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Systematic Review

Chewing Bite Wafers versus Conventional Analgesic Drugs to Relieve Self-Reported Pain Associated with Fixed Orthodontic Appliances: A Systematic Review and Meta-Analysis

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Abstract: (1) Objectives: To estimate the impact of chewing bite wafers in reducing pain associated with fixed orthodontic treatment (OT) compared with conventional analgesic drugs (CADs) (Ibuprofen or Acetaminophen). (2) Materials and methods: Unrestricted and manual searching was achieved up to November 2023 and PRISMA guidelines were followed. Randomized controlled trials (RCTs) were included. Meta-analyses were conducted using a random-effects model. The available evidence quality was considered using the GRADE approach. (3) Results: Seven RCTs were included. Five RCTs used the Visual Analog Scale for self-reported pain assessment, while two RCTs used the Numeric Rating Scale. Four RCTs had a high RoB, and three RCTs had a moderate RoB. Separate meta-analyses were performed by pooling quantitative data from two RCTs that compared self-reported orthodontic pain between the bite wafer and Ibuprofen groups and three RCTs that compared the bite wafer and Acetaminophen groups for the different timepoints after orthodontic treatment. None of the timepoints individually indicated a significant difference in pain scores between the bite wafer and control groups, except on day 3, indicating significantly lower pain scores in the bite wafer versus the Acetaminophen groups. The overall level of evidence was very low. (4) Conclusions: Chewing bite wafers is possibly a useful option for CADs to relieve pain during early fixed OT.

Keywords: bite wafer; ibuprofen; orthodontic treatment; pain; paracetamol

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1. Introduction

The revised International Association for the Study of Pain (IASP) (2020) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. Moreover, pain is a subjective response to a stimulus with significant variations, relying upon factors such as gender, age, the magnitude of the stimulus, the unique pain threshold, the patient's emotional state, cultural dissimilarities, and prior pain experiences [2,3]. Patients who undergo orthodontic treatment (OT) may experience pain associated with various fixed orthodontic appliances [4,5] and often describe the pain as tension, pressure, ache, or soreness of the teeth [4,6]. Orthodontic pain intensity begins from 2 h to a peak at bedtime or 24 h after the force is applied, and the pain gradually decreases after the seventh day [4,7,8]. Orthodontic pain results from inflammation, pressure, ischemia, and edema in the periodontal ligament (PDL) and tissues following the application of orthodontic forces [9,10]. The inflammatory

reaction is mediated by inflammatory mediators that work on target cells to eradicate the damaging agent and repair the tissue [11]. Various inflammatory mediators in the PDL, such as prostaglandins, histamine, bradykinin, serotonin, and substance P mediators, can be found in the bloodstream during inflammatory reactions or are created at the inflammation site [11,12]. Inflammatory mediators balance the inflammatory response by changing the local microenvironment [11,13]. These mediators stimulate vasodilation and increase vascular permeability in the inflammatory cycle, which are essential mechanisms connected with edema and hyperemia formation, which will induce pain and discomfort [11,13,14].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Ibuprofen are conventional analgesic drugs (CADs) used to reduce orthodontic pain [3,15]. Ibuprofen is a monocarboxylic acid that is propionic acid in which one of the hydrogens at position 2 is substituted by a 4-(2-methyl propyl) phenyl group, and the molecular formula is $C_{13}H_{18}O_2$ (Figure 1) [16,17]. The NSAIDs work by blocking the enzyme cyclooxygenase (COX) activity, which modulates the modification of prostaglandins from arachidonic acid in the cellular plasma membrane [15,18]. In this regard, NSAIDs decrease pain by COX inhibition, which represses prostaglandin production. However, prostaglandins, including PGE1 and PGE2, are crucial intermediates of bone resorption. Therefore, the interference in bone remodeling and orthodontic tooth movement (OTM) may occur by suppressing prostaglandin activity with NSAIDs [15,19]; nonetheless, the clinical impact of NSAIDs on the rate of OTM remains inconclusive. Further, Ibuprofen has systemic side effects, like allergic responses, thrombocytopenia, gastrointestinal discomfort, high blood pressure, and multiple unfavorable reactions [20–22]. Acetaminophen (Paracetamol) is another CAD used to relieve pain; it is suggested as a first-line pharmacological treatment by international guidelines as an analgesic and antipyretic for children [23]. Furthermore, Acetaminophen (Paracetamol) inhibits prostaglandin synthesis in the central nervous system, not in peripheral tissues [24,25], so Acetaminophen (Paracetamol) is not an anti-inflammatory agent and does not control prostaglandin synthesis and movement of the tooth, unlike NSAIDs [25,26]. Also, Acetaminophen (Paracetamol) is known as safe in suitable and controlled dosages [27,28]. However, possible side effects of Acetaminophen (Paracetamol) in children may include renal or hepatic collapse with overdoses or extended usage [23,29]. Thus, different studies have offered alternative non-pharmacological methods for managing orthodontic pain [30], such as chewing gum [31], low-level laser therapy [32], vibratory stimulation of the periodontium [33], transcutaneous electrical nerve stimulation [34], and bite wafers [2]. The potential mechanism for pain alleviation behind these methods is to release the pressure of the PDL fibers around the blood vessels and nerves and increase the circulation of the PDL's vascular and lymphatic vessels. Hence, this may preclude or reduce inflammation and edema and relieve pain and discomfort [21,35].

A recent meta-analysis concluded that chewing sugar-free gum can be a valuable alternative to CADs for relieving pain associated with fixed orthodontic appliances; however, circumstances have been presented regarding the impact of chewing gum on the breakage frequency of fixed orthodontic appliances [36]. A randomized controlled trial (RCT) [4] examined the influence of bite wafers on fixed OT, including its impact on pain alleviation. The results supported that bite wafers can be used as a nonpharmacologic option for pain control in adolescents undergoing OT. In addition, another RCT [21] concluded that a bite wafer could effectively relieve self-reported pain during OT compared to Ibuprofen. Regardless, the significance of bite wafers on self-reported orthodontic pain decrease has not been systematically estimated. It is, therefore, pertinent to compile data from relevant RCTs and critically appraise the level of currently available evidence regarding the impact of bite wafers on pain alleviation during fixed OT compared to CADs. This systematic review and meta-analysis strived to estimate the impact of chewing bite wafers to decrease self-reported pain associated with fixed OT compared with CADs (Ibuprofen or Acetaminophen (Paracetamol)).

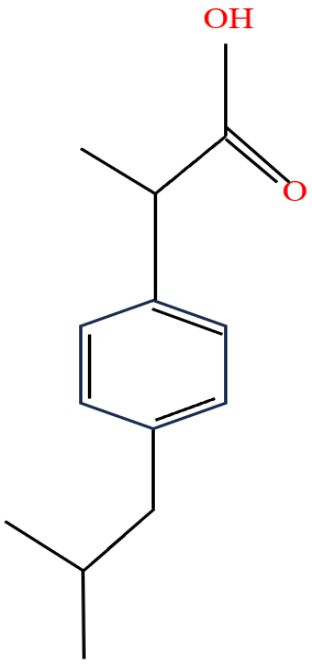

Figure 1. Graphical illustration of the Ibuprofen molecule.

2. Materials and Methods

2.1. Protocol and Registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [37], and the protocol of the present systematic review was registered in PROSPERO (CRD42022319489). In addition, the Population, Intervention, Control, Outcome, and Studies [PICOS: P = patients undergoing fixed OT; I = bite wafers; C = CADs (Ibuprofen or Acetaminophen (Paracetamol)); O = self-reported orthodontic pain levels; S = RCTs] format was used to formulate the following focused question: Is the use of bite wafers a feasible alternative to conventional pain medication (Ibuprofen and Acetaminophen (Paracetamol)) for soothing self-reported orthodontic pain in patients undergoing fixed OT?

2.2. Eligibility Criteria

The eligibility criteria were: (a) (RCTs); (b) patients experiencing fixed OT; (c) intervention group: use of bite wafers (d); control group: use of CADs (Ibuprofen and Acetaminophen (Paracetamol)); and (e) studies evaluating self-reported pain levels during fixed OT. Letters to the Editor, case series, case reports, reviews, commentaries, retrospective studies, experimental studies, non-randomized studies, and cross-sectional studies were excluded.

2.3. Information Sources, Search Strategy, and Study Selection

An electronic search of indexed databases (PubMed [National Library of Medicine], EMBASE, Scopus, ISI Web of Knowledge, Cochrane Library) and Google Scholar was performed without language and time restrictions from the beginning to and including November 2023. The following medical subject MeSH-terms were used: (1) bite wafers; (2) Ibuprofen; (3) Acetaminophen; (4) over-the-counter analgesics; (5) orthodontic treatment pain; (6) orthodontic treatment pain control; (7) orthodontic treatment pain measurement; and (8) fixed orthodontic appliances. These keywords were combined utilizing Boolean operators (OR, AND, -) to extend the search outcomes. Two authors (LJ and MA) screened the abstracts and titles of studies recognized with the protocol, as mentioned earlier, and entire texts of pertinent studies were read independently. Manual searching of the reference indexes of relevant review articles and original studies was also accomplished to specify

studies that might have been overlooked in the earlier phase. Conflicts were fixed through discussion and consultation with a third author (AB). The whole search strategy for each database is represented in (Table 1).

Table 1. Search strategy for electronic databases.

Database Search	Keywords	Results
PubMed	((Orthodontic treatment pain [MeSH Terms]) OR Orthodontic treatment pain [Title/Abstract]) OR Orthodontic treatment pain control [Title/Abstract]) OR orthodontic treatment pain measurement [Title/Abstract]) AND bite wafer AND ibuprofen [Title/Abstract]) OR over the counter analgesics [Title/Abstract]) OR acetaminophen [Title/Abstract])).	12
Embase	((‘orthodontic treatment pain measurement’ OR ((‘orthodontic’/exp OR orthodontic) AND (‘treatment’/exp OR treatment) AND (‘pain’/exp OR pain) AND (‘measurement’/exp OR measurement)) AND (‘bite wafer’/exp OR ‘bite wafer’ OR ((‘bite’/exp OR bite) AND (‘wafer’/exp OR wafer)) AND (‘ibuprofen’/exp OR ibuprofen) AND (‘orthodontic treatment pain control’ OR ((‘orthodontic’/exp OR orthodontic) AND (‘treatment’/exp OR treatment) AND (‘pain’/exp OR pain) AND (‘control’/exp OR control)) AND (‘bite wafer’/exp OR ‘bite wafer’ OR ((‘bite’/exp OR bite) AND (‘wafer’/exp OR wafer)) AND (‘ibuprofen’/exp OR ibuprofen) OR (‘orthodontic treatment pain’ OR ((‘orthodontic’/exp OR orthodontic) AND (‘treatment’/exp OR treatment) AND (‘pain’/exp OR pain)) AND (‘bite wafer’/exp OR ‘bite wafer’ OR ((‘bite’/exp OR bite) AND (‘wafer’/exp OR wafer)) AND ((‘orthodontic treatment pain’ OR ((‘orthodontic’/exp OR orthodontic) AND (‘treatment’/exp OR treatment) AND (‘pain’/exp OR pain)) AND (‘bite wafer’/exp OR ‘bite wafer’ OR ((‘bite’/exp OR bite) AND (‘wafer’/exp OR wafer)) AND (‘over the counter analgesics’ OR (over AND the AND (‘counter’/exp OR counter) AND (‘analgesics’/exp OR analgesics)) [Title/Abstract])).	9
Scopus	((TITLE-ABS-KEY (bite AND wafer AND over AND the AND counter AND analgesics)) AND (orthodontic AND treatment AND pain AND measurement AND bite AND wafer AND ibuprofen) OR (TITLE-ABS-KEY (bite AND wafer AND over AND the AND counter AND analgesics)) AND ((orthodontic AND treatment AND pain AND measurement AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND control AND bite AND wafer AND ibuprofen) OR ((TITLE-ABS-KEY (bite AND wafer AND over AND the AND counter AND analgesics)) AND ((orthodontic AND treatment AND pain AND measurement AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND control AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND bite AND wafer AND ibuprofen) OR (TITLE-ABS-KEY (bite AND wafer AND over AND the AND counter AND analgesics)) AND ((orthodontic AND treatment AND pain AND measurement AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND control AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND bite AND wafer AND ibuprofen)) AND (orthodontic AND treatment AND pain AND measurement AND bite AND wafer AND acetaminophen)) OR TITLE-ABS-KEY (Ibuprofen AND orthodontic AND treatment AND pain AND measurement TITLE-ABS-KEY ((orthodontic AND treatment AND pain OR orthodontic AND treatment AND pain AND control OR orthodontic AND treatment AND pain AND measurement) AND chewing AND gum AND acetaminophen) TITLE-ABS-KEY (bite AND wafer AND over AND the AND counter AND analgesics)).	9
Web of Science	((“Orthodontic treatment pain”) OR TOPICO: (“Orthodontic treatment pain control”) R TOPICO: (“Orthodontic treatment pain measurement”) OR TOPICO: (“bite wafer AND Ibuprofen”) ‘OR TOPICO: ((“bite wafer”) OR TOPICO: (“Ibuprofen”) OR TOPICO: (“over the counter analgesics “) OR TOPICO: (“acetaminophen”)).	7
Cochrane	((“Orthodontic treatment pain”): ti, ab, kw OR (“Orthodontic treatment pain control”): ti, ab, kw OR (“Orthodontic treatment pain measurement”): ti, ab, kw OR (“Chewing gum AND Ibuprofen”): ti, ab, kw OR (“Chewing gum”): ti, ab, kw OR (“Ibuprofen”) ti, ab, kw OR (“over the counter analgesics”) ti, ab, kw OR (“acetaminophen”)).	13
Google Scholar	((orthodontic treatment pain OR orthodontic treatment pain control OR orthodontic treatment pain measurement) + ((bite wafer AND Ibuprofen) OR bite wafer OR Ibuprofen OR over the counter analgesics OR acetaminophen)).	786

2.4. Data Collection and Data Items

The extracted data from eligible studies were accomplished independently by two authors (LJ and MA). All debates associated with the data extraction procedure were also settled through discussion. The following variables were documented: (a) reference; (b) study strategy; (c) subject features and study groups; (d) techniques of estimation; (e) study time; (f) primary outcomes calculated; (g) risk of bias examination; and (h) preliminary study results.

2.5. Risk of Bias in Individual Studies

The risk of bias (RoB) analysis of the included studies utilizing the Cochrane Collaboration's risk of bias tool (RoB) for RCTs was completed by two authors (LJ and AB) [38]. As declared previously, all disagreements in the RoB estimation were managed.

2.6. Summary Measures and Synthesis of Results

The intervention effect was organized to be displayed as mean difference (MD) along with the corresponding 95% confidence intervals (CIs). Due to the predicted heterogeneity in the intervention protocols, the random-effects model was designed to be utilized for quantitative assessment. To assess heterogeneity, the τ^2, I^2, and χ^2 statistics were estimated. A two-tailed p-value was established at 0.05 to describe the statistical significance. Forest plots were planned to be generated to represent the effect size of the intervention with the 95% CI.

2.7. Risk of Bias across Studies and Additional Analyses

Egger's test and funnel plots were utilized to evaluate documenting biases for meta-analyses with more than four studies. Moreover, subgroup analyses were prepared based on intervention and/or participant characteristics and the period of result estimation. Eventually, the available evidence quality was considered utilizing the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [39]. The statistical process was accomplished by the R Core Team software (version number 4. 1. 2) (2023). (_R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study Selection

The literature search and selection protocol are exhibited in the PRISMA flow chart (Figure 2). The electronic search retrieved 836 articles from six electronic databases. After removing duplicates, 354 studies remained, and following a manual search, two more articles were added (thus, 356 articles to be screened). The evaluation of the articles by title and abstract resulted in 329 eliminations. Finally, twenty-seven articles remained for eligibility assessment. After title, abstract, and full-text evaluations, 20 articles were excluded for different reasons explained in the list of excluded studies (Appendix A), leaving 7 for qualitative assessment. Seven RCTs [2,4,9,20,21,40,41] were included in the present qualitative analysis, and five RCTs were included in the quantitative analysis. Regarding missing data from the RCT's identified for quantitative analysis, a note was sent to the corresponding authors of the articles, but no responses were received.

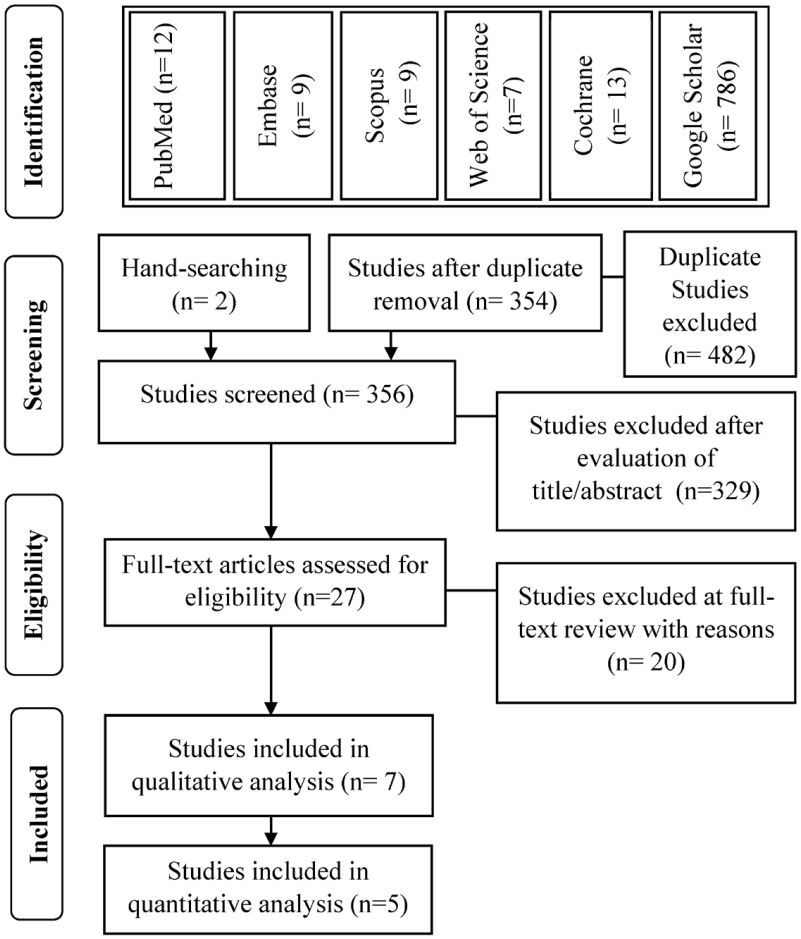

Figure 2. Study flowchart based on the PRISMA guidelines.

3.2. General Characteristics of the Included RCTs

All RCTs [2,4,9,20,21,40,41] included in the present systematic review had a parallel group design and included an experimental group (bite wafers) and a control group (Ibuprofen or Acetaminophen (Paracetamol)). In three RCTs [9,20,21], bite wafers were compared to Ibuprofen; in three RCTs [2,40,41], bite wafers were compared to Acetaminophen (Paracetamol) for pain reduction during fixed OT; and in one RCT [4], bite wafers were compared to a variety of pain medications that were combined in a single over-the-counter (OTC) group (40% NSAID, 50% non-NSAID, and 10% Percocet, Oxycodone, and Acetaminophen (Paracetamol)). The number of participants in the included RCTs ranged between 33 and 160, and the mean ± standard deviation (SD) age ranged between 12.3 ± 1.1 years and 24.65 ± 6.12 years. In five RCTs [2,4,9,40,41], it was reported that participants of both genders (male and female) were included; two RCTs [20,21] included only female patients. Three RCTs [9,20,21] reported that participants had mild to moderate dental crowding malocclusion, and three RCTs [2,4,40] did not report the type of malocclusion. Pascaline et al. [41] reported that participants had moderate to severe dental crowding malocclusion. Five RCTs [4,9,20,21,40] reported the size of the archwires, which ranged between 0.014-inch nickel–titanium archwire and 0.016-inch nickel–titanium archwire. Pascaline et al. [41] used 0.014-inch copper–nickel–titanium (Niti) archwire, and Gomaa et al. [2] did not report the archwire size. The study duration was 7 days in all the RCTs (Table 2).

Table 2. General characteristics of the included randomized, controlled clinical trials *.

Authors et al.	Number of Participants (Numbers Analyzed) (n)	Number of Parallel Groups	Mean ± SD Age in Years (Range)	Gender (M: F) Number (%)	Orthodontic Malocclusion	Methods Used for Orthodontic Pain Induction	Orthodontic Treatment	Study Duration
Bite Wafer group versus Ibuprofen group								
Al Shayea et al. [20]	Total n = 105 (90) Bite wafers n = 35 (30) Ibuprofen n = 35 (30)	Three parallel groups in 1:1:1 ratio. Bite wafers, Ibuprofen, and chewing gum	Bite wafer group: 21.75 ± 7.38 years (15–35) Ibuprofen group: 24.65 ± 6.12 years (15–35)	0 (0%): 105 (100%)	Mild dental crowding (1–4 mm)	0.016-inch nickel–titanium archwire	Archwire placement	7 days
Bayani et al. [9]	Total n = 100 (90) Bite wafers n = 20 (NA) Ibuprofen n = 20 (NA)	Five parallel groups in a 1:1:1:1:1 ratio. Bite wafer, Ibuprofen, LLRL, LLIL, and placebo	17.6 ± NA years (14–21)	34 (34%): 66 (66%)	Moderate dental crowding (4–8 mm)	0.014-inch nickel–titanium archwire	Archwire placement	7 days
Farzanegan et al. [21]	Total n = 50 Soft bite wafers n = 10 Hard bite wafers n = 10 Ibuprofen n = 10	Five parallel groups in a 1:1:1:1:1 ratio. Soft bite wafers, hard bite wafers, Ibuprofen, chewing gum, and placebo	NA ± NA years (13–18)	0 (0%): 50 (100%)	Moderate dental crowding (4–8 mm)	0.016-inch nickel–titanium archwire	Archwire placement	7 days
Bite wafer group versus Acetaminophen (Paracetamol) group								
Gomaa et al. [2]	Total n = 150 Bite wafers n = 50 Acetaminophen (Paracetamol) n = 50	Three parallel groups in 1:1:1 ratio. Bite wafers, Acetaminophen (Paracetamol), and control	Bite afer group: 17 ± 4 years (13–22) Acetaminophen (Paracetamol) group: 19 ± 3 years (13–22)	60 (40%): 90 (60%)	NA	NA	Archwire placement	7 days
Pascaline et al. [41]	Total n = 33 (30) Bite wafers n = 17 (15) Acetaminophen (Paracetamol) n = 16 (15)	Two parallel groups in 1:1 ratio. Bite wafer and Acetaminophen (Paracetamol)	Bite wafer group: 12.9 ± 1.8 years (11–17) Acetaminophen (Paracetamol) group: 12.3 ± 1.1 years (11–17)	10 (33%): 20 (67%)	Moderate to severe dental crowding (>4 mm)	0.014-inch copper–nickel–titanium (Niti)	Archwire placement	7 days
Saloom et al. [40]	Total n = 160 (110) Bite wafers n = 80 (55) Acetaminophen (Paracetamol) n = 80 (55)	Two parallel groups in 1:1 ratio. Bite wafer and Acetaminophen (Paracetamol)	NA ± NA years (12–24 years).	54 (49%): 56 (51%)	NA	0.014-inch nickel–titanium archwire	Archwire placement	7 days

Table 2. *Cont.*

Authors et al.	Number of Participants (Numbers Analyzed) (n)	Number of Parallel Groups	Mean ± SD Age in Years (Range)	Gender (M: F) Number (%)	Orthodontic Malocclusion	Methods Used for Orthodontic Pain Induction	Orthodontic Treatment	Study Duration
Bite wafer group versus mixed over-the-counter (OTC) ** group								
Murdock et al. [4]	Total n = 56 (49) Bite wafers n = 26 (24) OTC n = 30 (25)	Two parallel groups in 1:1 ratio. Bite wafer and OTC	Bite wafer group: 13.6 ± 2.0 years (8–18) OTC group: 13.7 ± 1.7 years (8–18)	BW = 11 (46%): 13 (54%); OTC = 12 (48%): 13 (52%)	NA	0.014-inch nickel–titanium archwire	Archwire placement	7 days

SD, standard deviation; M, male; F, female; NA, not available; OTC, over the counter. * Experimental group: bite wafers; control group: conventional analgesic drugs (Ibuprofen or Acetaminophen). ** 40% NSAID, 50% non-NSAID, and 10% Percocet, Oxycodone, and Acetaminophen (Paracetamol).

3.3. Study Characteristics Related to the Use of Bite Wafer versus Ibuprofen

In three RCTs [9,20,21], the participants used a bite wafer to chew in the intervention group. In two of the RCTs [20,21], the participants chewed the bite wafer for 5 min and at 8 h intervals for one week. In the RCT by Bayani et al. [9], the participants chewed the bite wafer following archwire placement and at 8 h intervals for one week. In the three RCTs [9,20,21], the Ibuprofen dosage was a 400 mg tablet. The three RCTs [9,20,21] reported that the evaluation of pain intervals occurred seven times: at 2 h, 6 h, bedtime, 24 h, 2 d, 3 d, and 7 d. The three RCTs [9,20,21] used the Visual Analog Scale (VAS) for self-reported pain assessment (Table 3).

Table 3. Study characteristics related to bite wafer and conventional analgesic drugs (Ibuprofen and Acetaminophen (Paracetamol)).

Authors et al.	Type of Bite Wafers	Bite Wafer Intervals	Analgesic Drugs Dosage	Analgesic Drug Intervals	Pain Interval Evaluation	Pain Measurement
Bite wafer group versus Ibuprofen group						
Al Shayea et al. [20]	Bite wafers (Dentakit Company)	Chewing wafer for 5 min after archwire placement and at 8 h intervals for one week	400 mg Ibuprofen tablet	Take a tablet after the archwire placement and at 8 h intervals for one week	2 h, 6 h, bedtime, 24 h, 2 d, 3 d, 7 d	VAS
Bayani et al. [9]	Bite wafers (Ortho Organizers)	Chewing wafer following archwire placement and at 8 h intervals for one week	400 mg Ibuprofen tablet	Take a tablet after archwire placement and at 8 h intervals for one week	2 h, 6 h, bedtime, 1 d, 2 d, 3 d, and 7 d	VAS
Farzanegan et al. [21]	Bite wafers (soft viscoelastic and hard viscoelastic)	Chewing wafer for 5 min after archwire placement and at 8 h intervals for one week	400 mg Ibuprofen tablet	Take a tablet after the archwire placement and at 8 h intervals for one week	2 h, 6 h, bedtime, 24 h, 2 d, 3 d, 7 d	VAS

Table 3. *Cont.*

Authors et al.	Type of Bite Wafers	Bite Wafer Intervals	Analgesic Drugs Dosage	Analgesic Drug Intervals	Pain Interval Evaluation	Pain Measurement
Bite wafer group versus Acetaminophen (Paracetamol) group						
Gomaa et al. [2]	Bite wafers (Dentsply Sirona Global)	NA	500 mg Acetaminophen (Paracetamol) tablet	Take a tablet 30 min before the archwire placement	4 h, 12 h, 24 h, 4 d, and 7 d	VAS
Pascaline et al. [41]	Bite wafers (ethyl-vinyl-acetate)	Chewing wafer for 20 min after archwire placement for one week	250 mg Acetaminophen (Paracetamol) tablet	Take a tablet after archwire placement for one week	1 d (E), 2 d (M) & (E), 3 d (E), 4 d (E), 5 d (E), 6 d (E), and 7 d (E)	NRS
Saloom et al. [40]	Bite wafers (NA)	Chewing wafer for 10–12 min within an hour after archwire placement	500 mg Acetaminophen (Paracetamol) tablet	Ask the patients to take a tablet whenever they need to relieve pain	1 d, 2 d, 3 d, 4 d, 5 d, 6 d, and 7 d	VAS
Bite wafer group versus mixed over-the-counter (OTC) group						
Murdock et al. [4]	Bite wafers (Dynaflex Therapy Wafers)	Chewing wafer for 10–12 min within an hour after archwire placement and an average of 3 times a day	NA	Take an average of 1.5 tablets a day	2 h, 6 h, bedtime, 24 h, 2 d, 3 d, 5 d, and 7 d	NRS

mg, milligram; h, hour; d, day; NA, not available; E, evening; M, morning; VAS, Visual Analog Scale; NRS, Numeric Rating Scale.

3.4. Study Characteristics Related to the Use of Bite Wafer versus Acetaminophen (Paracetamol)

In three RCTs [2,40,41], the participants used a bite wafer to chew in the intervention group. Gomaa et al. [2] did not report the bite wafer intervals. Pascaline et al. [41] reported that the participants chewed the bite wafer for 20 min after archwire placement for one week. Saloom et al. [40] reported that the participants chewed the bite wafer for 10–12 min within an hour after orthodontic archwire placement. In both RCTs [2,40] the Acetaminophen (Paracetamol) dosage was 500 mg per tablet, while in the study by Pascaline et al. [41], the Acetaminophen (Paracetamol) dosage was 250 mg per tablet. In the RCT by Gomaa et al. [2], the participants took one tablet 30 min before the archwire placement. Pascaline et al. [41] asked the patients to take a tablet to relieve pain for up to seven days. Saloom et al. [40] asked the patients to take a tablet whenever they needed to relieve pain. Gomaa et al. [2] reported that the evaluation of pain intervals occurred five times: at 4 h, 12 h, 24 h, 4 d, and 7 d. Pascaline et al. [41] reported that the evaluation of pain intervals occurred 8 times: at 1 d (evening), 2 d (morning), 2 d (evening), 3 d (evening), 4 d (evening), 5 d (evening), 6 d (evening), and 7 d (evening). Saloom et al. [40] reported that the evaluation of pain intervals occurred 7 times: at 1 d, 2 d, 3 d, 4 d, 5 d, 6 d, and 7 d. Two of these RCTs [2,40] used the VAS for self-reported pain assessment, while Pascaline et al. [41] used the NRS for self-reported pain assessment (Table 3).

3.5. Study Characteristics Related to the Use of Bite Wafers versus Mixed OTC Drugs

Murdock et al. [4] reported that the participants in the intervention group chewed the bite wafer for 10–12 min within an hour after archwire placement and an average of three times a day. Moreover, they reported that 40% of the participants in the OTC group took a preparation containing 40% NSAID, 50% non-NSAID, and 10% Percocet, Oxycodone,

and Acetaminophen (Paracetamol), with an average of 1.5 tablets a day. In addition, the evaluation of pain intervals occurred 8 times: at 2 h, 6 h, bedtime, 24 h, 2 d, 3 d, 5 d, and 7 d. Finally, Murdock et al. [4] used the Numeric Rating Scale (NRS) for self-reported pain assessment (Table 3).

3.6. Main Outcomes of Individual Studies

Two RCTs [20,21] reported that there were no significant differences at any timepoint in the results regarding VAS scores between bite wafer and Ibuprofen groups. Bayani et al. [9] did not report statistical group comparisons regarding VAS scores between the bite wafer and Ibuprofen groups. Gomaa et al. [2] reported that there were no significant differences at any timepoint in the results regarding VAS scores between the bite wafer and Acetaminophen (Paracetamol) groups. Pascaline et al. [41] reported that there were no significant differences at any timepoint in the results regarding NRS scores between bite wafer and Acetaminophen (Paracetamol) groups. Saloom et al. [40] reported that there were significant differences at all timepoints in the results regarding VAS scores between the bite wafer and Acetaminophen (Paracetamol) groups, favoring the use of bite wafers. Murdock et al. [4] did not report statistically significant differences regarding VAS scores between the bite wafer and over-the-counter (OTC) groups (Table 4).

Table 4. Main study outcomes.

Authors	Results Regarding Visual Analog Scale and Numeric Rating Scale			Statistical Group Comparisons		Conclusion
	Bite Wafer Group versus Ibuprofen Group					
	Time Period	Bite Wafer Group (Mean ± SD)	Ibuprofen Group (Mean ± SD)	Period	*p*-Value	
Al Shayea et al. [20]	2 h	3.53 ± 1.35	3.88 ± 1.52	2 h	NS	Bite wafers were comparable to Ibuprofen in reducing pain following the initial activation of fixed orthodontic appliances.
	6 h	4.08 ± 1.34	4.50 ± 1.73	6 h	NS	
	Bedtime	4.93 ± 1.01	5.08 ± 1.73	Bedtime	NS	
	24 h	4.36 ± 1.18	5.08 ± 1.61	24 h	NS	
	2 d	2.60 ± 1.43	3.25 ± 1.25	2 d	NS	
	3 d	1.65 ± 1.31	2.10 ± 1.17	3 d	NS	
	7 d	0.80 ± 1.06	0.95 ± 0.83	7 d	NS	
Bayani et al. [9]	2 h 6 h Bedtime 1 d 2 d 3 d 7 d	NA	NA	2 h 6 h Bedtime 1 d 2 d 3 d 7 d	NA	Chewing on the bite wafer was effective for orthodontic pain control and produced results that were comparable to the Ibuprofen.
Farzanegan et al. [21]		Soft BW	Hard BW			Chewing on bite wafers can be an appropriate substitute for Ibuprofen in orthodontic pain reduction.
	2 h	2.87 ± 2.42	5.29 ± 2.75	4.80 ± 3.06	2 h	NS
	6 h	4.40 ± 2.51	5.25 ± 3.28	6.45 ± 2.58	6 h	NS
	Bedtime	5.23 ± 2.78	4.85 ± 3.24	6.96 ± 2.13	Bedtime	NS
	24 h	7.15 ± 2.83	4.22 ± 2.83	7.47 ± 2.73	24 h	NS
	2 d	5.32 ± 2.01	3.34 ± 3.16	6.64 ± 3.11	2 d	NS
	3 d	3.18 ± 1.84	2.50 ± 2.90	5.04 ± 3.07	3 d	NS
	7 d	1.55 ± 1.72	1.14 ± 1.75	4.02 ± 2.77	7 d	NS

Table 4. *Cont.*

Bite wafer group versus Acetaminophen (Paracetamol) group						
	Period	Bite wafer group (Mean ± SD)	Acetaminophen (Paracetamol) group (Mean ± SD)	Period	*p*-value	Chewing on bite wafers can be an appropriate substitute for Acetaminophen (Paracetamol) in orthodontic pain reduction.
Gomaa et al. [2]	4 h	2.72 ± 1.62	2.56 ± 1.21	4 h	NS	
	12 h	1.82 ± 1.16	1.76 ± 0.98	12 h	NS	
	24 h	0.48 ± 0.71	0.42 ± 0.67	24 h	NS	
	4 d	0.18 ± 0.39	0.20 ± 0.40	4 d	NS	
	7 d	0.14 ± 0.35	0.10 ± 0.30	7 d	NS	
Pascaline et al. [41]	1 d (E)	6.27 ± 3.283	6.40 ± 2.558	1 d (E)	NS	Chewing on bite wafers can be an appropriate substitute for Acetaminophen (Paracetamol) in orthodontic pain reduction.
	2 d (M)	5.53 ± 2.560	5.07 ± 2.434	2 d (M)	NS	
	2 d (E)	4.73 ± 3.127	4.13 ± 2.722	2 d (E)	NS	
	3 d (E)	4.07 ± 2.492	3.87 ± 2.356	3 d (E)	NS	
	4 d (E)	3.13 ± 2.416	3.40 ± 2.720	4 d (E)	NS	
	5 d (E)	2.67 ± 2.320	2.00 ± 1.964	5 d (E)	NS	
	6 d (E)	2.07 ± 2.344	1.53 ± 1.356	6 d (E)	NS	
	7 d (E)	1.53 ± 1.807	1.07 ± 1.100	7 d (E)	NS	
Saloom et al. [40]		Adolescent	Adult	Adolescent	Adult	Chewing of bite wafers was more effective in reducing pain compared to Acetaminophen (Paracetamol), especially in adolescents.
	1 d	1.2 ± 0.8	0.7 ± 0.7	7.3 ± 1.7	1.8 ± 0.8	1 d S
	2 d	0.7 ± 0.6	0.6 ± 0.7	5.7 ± 2.2	1.9 ± 0.9	2 d S
	3 d	0.5 ± 0.6	0.6 ± 0.5	1.7 ± 1.0	1.2 ± 0.9	3 d S
	4 d	0.2 ± 0.4	0.1 ± 0.4	2.5 ± 1.1	1.4 ± 0.6	4 d S
	5 d	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 0.7	0.3 ± 0.5	5 d S
	6 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	6 d S
	7 d	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	7 d S
Bite wafer group versus mixed over-the-counter (OTC) group						
	Period	Bite wafer group (Mean ± SD)	Over-the-counter group (Mean ± SD)	Period	*p*-value	The use of a bite wafers was comparable to various OTC medications that were used for the management of pain after the placement of orthodontic archwires.
Murdock et al. [4]	2 h	2.3 ± 2.5	3.7 ± 3.5	2 h	NA	
	6 h	4.2 ± 3.0	4.3 ± 3.5	6 h	NA	
	Bedtime	4.7 ± 3.0	6.2 ± 3.4	Bedtime	NA	
	24 h	5.2 ± 3.3	5.5 ± 2.8	24 h	NA	
	2 d	4.6 ± 3.1	5.6 ± 3.1	2 d	NA	
	3 d	3.5 ± 3.0	4.7 ± 3.0	3 d	NA	
	5 d	1.9 ± 1.8	2.2 ± 2.4	5 d	NA	
	7 d	0.6 ± 1.2	1.6 ± 2.2	7 d	NA	

SD, standard deviation; BW, bite wafer; E, evening; M, morning; NS, non-statistically-significant difference; S, statistically significant difference; NA, not available.

3.7. Risk of Bias within Studies

Four RCTs [2,20,21,40] had a high RoB, and three RCTs [4,9,41] had a moderate RoB (Table 5) (Figure 3). The main reasons for high RoB in the RCTs included the lack of blinding of participants and researchers, lack of blinding of outcome assessment, and inclusion of only female patients in two RCTs. Power analysis for sample-size estimation was performed in three RCTs [4,20,41].

Table 5. Risk of bias of the included randomized controlled clinical trials.

Domain	Al Shayea et al. [20]	Bayani et al. [9]	Farzanegan et al. [21]	Gomaa et al. [2]	Murdock et al. [4]	Pascaline et al. [41]	Saloom et al. [40]
Random sequence generation	Low	Low	Low	High	Low	Low	Low
Allocation concealment	Low	High	High	High	Low	Low	High
Blinding of participants and researchers	High	High	High	High	High	High	High
Blinding of outcome assessment	High	Low	High	High	High	High	High
Incomplete outcome data	Low	Low	Low	Low	Low	Low	High
Selective outcome reporting	Low	Low	Low	Low	Low	Low	Low
Other bias	High	Low	High	Low	Low	Low	Low
Overall	High	Moderate	High	High	Moderate	Moderate	High

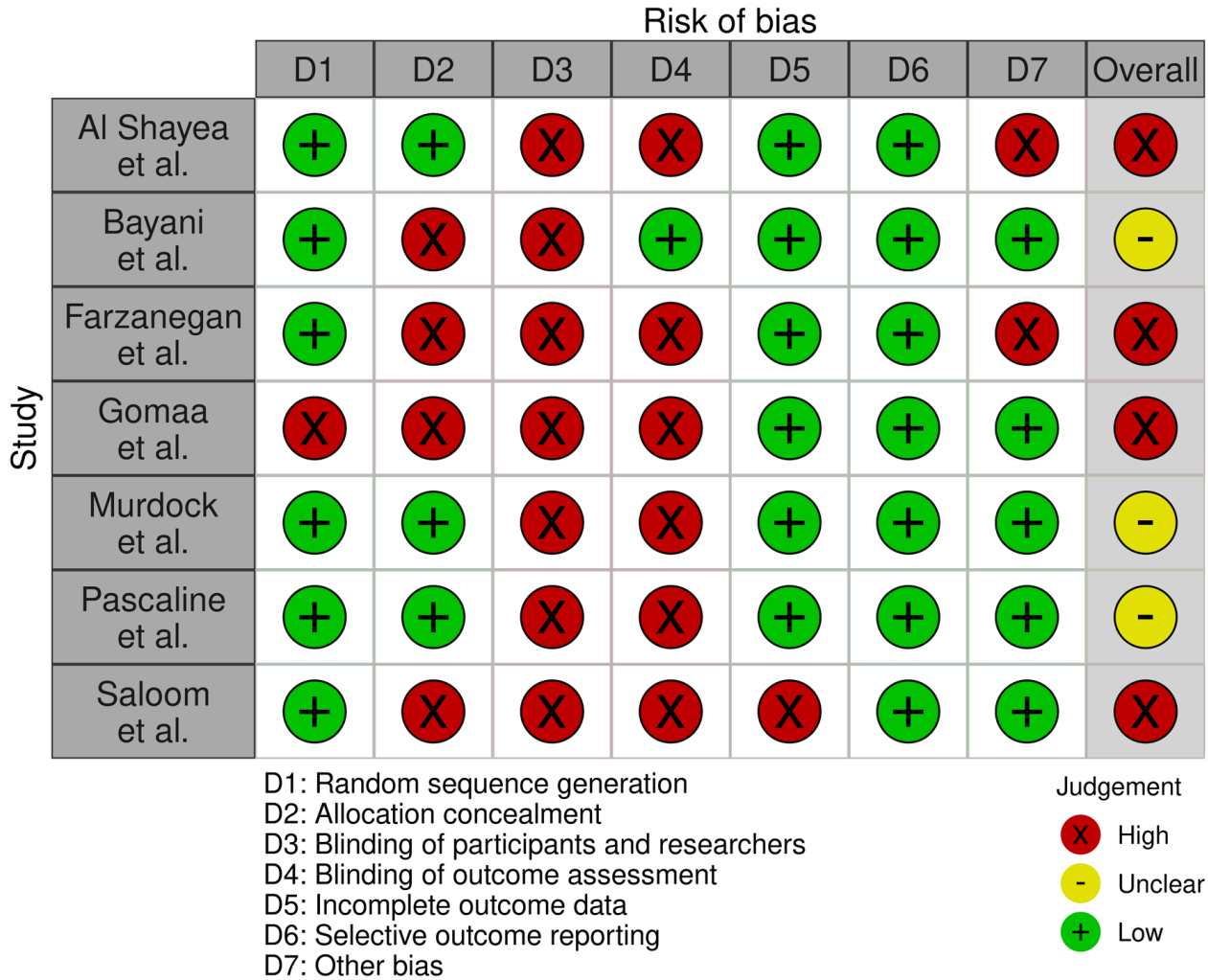

Figure 3. Risk of bias [2,4,9,20,21,40,41].

3.8. Synthesis of the Results

Separate meta-analyses were performed by pooling quantitative data from two RCTs [20,21] that compared orthodontic pain between the bite wafer (soft and/or hard) and Ibuprofen groups and three RCTs [2,40,41] that compared the bite wafer and Acetaminophen (Paracetamol) groups (for adolescent and/or adult participants). Moreover,

subgroup analyses were performed based on the timepoints of pain interval evaluation. The RCTs included in the meta-analyses assessed self-reported orthodontic pain for the following timepoints: 2 h; 6 h; bedtime; 24 h; 1 day; 2 days; 3 days; 4 days; 5 days; 6 days; and 7 days. None of the timepoints individually indicated a significant difference in self-reported pain scores between bite wafer and control groups (Ibuprofen and Acetaminophen), except on day 3, indicating significantly lower pain scores in the bite wafer versus Acetaminophen (Paracetamol) groups (Figures 4 and 5).

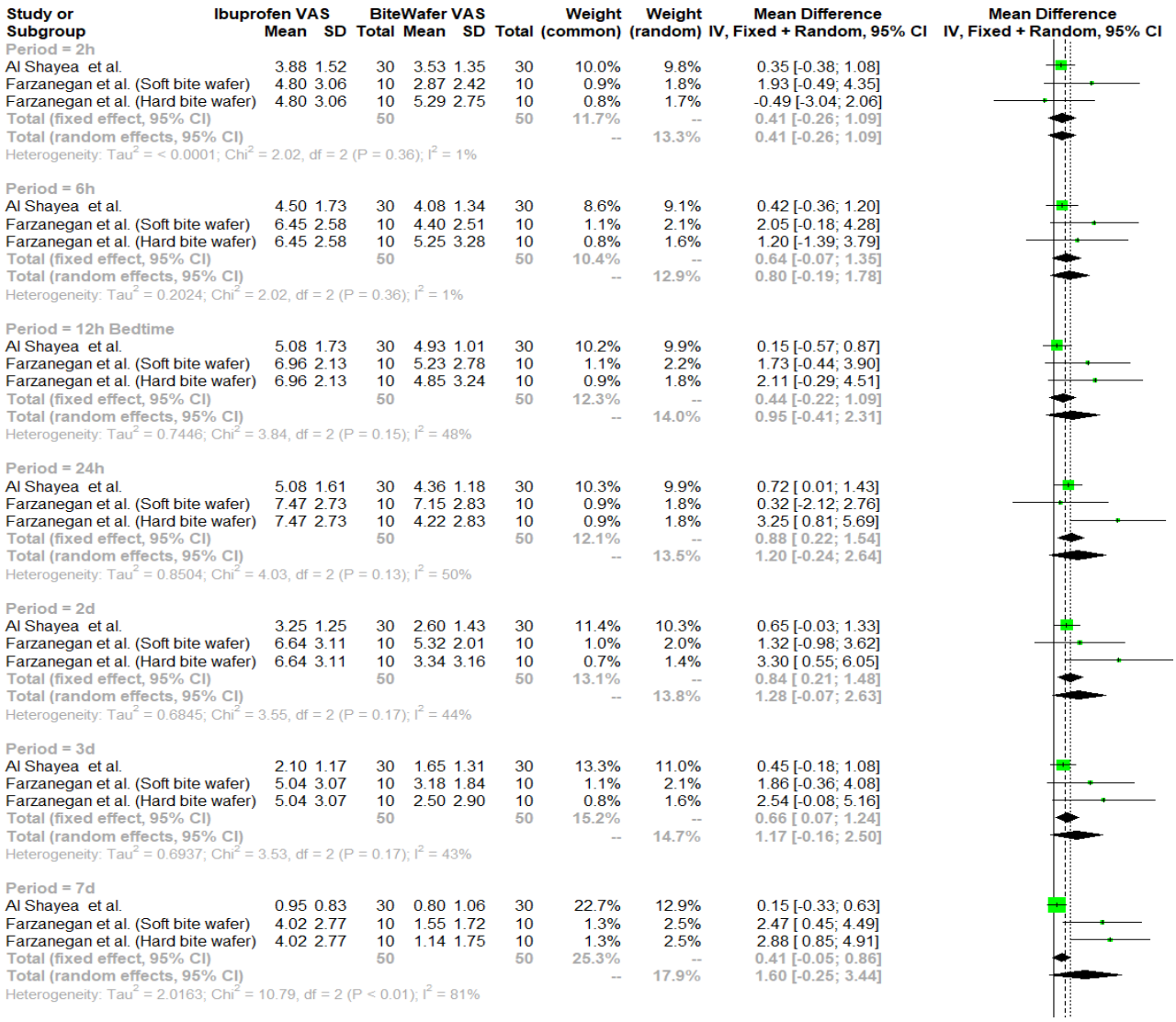

Figure 4. Meta-analysis was performed by pooling quantitative data (bite wafer vs. Ibuprofen). SD, standard deviation; CI, confidence interval; df, degrees of freedom; h, hour; d, day [20,21].

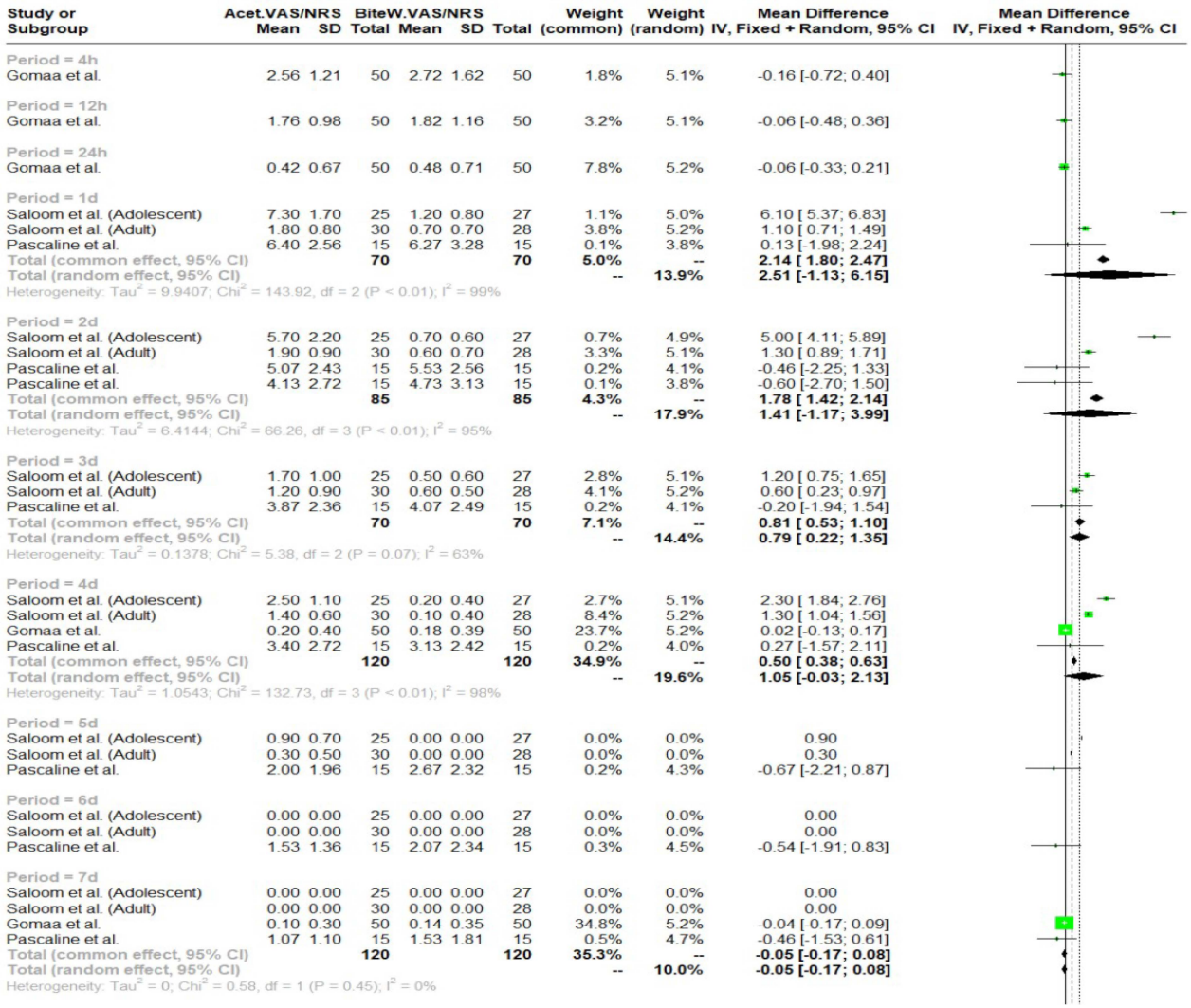

Figure 5. Meta-analysis was performed by pooling quantitative data (bite wafer vs. Acetaminophen). Acet., Acetaminophen; BiteW, Bite Wafer; SD, standard deviation; CI, confidence interval; df, degrees of freedom; h, hour; d, day [2,40,41].

3.9. Risk of Bias across Studies and Additional Analyses

According to the GRADE estimation, the level of confidence regarding the comparison of the bite wafer and Ibuprofen was low (Table 6), and the comparison of the bite wafer and Acetaminophen (Paracetamol) was very low regarding the level of confidence (Table 7). Moreover, sensitivity analysis and assessment of publication bias were not conducted due to the small number of studies.

Table 6. Quality of available evidence using GRADE (bite wafer vs. Ibuprofen).

Certainty Assessment							№ of Patients		Effect		Certainty	Importance
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Bite Wafer**	**Ibuprofen**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomized trials	very serious	not serious	not serious	not serious	none	50	50	-	MD * 0.81 VAS higher (0.47 higher to 1.16 higher)	⊕⊕◯◯ Low	CRITICAL

GRADE: Grading of Recommendation Assessment, Development, and Evaluation; CI, confidence interval; MD, mean difference; * This is the mean difference of the total random effect from all timepoints.

Table 7. Quality of available evidence using GRADE (bite wafer vs. Acetaminophen).

Certainty Assessment							№ of Patients		Effect		Certainty	Importance
№ of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Bite Wafer**	**Acetaminophen**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomized trials	very serious	serious	not serious	serious	publication bias strongly suspected	120	120	-	MD * 1.41 VAS/NRS higher (0.35 higher to 2.47 higher)	⊕◯◯◯ Very low	CRITICAL

GRADE: Grading of Recommendation Assessment, Development, and Evaluation; CI, confidence interval; MD, mean difference; * This is the mean difference of the total random effect from all timepoints.

4. Discussion

The unrestricted proof regarding the application of bite wafers as an alternative to CADs for orthodontic pain alleviation was assessed and outlined by the authors of this review. Following the PRISMA guidelines and by applying strict eligibility criteria, the authors identified seven RCTs that were processed for data extraction (three RCTs [9,20,21] compared bite wafers with Ibuprofen, three RCTs [2,40,41] compared bite wafers with Acetaminophen (Paracetamol), and one RCT [4] compared bite wafers with mixed OTC medications). Qualitative assessment of the individual study results indicated that in all RCTs, chewing of bite wafers was at least as effective as CADs for pain alleviation for up to 7 days after the placement of orthodontic archwires. The present study's authors strived to pool all pertinent data from the included RCTs for quantitative analysis (meta-analysis). Since Murdock et al. [4] included a variety of OTC medications in the control group without providing separate pain scores for each type of medication, it was not possible to include this study for quantitative assessment.

Moreover, since Bayani et al. [9] did not record numerical data [mean (±sd) pain scores], a meta-analysis regarding the comparison of bite wafer and Ibuprofen was accomplished by pooling data from two RCTs [20,21]. The quantitative assessment was performed for RCTs using soft and hard bite wafers in Farzanegan et al. [21] and adolescents and adults in Saloom et al. [40] to maximize the pooled data. Furthermore, subgroup analyses were completed for each timepoint of pain assessment. Finally, a random effects model was used to pool the individual study results and revealed that the pooled difference in pain alleviation between the bite wafer and Ibuprofen groups for each of the timepoints did not significantly favor one of the groups. The pooled difference in pain alleviation between the bite wafer and Acetaminophen (Paracetamol) was not significant for the majority of timepoints assessed, except for day 3, which was a significant assessment favored the bite wafer. Critical appraisal of the available evidence indicates that the included RCTs had a moderate to high RoB, and the overall confidence in the meta-analysis results was very low. Based on individual and pooled study results, it appears that bite wafers are at least as effective as CADs for pain alleviation during the early stages (up to 7 days) of OT.

5. Strengths and Limitations of the Systematic Review

The present review has several strengths. It included an a priori and registered protocol, a comprehensive literature search strategy, and strict eligibility criteria. Efforts were made to compile the maximum amount of available information, and the use of recommended tools was utilized to critically appraise the risk of bias in individual studies and assess the quality of available evidence. Some limitations should be considered before finalizing whether a bite wafer is a practical choice in place of CADs after the placement and/or adjustment of fixed orthodontic appliances, such as whether the meta-analyses included only a limited number of studies with inconsistent methodologies. For example, a variation was observed in patients' ages as studies included adolescent and adult patients. Moreover, it has been documented that pain perception differs depending on an individual's age and growth status [42,43], which may have impacted the noted results. In addition, variability was noted regarding the analgesic drug dosages and consumption intervals, as well as the bite wafer use intervals and duration.

Further, Pascaline et al. [41] reported that the bite wafer was made in the laboratory due to the difficulty of obtaining this type of industrial product in Belgium. In addition, the material used was less flexible than an industrial product. Also, orthodontic pain was generated by different orthodontic archwires (such as 0.014-inch and 0.016-inch nickel–titanium archwires and/or 0.014-inch copper–nickel–titanium (Niti)). These orthodontic appliances and auxiliaries may lead to dissimilar force magnitudes and tissue reactions during orthodontic force application [44,45], which may influence a person's pain perception and reaction to pain management methods like pharmacological and non-pharmacological interventions. Furthermore, the participants' malocclusion status ranged from mild to severe crowding, and it could be speculated that patients with moderate crowding might

have undergone heavier orthodontic forces after orthodontic archwire placement compared to patients with mild crowding, which may impact the resultant pain perception. However, additional studies are required for the latter consideration. In addition, gender dissimilarities have been noted concerning pain perception and tolerance [46]; thus, studies including female patients might have been subjected to selection bias. Nevertheless, based on the presently available evidence, it is challenging to recognize the optimal protocol for bite wafer usage and/or analgesic consumption after fixed orthodontic appliance placement and to draw conclusions regarding the long-term success of bite wafer as a pain management protocol during fixed OT.

It is of merit to note that four RCTs [2,20,21,40] had a high RoB and three RCTs [4,9,41] had a moderate RoB. The absence of blinding absence of researchers and participants, the inclusion of only female patients in two RCTs, and the shortage of blinding for outcome estimation are considered the major causes that raised the probable biases in the RCTs included. Because of the character of the studies (bite wafer and consumption of analgesics), one can contest the blinding of the study participants. Hence, the authors suppose that participants consuming analgesics might experience reduced self-perceived pain levels due to a placebo effect. Also, power analysis for sample size estimation was performed in three [4,20,41] of seven RCTs. This warrants a warning in interpreting their statistical results due to the probability of Type II errors. In three RCTs [9,20,21], adjustments were made for multiple testing when comparing intervention with control groups, such as Tukey's test. The authors of the present systematic review perceive that *p*-values in all included RCTs should have been modified utilizing multiplicity correction for accounting for the multiple group comparisons among several timepoints. The authors used GRADE analysis to specify the level of certainty of the meta-analysis results, indicating a very low level of evidence regarding the comparison of bite wafer and Acetaminophen (Paracetamol) and a low level of confidence regarding the comparison of bite wafer and Ibuprofen. Due to the restricted number of RCTs, achieving a sensitivity analysis or a subgroup analysis for the patient and intervention-related characteristics and estimating the risk of publication bias across studies was not possible.

6. Clinical Implications and Recommendations for Further Research

Orthodontists and other specialists suggest that patients avoid hard or sticky food during fixed OT due to the possibility of appliance breakage. In this systematic review, one RCT [20] reported that chewing on a bite wafer did not raise the incidence of orthodontic appliance breakages; however, further studies are needed to assess the clinical application of bite wafers for pain relief in patients undergoing fixed OT. Additionally, it would be interesting in the future to also evaluate the effect of different scales on pain measurement [47]. Also, the possible role of specific questionnaires evaluating the quality of life could be explored [48].

Due to the low level of existing evidence, further well-designed RCTs have to estimate the effectiveness of chewing bite wafers for pain management in patients undergoing fixed OT. For example, studies should be power-adjusted and execute blinding for the outcome assessment to minimize RoB, as well as consider further clinical effects such as clinical periodontal parameters and rate of appliance breakage. Nonetheless, the use of bite wafers and/or chewing sugar-free gum may be considered as a method to control orthodontic pain in patients undergoing fixed OT, especially if CADs are contraindicated due to underlying medical conditions such as allergies, hepatic impairment, or renal diseases.

7. Conclusions

The literature reports that bite wafers can be used as a nonpharmacologic option for pain relief during orthodontic treatment. However, this systematic review and meta-analysis established that there is an overall very low level of available evidence supporting chewing a bite wafer as a useful option in pain relief compared to using CADs during early fixed OT.

Author Contributions: L.J. was responsible for conceptualization, methodology, validation, and writing the original draft; M.A. was responsible for methodology, validation, writing—review and editing; A.B.B. was responsible for formal analysis and interpreting data; P.E.R. was responsible for writing—review and editing and supervision; and D.M. was responsible for validation, writing—review and editing, supervision, and project administration. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical review and approval were waived for this study, which is a systematic review of pertinent indexed literature.

Data Availability Statement: All data are incorporated into the article and related tables and figures.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Appendix A. List of Excluded Studies at Full-Text Review with Reasons for Exclusion

Studies Excluded	Reasons for the Exclusion
Bavbek et al. (2016) PMID: 27172508	Bite wafer compared with finger pressure and stress relief
Karobari et al. (2021) PMID: 33747083	Bite wafer compared with finger pressure and stress relief
Mangnall et al. (2013) PMID: 24009318	Bite wafer compared with the control group
Gupta et al. (2022) PMID: 35229220	Paracetamol compared with finger pressure and stress relief
Salmassian et al. (2009) PMID: 19361739	Paracetamol compared with Ibuprofen
Polat et al. (2005) PMID: 15825785	Paracetamol compared with Ibuprofen and other medications
Polat et al. (2005) PMID: 16279825	Ibuprofen compared with naproxen sodium
Alqahtani et al. (2017) PMID: 30166905	Paracetamol compared with Ibuprofen and control group
Bird et al. (2007) PMID: 17920504	Paracetamol compared with Ibuprofen
Santos et al. (2021) PMID: 34556589	Paracetamol compared with Ibuprofen and sugar-free chewing gum
Alshammari et al. (2019) PMID: 30590573	Paracetamol compared with sugar-free chewing gum
Ireland et al. (2016) PMID: 27476354	Paracetamol compared with sugar-free chewing gum
Azeem et al. (2018) Google Scholar	Ibuprofen compared with sugar-free chewing gum
Elvina et al. (2018) Google Scholar	Paracetamol compared with sugar-free chewing gum
Delavarian et al. (2019) Google Scholar	Ibuprofen compared with sugar-free chewing gum
UL-Hamid et al. (2016) Google Scholar	Ibuprofen compared with sugar-free chewing gum
Law et al. (2000) PMID: 11113797	Ibuprofen compared with lactose placebo
Bernhardt et al. (2001) PMID: 11455373	Ibuprofen compared with lactose placebo
Bradley et al. (2007) PMID: 17920505	Paracetamol compared with Ibuprofen
Hosseinzadeh et al. (2016) PMID: 27424011	Paracetamol compared with Ibuprofen

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5

INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2–5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	11–18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	19
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	21
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	21
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	21
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	21
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	21
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	24
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	25–26
	23b	Discuss any limitations of the evidence included in the review.	26–28
	23c	Discuss any limitations of the review processes used.	26–28
	23d	Discuss implications of the results for practice, policy, and future research.	28–29
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	29
Competing interests	26	Declare any competing interests of review authors.	30
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

References

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