth movement	Orthodontic, orthodontics, Orthodontic tooth movement, tooth movement, tooth movement technique, orthodontic appliances	Tooth movement technique (MeSH Term)

((“lithium”[MeSH Terms] OR “lithium”[All Fields]) OR ((“lithium”[MeSH Terms] OR “lithium”[All Fields]) AND (“sodium chloride”[MeSH Terms] OR (“sodium”[All Fields] AND “chloride”[All Fields]) OR “sodium chloride”[All Fields] OR “salt”[All Fields])) OR (“lithium compounds”[MeSH Terms] OR (“lithium”[All Fields] AND “compounds”[All Fields]) OR “lithium compounds”[All Fields] OR (“lithium”[All Fields] AND “compound”[All Fields]) OR “lithium compound”[All Fields])) AND ((“tooth movement techniques”[MeSH Terms] OR (“tooth”[All Fields] AND “movement”[All Fields] AND “techniques”[All Fields]) OR “tooth movement techniques”[All Fields] OR (“orthodontic”[All Fields] AND “tooth”[All Fields] AND “movement”[All Fields]) OR “orthodontic tooth movement”[All Fields]) OR (“tooth movement techniques”[MeSH Terms] OR (“tooth”[All Fields] AND “movement”[All Fields] AND “techniques”[All Fields]) OR “tooth movement techniques”[All Fields] OR (“tooth”[All Fields] AND “movement”[All Fields] AND “technique”[All Fields]) OR “tooth movement technique”[All Fields]) OR Orthodontic[All Fields])

5) blinding, 6) random outcome assessment, 7) incomplete data outcome, 8) selective outcome reporting, and 9) other sources of bias.

RESULTS

Study Selection

The initial search identified 656 potential manuscripts. Thirty manuscripts were duplicates, and 621 articles did not address the focused question and/or eligibility criteria. Five animal studies that fulfilled the eligibility criteria were included in this systematic review and processed for data extraction.[3,15-18] (Figure 1).

General Characteristics of the Included Studies

All the included studies[3,15-18] in this review were conducted in rodents. No clinical studies were available at the time of the search. The included studies had an experimental study design. The mean age of the rodents ranged from 7 to10 weeks, and the weight of the rodents ranged from 194 to 350 g. The study duration for the included studies ranged from 14 to 51 days. Three studies included male rats and two studies included female rats (Table 2).

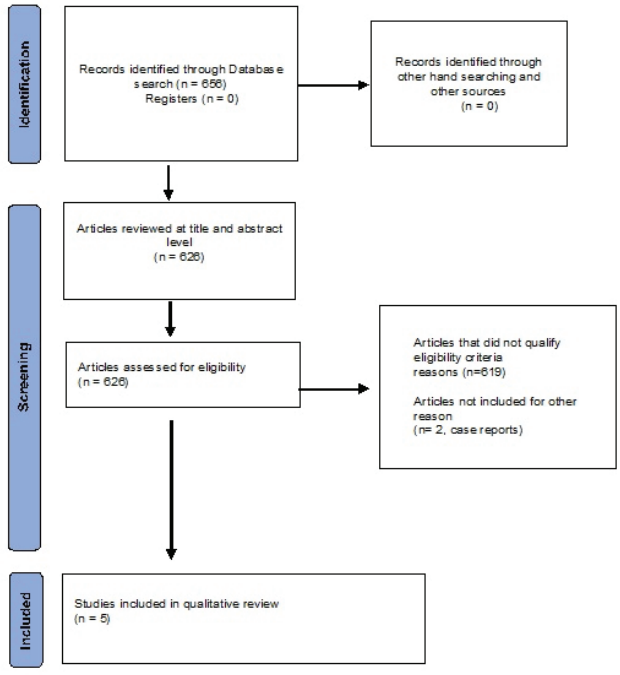

Figure 1. PRISMA flow chart
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

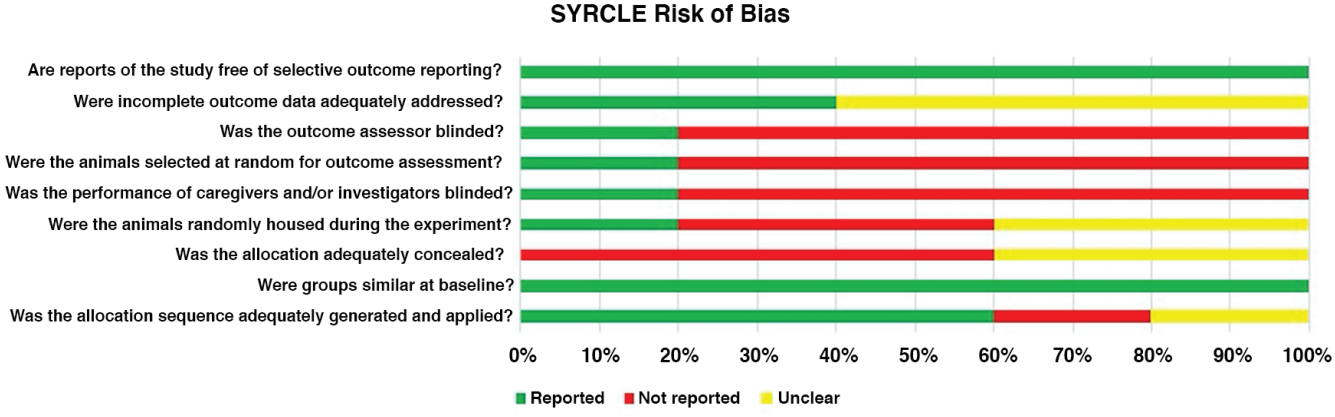

Figure 2. Risk of bias in included studies

Table 2. General characteristics of the included studies

Author	Country of study	Publication year	Number of animals	Sex	Rodent type	Mean age (weeks)	Weight (g=grams)	Groups	Study duration
Ino-Kondo et al.[15]	Japan	2018	32	Female	Sprague-Dawley rats	10	194-234 g	(4 groups, n=8 rats/group) Group 1=Saline only (Control Group) Group 2=0.32 mM/kg of LiCl (Exp Group) Group 3=0.64 mM/kg of LiCl (Exp Group) Group 4=1.28 mM/kg of LiCl (Exp Group)	14 days
Pan et al.[16]	China	2017	42	Male	Wistar Rats	8	200+10 g	OTM induced 14 days and divided equally into 2 groups, Group 1=LiCl, n=18 Group 2=Saline, n=18 Rats were randomly sacrificed post OTM on days 3, 7, and 14 (n=6/group) Initial control (n=6)	14 days of OTM followed by days 0, 3, 7, and 14 of the retention phase
da Silva Kagy et al.[17]	Brazil	2016	192	Male	Wistar Rats	9	300-350 g	(3 groups, n=64 rats/group) L group received 60 mg/kg LC in saline solution, resulting in serum lithium levels of 1.30 +/- 0.55 mmol/L at 90 min after administration The LM group received prior daily administration of LC for 30 days and then subdivided into groups that subsequently received additional LC for 3, 7, 14, or 21 days. All groups had serum lithium levels of 1.34 +/- 0.53 mmol/L SM=Saline group	16 rats from each group were euthanized on days 33, 37, 44, and 51 to measure OTM
Wang et al.[3]	China	2013	10	Male	Sprague-Dawley rats	8	200+10 g	2 groups, n=5 rats/group Group 1=lithium chloride Group 2=Control group (NR)	14 days
Huang et al.[18]	China	2021	42	Female	C57BL/6 mice	7	NR	2 groups Group 1=Sham, n=15 Group 2=Ovariectomy, n=27. In this group, 12 of 27 mice received LiCl only.	14 days

OTM, orthodontic tooth movement; LiCl, lithium chloride; LC, lithium carbonate; Exp Group, experimental group; NR, not reported; g, grams; n, number of animals.

Characteristics of studies involving lithium

Four studies[3,15,16,18] used lithium chloride (LiCl) versus one study that used lithium carbonate (LC).[17] Two studies[3,17] administered lithium intraperitoneally, whereas three studies[3,16,18] used gavages. Ino-Kondo et al.[15] administered LiCl at 0, 0.32, 0.64, and 1.28 mM/kg of body weight, which was dissolved in saline and administered daily. In the study by Pan et al.,[16] the animals received 200 mg/kg, whereas the study by da Silva Kagy et al.[17] administered LC at the rate of 60 mg/kg in 3 groups: L group (that resulted in lithium serum levels of 1.30 +/- 0.55 mmol/L), LM group (that resulted in lithium serum levels of 1.34 +/- 0.53 mmol/L), and SM (saline group, no changes). In addition, the LM group received the drug subsequently at 3, 7, 14, and 21 days, corresponding to the induced tooth movement. Wang et al.[3] administered 200 mg/kg of LiCl, whereas Huang et al.[18] administered 200 mg/kg daily for 14 days (Table 3).

Characteristics of Orthodontic Force Application and Tooth Displacement

Four studies[3,15-17] mentioned closed-coil springs in their experiments with Ino-Kondo et al.[15], using 10 cN; Pan et al.,[16] Wang et al.,[3] using 50 g; da Silva Kagy et al.,[17] using 30 cN of force; and Huang et al.,[18] using 10g of force to induce OTM with a customized closed coil spring. The duration of OTM ranged from 14 to 51 days. Ino-Kondo et al.[15] reported that the higher the dose of LiCl administered, the lower was the OTM,

Table 3. Characteristics of studies involving lithium

Authors	Lithium salt	Dilution medium	Dosage	Delivery method and duration of administration	Frequency of administration
Ino-Kondo et al.[15]	Lithium chloride	Saline	4 groups with 4 independent doses Group 1=Saline only Group 2=0.32 of LiCl mM/kg of body weight. Group 3=0.64 of LiCl mM/kg of body weight. Group 2=1.28 of LiCl mM/kg of body weight.	Intraperitoneal (immediate)	Daily
Pan et al.[16]	Lithium chloride	NR	Group 1=200 mg/kg of LiCl Group 2=200 mg/kg of saline	Gavage (immediate)	Daily
da Silva Kagy et al.[17]	Lithium carbonate	Saline	Group 1=L group, 60 mg/kg of LC Group 2=LM group, 60 mg/kg of LC Group 3=Saline group, 60 mg/kg of LC	Intraperitoneal (immediate)	Daily
Wang et al.[3]	Lithium chloride	NR	Group 1=200 mg/kg of LiCl (Exp group) Group 2=Control (No treatment)	Gavage (immediate)	Every 48 h
Huang et al.[18]	Lithium chloride	Double-distilled H_2O	Group 1=200 mg/kg of LiCl (Exp group) Group 2=Control (Sham)	Gavage (immediate)	Daily

LiCl, lithium chloride; LC, lithium carbonate.

Table 4. Characteristics of orthodontic force application and tooth displacement

Authors	Orthodontic appliance and material	Site of the OTM	Duration of the OTM	Force	Tooth displacement evaluation	Magnitude of OTM in the control groups	Magnitude of OTM in the experimental (lithium) group
Ino-Kondo et al.[15]	Nickel-Titanium closed-coil spring	Distal surface of the maxillary left first molar and mesial surface of the maxillary left second molar	14 days	10 cN	1. Measure OTM between maxillary 1st and 2nd molars 2. ShD between CPD 3. TIA 4. RAD	ShD 0.3-0.4 mm Distance between CPD was between 0.5 and 0.6 mm	0.32 group: ShD was 0.3-0.4 mm. Distance between CPD was 0.4-0.5 mm 0.64 group: ShD was 0.2-0.3 mm. Distance between CPD was 0.3-0.4 mm 1.28 group: ShD was 0.2-0.3 mm. CPD was 0.3-0.4 mm
Pan et al.[16]	Closed-coil spring	Maxillary left first molar and incisor	OTM for 14 days and retention measured on days 3, 7 and 14	50 g	Distance between maxillary 1st and 2nd molars	The mesial movement achieved between maxillary 1st and 2nd molars remained the same during the retention phase	The mesial movement achieved between maxillary 1st and 2nd molars remained the same during the retention phase
da Silva Kagy et al.[17]	Nickel-Titanium closed-coil spring	Central incisors and 1st molar	Days 33, 37, 44, and 51 per group	30 cN	Distance between the central incisors and 1st molar	Day 33=4.05+/-3.61 mm Day 37=5.23+/-3.23 mm Day 44=6.22+/-3.90 mm Day 51=6.13+/-3.53 mm	Day 33=1.76+/-1.29 mm Day 37=3.02+/-2.0 0 mm Day 44=1.84+/-1.49 mm Day 51=3.14+/-2.10
Wang et al.[3]	Nickel-Titanium closed-coil spring	Nearest points between the first and second molars	14 days	50 g	Distance between maxillary 1st and 2nd molars	0.1120+/-0.061 mm	0.1755+/-0.106 mm
Huang et al.[18]	Customized nickel-titanium spring	Nearest points between the first and second molars	14 days	10 g	Distance between maxillary 1st and 2nd molars	0.11 mm	0.14 mm

cN, centinewton of force; mm, millimeters; CPD, distance between contact points; TIA, angle of tooth inclination; RAD, the distance of movement of the root apex; OVX group, group that received ovariectomies; ShD, shortest distance.

as measured by the distance between tooth contact points.[15] Pan et al.,[16] reported that the mesial movement achieved between maxillary 1st and 2nd molars remained the same during the retention phase; however, these measurements were not reported in the paper. da Silva Kagy et al.[17] reported that the distance between maxillary 1st and 2nd molars on day 33 was 4.05 +/- 3.61 mm vs 1.76 +/- 1.29 mm in the control vs. experimental group, respectively; 5.23 +/- 3.23 mm vs. 3.02 +/- 2.00 mm in the control vs. experimental group on day 37, respectively; 6.22 +/- 3.90 mm vs. 1.84 +/- 1.49 mm in the control vs. experimental groups on day 44, and 6.13 +/- 3.53 mm vs 3.14 +/- 2.10 mm in the control vs. experimental group on day 51. Wang et al.[3] reported that the distance between maxillary 1st and 2nd molars on day 14 was 0.1120 +/- 0.061 mm for the control and 0.1755 +/- 0.106 mm for the experimental group. Huang et al.[18] reported that the distance between maxillary 1st and 2nd molars was 0.11 mm in the sham group vs. 0.14 mm in the experimental (osteoporotic model) group on day 14 (Table 4).

Study Outcomes

The first study[15] measured 4 parameters between maxillary 1st and 2nd molars: shortest distance (ShD), distance between contact points (CPD), angle of tooth inclination, and distance of movement of the root apex. The second study[16] measured the effect of lithium on OTM during the retention phase. In addition, histology and immunohistochemistry were performed to measure bone volume and total volume in the regions of interest, which were the distal buccal root of the maxillary first molar and the adjacent periodontal ligament and alveolar bone. In the third study,[17] in addition to studying OTM, biochemical analysis was performed to record the plasma levels of inorganic serum phosphate (PO4), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and creatinine as well as serum levels of lithium, calcium, and albumin. The fourth study[3] also studied the root resorption area ratio. The fifth study[18] studied OTM in the presence in an osteoporotic model with ovariectomise.

The first study[15] noted that there was no significant difference in the ShD between the control and experimental groups. The distance between contact points mildly decreased with lithium administration, and the root apex moved distally in tipping tooth movement in the control and experimental groups receiving a dose of 0.32 mM/kg of LiCl. The root apex moved mesially during tipping tooth movement in the experimental group receiving 0.64 and 1.28 mM/kg of LiCl. It was concluded that lithium reduced orthodontically induced root resorption, which included mesial movement. The second study[16] reported that lithium promotes alveolar bone formation during orthodontic retention and may have therapeutic potential in shortening the retention period. We also noted that the osteogenic activity of lithium may be related to the activation of the Wnt signaling pathway and enhancement of Runx2 and Osterix expression. Resorption lacunae and multinucleated osteoclasts seen on day 0 disappeared by day 14. Monolayers of osteoblasts lined the lacunae on the surface of the newly developing alveolar bone. The LiCl experimental group exhibited significantly more osteoblasts than the control group on day 14. Immunohistochemistry revealed that the expression of Runx2 and Osterix increased markedly on days 7 and 14 compared with the controls. This study concluded that lithium promotes alveolar bone formation. This may also have therapeutic potential in shortening the retention period. The third study[17] noted that the lithium group showed a lower rate of movement on day 44 than the saline group. Higher serum lithium levels were observed in the L and LM experimental groups; higher PO4 were observed in the SM saline (control) group. The LM group showed a higher mean value than the L experimental group. Higher ALP values were verified in the L experimental group compared with the SM and LM experimental groups. Serum creatinine was found in lower levels in the LM experimental group than in the L experimental and SM groups. The weight variation was higher in the L and LM experimental groups. No statistical differences were observed in the SM and LM experimental groups at any time point, although there was a tendency toward a reduction in the number of osteoclasts in the LM experimental group at 44 days. This study concluded that the induced tooth movement associated with chronic lithium lowered the rate of tooth movement during 14 days, possibly due to a reduction in the number of osteoclasts. The fourth study[3] noted that the average distance measurement in the control group was slightly higher than that in the lithium group. It was also noted that the mean root resorption area ratio of the control group was significantly greater than that of the lithium group. The fifth study concluded that the lithium group protects tooth movement in osteoporosis by upregulating osteogenic differentiation and suppressing apoptosis in bone marrow-derived mesenchymal stem cells, in turn reducing OTM compared with the group that did not receive LiCl. It stated that LiCl promoted autophagy, inhibited apoptosis, and osteoclastogenesis, and effectively restored bone formation in preexisting osteoporotic alveolar bone. We concluded that the average distance of OTM measured in the control and osteoporotic groups was slightly higher than that in the group that received LiCl[18] (Table 5).

ROB of the included Studies

Regarding individual criteria, the maximum frequencies of reporting were recorded for abstract, background, objectives (introduction-based), ethical statement, study design, experimental procedures, experimental animals used in the study, housing of animals, sample size, allocation of test groups and experimental outcomes, baseline data, number of animals analyzed, outcomes and estimations and scientific implications, study generalizability, and statistical methods results for each analysis. Funding was reported in only 80% of the studies only, and no adverse events were reported. The allocation sequence was adequately generated in 3 studies,[15,16,18] but it was unclear in 1 study and was not adequately generated in 1 study.[3] All five studies have groups similar at baseline.[3,15-18] Allocation was not adequately concealed in 3 studies[15-17] and was unclear in 2 studies.[3,18] Animals were not randomly housed in 2 studies,[15,17]

Table 5. Study outcomes regarding the effect of lithium on orthodontic tooth movement

Authors	Primary methods of evaluation	Primary study outcome	Secondary study outcome	Conclusions	Statistical analysis	P value	Power analysis
Ino-Kondo et al.[15]	- Micro CT - Scanning Electron Microscope - Scanning Laser Microscope Images	- LiCl reduced OIRR - No significant difference in ShD between the groups - CPD mildly decreased with lithium administration - Root apex moved distally in tipping tooth movement in the control and 0.32 exp groups versus mesially in 0.64 and 1.28 exp groups	- No significant difference in body weight between the various groups - OIRR correlated with cortical bone morphometry	- Lithium reduced orthodontically induced root resorption, which included mesial movement	- One-Way ANOVA	- Reported as significant	NR
Pan et al.[16]	- Micro CT	- Lithium promotes alveolar bone formation during orthodontic retention - May have therapeutic potential in shortening the retention period - Osteogenic activity of lithium may be related to activation of the Wnt signaling pathway and enhancement of Runx2 and Osterix gene expression	- Resorption lacunae and multinucleated osteoclasts disappeared by day 14 - Monolayer of osteoblasts lined the lacunae on the surface of newly developing alveolar bone - The LiCl group exhibited significantly higher osteoblasts on day 14 - Expression of Runx2 and Osterix genes increased significantly on days 7 and 14	- Lithium promotes alveolar bone formation	- Two-Way ANOVA	- Reported as insignificant on 3, significant on days 7 and 14	NR
da Silva Kagy et al.[17]	- Digital Caliper	- Lithium group showed a lower rate of movement on day 44	- Higher serum lithium levels were observed in the L and LM groups - Higher values of ALP were reported in the L group compared to the SM and LM groups - Serum creatinine levels were lower in the LM group than in the L and SM groups - No. of osteoclasts in the L group remained constant at all times	- Chronic use of lithium lowered rate of tooth movement, possibly due to reduction in the number of osteoclasts	- One-Way ANOVA	- Reported as insignificant. ($p>0.05$)	NR
Wang et al.[3]	- Micro CT	- Average distance measurement in the control group slightly higher than that in the lithium group	- The root resorption area ratio of the control group was significantly higher compared to the lithium group	- The average distance of OTM measured in the control group was slightly higher than that in the experimental group	- One-Way ANOVA	- Reported as insignificant	NR
Huang et al.[18]	- Micro CT	- Lithium group protects tooth movement in osteoporosis by upregulating osteogenic differentiation and suppressing apoptosis in bone marrow-derived mesenchymal stem cells, in turn reducing OTM	- LiCl promoted autophagy and inhibited apoptosis and osteoclastogenesis - LiCl effectively restored bone formation in preexisting osteoporotic alveolar bone	- The average distance of OTM measured in the control and osteoporotic groups was slightly higher than that in the group that received LiCl	- Two-Way ANOVA	- Reported as significant	NR

CT, computed tomography scan; ANOVA, analysis of variance; OTM, orthodontic tooth movement; ALP, alkaline phosphatase; PO4, serum phosphate; OIRR, orthodontic-induced root resorption.

were unclear in 2 other studies,[3,16] and were randomly housed in 1 study.[18] Caregivers and/or investigators were blinded in 1 study[16] and unblinded in 4 studies.[3,15,17,18] All five studies did not randomly select animals for outcome assessment. The outcome assessor was blinded in 1 study,[16] whereas addressing the outcome data was unclear in 3 studies and adequately addressed adequately in 2 studies.[16,18] All five studies were free of selective outcome reporting. Among all the included studies, 3 studies[3,15,17] had a very high ROB, 1 study[16] had a high ROB, and 1 study[18] had a moderate ROB (Table 6).

DISCUSSION

Studies have shown that lithium can activate the Wnt/beta-catenin pathway,[21-23] which may have an impact on bone mass. Wnt/β-catenin signaling stimulates the generation of osteoblastic cells by promoting the differentiation of pluripotent mesenchymal stem cells (MSCs) toward the osteoblastic lineage, while simultaneously suppressing commitment to the chondrogenic and adipogenic lineages.[24] In particular, Wnt/β-catenin signaling has promoted the progression of Osterix1-expressing cells to osteoblasts that produce bone. In addition, Wnts signaling has been shown to prevent apoptosis of mature osteoblastic cells and thereby increasing their lifespan by both β-catenin independent as well as β-catenin dependent pathways.[25]

All five studies included in this review reported a reduction in the active phase of OTM upon lithium administration and had a direct effect on the retention phase after OTM was achieved. Huang et al.[18] provided evidence to support the use of LiCl in providing safe orthodontic treatment to osteoporotic patients with better and more controllable outcomes. Pan et al.[16] reported that LiCl strongly reduced the area, depth, and volume of orthodontically induced root resorption (OIRR). Subsequently, the ratio of OIRR per CPD was significantly smaller in the 0.64 and 1.28 mM/kg experimental groups than in the control group. These results suggested that LiCl inhibited OIRR more efficiently than OTM. The osteogenic activity of lithium may be related to the activation of the Wnt signaling pathway and the enhancement of Runx2 and Osterix gene expression, which are cytoplasmic markers of osteoblasts.

Strengths of this review include the utilization of an well-established method. A comprehensive search was conducted up to June 2021 without any pre-determined limitations regarding the status of publication and languages. Processes for verifying eligibility, screening, and abstraction of information from studies involving both animal and human subjects were performed in duplicate. However, limitations of this review are based on the number of experiments; thus, additional studies are warranted to confirm the above findings. Furthermore, this review relies on animal model studies. Based on the search criteria, no human studies were identified. In addition, there was inconsistency in the species of rats or mice included in the studies, and tooth displacement was measured at different sites within the oral cavity. In addition to other limitations, the assessment of OTM using micro CT, considered the gold standard, was not as effective as da Silva Kagy et al.[17] who used a digital caliper for the measurement. In studies by Pan et al.[16] and Huang et al.[18], OTM in the LiCl group was not recorded, which is a significant shortcomings.

OTM can be performed via traditional fixed appliances, which have been used for decades, as well as clear aligners, which have become extremely popular in the past decade. The normal orthodontic treatment duration with aligners is approximately 12-18 months depending on the severity of malocclusion. In this day and age, the current trend and high demand for cosmetic dentistry in any age group is rising significantly. More and more people are receptive about their smile, and orthodontists often offer home remedies for managing malocclusion. In addition, as the stigma of mental health is narrowing in society, it is important that both the patient and healthcare provider have an understanding of how either of these conditions can affect each other. The normal orthodontic treatment duration with fixed treatment or aligners is approximately 12-24 months depending on the severity of malocclusion. Based on the aforementioned studies, lithium may affect the treatment periods for OTM. Based on the current literature of studies published only on animal studies, there is limited evidence of the effect of lithium on OTM. Further standardized prospective studies mainly on humans are warranted to evaluate the influence of lithium on OTM.

CONCLUSION

Lithium, a commonly used drug used for decades for the treatment of BD, has primarily been studied in animal models. These studies indicate decreased rates of OTM during the active treatment phase by increasing bone density and bone volume and reducing root resorption. In addition, lithium enhances alveolar bone formation during the orthodontic retention

Table 6. Risk of bias using SYRCLE

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall risk	ROB
Ino-Kondo et al.[15]	Yes	Yes	No	No	No	No	No	UC	Yes	33.3%	Very high
Pan et al.[16]	Yes	Yes	No	UC	Yes	No	Yes	Yes	Yes	55.5	High
da Silva Kagy et al.[17]	UC	Yes	No	No	No	No	No	UC	Yes	22.2%	Very high
Wang et al.[3]	No	Yes	UC	UC	No	No	No	UC	Yes	22.2%	Very high
Huang et al.[18]	Yes	Yes	UC	Yes	No	Yes	No	Yes	Yes	66.6%	Moderate

UC, unclear; ROB, Risk of Bias.

phase. These findings have significant clinical implications, potentially affecting treatment duration and retention phase in long-term lithium medication patients. Further clinical studies are warranted to assess the impact of lithium on OTM.

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.W., K.K., S.T., M.K., G.K., J.K.; Design - A.W., K.K., S.T., M.K., G.K., J.K.; Data Collection and/or Processing - A.W., K.K., S.T., M.K., G.K., J.K.; Analysis and/or Interpretation - A.W., K.K., S.T., M.K., G.K., J.K.; Literature Review - A.W., K.K., S.T., M.K., G.K., J.K.; Writing - A.W., K.K., S.T., M.K., G.K., J.K.

Declaration of Interests: All authors declare that they have no conflict of interest.

Funding: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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