Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for pain relief during orthodontic treatment (Review)

Monk AB, Harrison JE, Worthington HV, Teague A

Monk AB, Harrison JE, Worthington HV, Teague A.
Pharmacological interventions for pain relief during orthodontic treatment.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003976.
DOI: 10.1002/14651858.CD003976.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Pharmacological interventions for pain relief during orthodontic treatment

Aoife B Monk[1], Jayne E Harrison[1], Helen V Worthington[2], Annabel Teague[3]

[1]Orthodontic Department, Liverpool University Dental Hospital, Liverpool, UK. [2]Cochrane Oral Health, Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. [3]Orthodontic Department, University Hospital Waterford, Waterford, Ireland

Contact address: Jayne E Harrison, Orthodontic Department, Liverpool University Dental Hospital, Pembroke Place, Liverpool, L3 5PS, UK. jayne.harrison@rlbuht.nhs.uk, jeharrison@hotmail.co.uk.

Editorial group: Cochrane Oral Health Group
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2017.

Citation: Monk AB, Harrison JE, Worthington HV, Teague A. Pharmacological interventions for pain relief during orthodontic treatment. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD003976. DOI: 10.1002/14651858.CD003976.pub2.

ABSTRACT

Background

Pain is a common side effect of orthodontic treatment. It increases in proportion to the amount of force applied to the teeth, and the type of orthodontic appliance used can affect the intensity of the pain. Pain during orthodontic treatment has been shown to be the most common reason for people wanting to discontinue treatment, and has been ranked as the worst aspect of treatment. Although pharmacological methods of pain relief have been investigated, there remains some uncertainty among orthodontists about which painkillers are most suitable and whether pre-emptive analgesia is beneficial. We conducted this Cochrane Review to assess and summarize the international evidence relating to the effectiveness of analgesics for preventing this unwanted side effect associated with orthodontic treatment.

Objectives

The objectives of this review are to determine:

- the effectiveness of drug interventions for pain relief during orthodontic treatment; and
- whether there is a difference in the analgesic effect provided by different types, forms and doses of analgesia taken during orthodontic treatment.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: the Cochrane Oral Health Trials Register (to 19 June 2017), the Cochrane Central Register of Controlled Trials (CENTRAL;the Cochrane Library 2016, Issue 7), MEDLINE Ovid (1946 to 19 June 2017), Embase Ovid (1980 to 19 June 2017) and CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 19 June 2017). The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched on the 19 June 2017 for ongoing studies. We placed no restrictions on language or date of publication when searching the electronic databases.

Selection criteria

We included randomized controlled trials (RCTs) relating to pain control during orthodontic treatment. Pain could be measured on a visual analogue scale (VAS), numerical rating scale (NRS) or categorical scale.

Data collection and analysis

Two review authors independently screened the search results, agreed the studies to be included and extracted information from the included studies regarding methods, participants, interventions, outcomes, harms and results. We planned to resolve any discrepancies or disagreements through discussion. We used the Cochrane 'Risk of bias' tool to assess the risk of bias in the studies.

Main results

We identified 32 relevant RCTs, which included 3110 participants aged 9 to 34 years, 2348 of whom we were able to include in our analyses. Seventeen of the studies had more than two arms. We were able to use data from 12 trials in meta-analyses that compared analgesics versus control (no treatment or a placebo); nine that compared non-steroidal anti-inflammatories (NSAIDs) versus paracetamol; and two that compared pre-emptive versus post-treatment ibuprofen for pain control following orthodontic treatment. One study provided data for the comparison of NSAIDs versus local anaesthetic.

We found moderate-quality evidence that analgesics effectively reduced pain following orthodontic treatment when compared to no treatment or a placebo at 2 hours (mean difference (MD) -11.66 mm on a 0 to 100 mm VAS, 95% confidence interval (CI) -16.15 to -7.17; 10 studies, 685 participants), 6 hours (MD -24.27 mm on a VAS, 95% CI -31.44 to -17.11; 9 studies, 535 participants) and 24 hours (MD -21.19 mm on a VAS, 95% CI -28.31 to -14.06; 12 studies, 1012 participants).

We did not find any evidence of a difference in efficacy between NSAID and paracetamol at 2, 6 or 24 hours (at 24 hours: MD -0.51, 95% CI -8.93 to 7.92; 9 studies, 734 participants; low-quality evidence).

Very low-quality evidence suggested pre-emptive ibuprofen gave better pain relief at 2 hours than ibuprofen taken post treatment (MD -11.30, 95% CI -16.27 to -6.33; one study, 41 participants), however, the difference was no longer significant at 6 or 24 hours.

A single study of 48 participants compared topical NSAIDs versus local anaesthetic and showed no evidence of a difference in the effectiveness of the interventions (very low-quality evidence).

Use of rescue analgesia was poorly reported. The very low-quality evidence did not show evidence of a difference between participants taking ibuprofen and participants taking paracetamol (relative risk (RR) 1.5, 95% CI 0.6 to 3.6). Nor did we find evidence of a difference between groups in likelihood of requiring rescue analgesia when ibuprofen was taken pre-emptively compared to after treatment (RR 0.8, 95% CI 0.3 to 1.9).

Adverse effects were identified in one study, with one participant developing a rash that required treatment with antihistamines. This was provisionally diagnosed as a hypersensitivity to paracetamol.

Authors' conclusions

Analgesics are more effective at reducing pain following orthodontic treatment than placebo or no treatment. Low-quality evidence did not show a difference in effectiveness between systemic NSAIDs compared with paracetamol, or topical NSAIDs compared with local anaesthetic. More high-quality research is needed to investigate these comparisons, and to evaluate pre-emptive versus post-treatment administration of analgesics.

PLAIN LANGUAGE SUMMARY

Painkillers for relieving pain caused by orthodontic treatment

Review question

Do painkillers, taken before or after orthodontic treatment, help relieve pain? If so, which painkillers work best?

Background

Pain is a common side effect of orthodontic treatment. The pain resulting from orthodontic treatment may differ depending on the amount of force applied and the type of braces used. It may also change over the first few days following treatment. Pain has been ranked as the worst aspect of treatment and is the most common reason for people wanting to discontinue orthodontic treatment. Painkillers, swallowed or applied directly to the sore areas of the mouth following treatment, are thought to relieve the pain, making brace treatment more comfortable and acceptable. These painkillers are often cheap, readily available, easy to use and do not cause serious side effects.

Study characteristics

Authors working with Cochrane Oral Health carried out a review of existing studies and the evidence is current up to 19 June 2017. This review includes 32 studies published from 1993 to 2016 in which 3110 participants aged 9 to 34 years (2348 of whom were included in the analyses) were randomly allocated to groups to receive:

1) painkillers versus no treatment,

2) painkillers versus a placebo (pretend or 'dummy' medicine),

3) one painkiller versus a different painkiller, or

4) a painkiller taken at different time intervals.

The severity of pain experienced by the study participants was compared. Nearly all the evidence was from adults who received oral painkillers versus no treatment, or one oral painkiller versus another oral painkiller. This evidence fell into two main groups:

1) adults receiving paracetamol; or

2) adults receiving non-steroidal anti-inflammatory drugs (NSAIDs).

A small amount of evidence also investigated the effect of local anaesthetic and opioids (tramadol).

Key results

Analgesic versus placebo or no treatment

We found evidence that paracetamol, NSAIDs and local anaesthetic were effective at reducing pain intensity at 2 hours, 6 hours and 24 hours following orthodontic treatment when compared with either a placebo or no treatment group.

NSAID versus paracetamol

We found no clear evidence of a difference between the effect of ibuprofen and paracetamol for reducing pain intensity at 2 hours, 6 hours or 24 hours following either the placement of separators (between teeth) or placement of an initial aligning archwire.

Pre-emptive NSAID versus post-treatment NSAID

We found some very low-quality evidence that ibuprofen taken 1 hour prior to separator placement significantly reduces pain intensity 2 hours afterwards when compared to ibuprofen taken post-treatment. However, at 6 hours and 24 hours, we detected no clear difference.

NSAID versus local anaesthetic

There was no evidence of a difference between the interventions.

Quality of the evidence

The evidence available for the main outcome of pain relief is of moderate to low quality, whilst the quality of the rest of the evidence was very low. We judged only one study to be at low risk of bias.

Summary of findings for the main comparison. Analgesic compared to control (placebo or no treatment) for pain relief during orthodontic treatment

Analgesic compared to control (placebo or no treatment) for pain relief during orthodontic treatment

Population: people undergoing orthodontic treatment

Setting: any dental setting

Intervention: analgesic
Comparison: control (placebo or no treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with analgesic				
Pain assessed with VAS (0 to 100 mm where 0 = no pain) Follow-up: mean 2 hours	Mean pain ranged from 10 mm to 73 mm on a VAS	MD 11.66 mm lower (16.15 mm to 7.17 mm lower)	-	685 (10 RCTs)	⊕⊕⊕⊖ **moderate**[1]	Effect estimates for 6 and 24 hours were larger. • 6 hours -24.27 mm (95% CI -31.44 to -17.11) • 24 hours -21.19 mm (95% CI -28.31 to -14.06)
Rescue analgesia	Not reported					
Adverse events	Not reported					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **MD:** mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for risk of bias as four of the studies were at high risk of bias and the remaining six were at unclear risk of bias. Not downgraded for heterogeneity as effects were all in same direction.

Summary of findings 2. NSAID compared to paracetamol for pain relief during orthodontic treatment

NSAID compared to paracetamol for pain relief during orthodontic treatment

Population: people undergoing orthodontic treatment
Setting: any dental setting
Intervention: NSAID
Comparison: paracetamol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with paracetamol	Risk with ibuprofen				
Pain assessed with VAS (0 to 100 mm where 0 = no pain) Follow-up: mean 2 hours	Mean pain ranged from 8.8 mm to 32.4 mm on a VAS	MD 2.92 mm lower on the VAS (8.48 mm lower to 2.65 mm higher)	-	664 (7 RCTs)	⊕⊕⊖⊖ **low**[1, 2]	Findings at 6 and 24 hours were similar and not statistically significant
Rescue analgesia	91 per 1000	136 per 1000 (55 to 327)	RR 1.5 (0.6 to 3.6)	159 (1 RCT)	⊕⊖⊖⊖ **very low**[3]	Study does not report any additional information regarding class, dose or timing of rescue analgesics taken
Adverse events	In one study, one participant (< 1%) in the paracetamol group experienced drug hypersensitivity involving a "red, blotchy and itchy rash", which resolved without treatment within 1 week.		-	(1 RCT)	⊕⊖⊖⊖ **very low**[3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **NSAID:** non-steroidal anti-inflammatory; **RR:** risk ratio; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for risk of bias: three studies at high risk of bias and two at unknown risk of bias; only one study of low risk of bias.
[2] Downgraded one level for imprecision of estimate.
[3] Downgraded as only one trial reported on this.

Summary of findings 3. Pre-emptive ibuprofen compared to ibuprofen post-treatment for pain relief during orthodontic treatment

Pre-emptive ibuprofen compared to ibuprofen post-treatment for pain relief during orthodontic treatment

Population: pain relief during orthodontic treatment
Setting: dental hospital

Intervention: ibuprofen pre-emptively
Comparison: ibuprofen post-treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ibuprofen post-treatment	Risk with ibuprofen pre-emptively				
Pain assessed with VAS (0 to 100 mm where 0 = no pain) Follow-up: mean 2 hours	Mean pain ranged from 19.1 mm to 20.5 mm	MD 11.30 mm lower (16.27 mm lower to 6.33 mm lower)	-	41 (1 RCT)	⊕⊖⊖⊖ **very low** [1, 2, 3]	Effect no longer seen at 6 or 24 hours (2 studies with 69 participants)
Rescue analgesia	316 per 1000	253 per 1000 (95 to 600)	RR 0.8 (0.3 to 1.9)	41 (1 RCT)	-	
Adverse events	Not reported					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level for risk of bias: high risk of attrition bias.
[2] Downgraded one level as single small study.
[3] Downgraded one level for imprecision: the confidence interval is wide and crosses no difference.
[4] Downgraded one level for inconsistency: significant heterogeneity.

Summary of findings 4. NSAID compared to local anaesthetic for pain relief during orthodontic treatment

NSAID compared to local anaesthetic for pain relief during orthodontic treatment

Patient or population: pain relief during orthodontic treatment
Setting: any dental setting
Intervention: NSAID
Comparison: local anaesthetic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with local anaesthetic	Risk with NSAID				
Pain assessed with VAS (0 to 100 mm where 0 = no pain) Follow-up: mean 2 hours	Mean pain was 51 mm	MD 13 mm higher (3.45 mm lower to 29.45 mm higher)	-	48 (1 RCT)	⊕⊖⊖⊖ **very low**[1, 2]	Nor was a difference between groups seen at 6 or 24 hours
Rescue analgesia	Not measured					
Adverse events	Not measured					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **NSAID:** non-steroidal anti-inflammatory; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels as single, small study at unclear risk of bias
[2] Downgraded one level for imprecision: the confidence interval crosses the line of no difference.

BACKGROUND

Pain relief in dentistry has been fairly well studied in the literature, but the management of pain associated with orthodontic treatment is less well understood. As clinicians we are often asked whether it will be necessary for patients to take painkillers during orthodontic treatment, and, if so, which are likely to be the most effective. Some studies have shown that pretreatment doses of non-steroidal anti-inflammatory drugs (NSAIDs) may help to reduce the amount of pain experienced immediately after treatment (Steen-Law 2000). However, there is some uncertainty among orthodontists regarding which painkillers are most suitable and whether pre-emptive analgesia is beneficial.

We investigated relief of pain arising during and after the placement of orthodontic appliances (such as separators, fixed braces, removable braces and headgear) and during routine treatment to adjust appliances and replace archwires. We did not include pain relief following tooth extraction or surgical procedures associated with orthodontic treatment.

Description of the condition

Orthodontics is the area of dentistry concerned with the growth of the jaws and face, development of dentition and relationship between dentition, jaws and face. It also involves treatment of teeth and jaws when they are irregular in their alignment, morphology or function. Typically, orthodontic treatment is carried out to improve the functioning and appearance of the teeth. This may involve moving teeth by applying a force via:

- fixed appliances (braces that are attached to the teeth for the duration of the treatment);
- removable appliances (braces that are normally worn full-time during treatment but can be removed for cleaning); and/or
- functional appliances (removable or fixed braces that aim to move the teeth and modify the direction of growth of the jaws to induce an orthopaedic change) (British Orthodontic Society).

Orthodontic treatment may also involve: extraction of teeth in order to provide space for other teeth to be aligned; surgery to expose unerupted teeth in an attempt to guide them into alignment; and, occasionally, jaw surgery to correct the underlying position of the jaws. Most people undergoing orthodontic treatment are children or adolescents, although an increasing number of adults are seeking treatment. (Buttke 1999).

Treatment typically begins with construction and placement of an orthodontic appliance (whether fixed, removable or functional) over two visits of 30 to 45 minutes each. Routine adjustments are then carried out every four to six weeks over the course of treatment, which normally lasts approximately 12 to 24 months. Following treatment, removal of fixed appliances takes approximately 30 to 45 minutes and retainers are then provided to maintain teeth in their newly aligned position.

Pain resulting from orthodontic treatment increases in proportion to the amount of force applied to the teeth. Different types of orthodontic appliances affect the intensity of the pain. Fixed orthodontic appliances seem to cause more pain than removable braces, or functional appliances, which are used to help modify facial growth (Sergl 1998). Acute pain is experienced during or immediately after placement of separators. People may also experience pain for one to two days following each four- to six-weekly adjustment appointment. Pain may also be experienced acutely or continuously between adjustment visits. It is thought that the pain associated with orthodontic treatment is related to a reduction in the blood supply to the fibres that attach the tooth to the surrounding bone. This happens when a force is applied to the tooth via a brace. The reduction in blood supply causes inflammation and the release of several chemicals that greatly increase the transmission of painful stimuli (Proffit 2000).

Pain during orthodontic treatment has been shown to be the most common reason for patients wanting to discontinue treatment, and was ranked as the worst aspect of the treatment (Oliver 1985). Jones 1992 found that patients who underwent both premolar extractions and orthodontic tooth movement experienced more pain 24 hours after initial arch wire placement than 24 hours after tooth extraction. When separators (small rubber bands that make space for metal orthodontic band attachments around the back teeth) are placed between teeth, pain gradually increases, peaking the day after placement, and then decreases. By seven days, pain levels have decreased to the same level as at two hours following treatment (Bernhardt 2001). The amount of pain experienced depends upon the type of tooth movement occurring (tipping or bodily movement), and, in particular, the pain threshold of the individual. It is likely that patients only require drug-assisted pain relief for two to three days out of every four to six weeks, so the long-term implications of drug treatment are probably small.

Description of the intervention

Pharmacological management of pain involves the use of analgesics applied locally or systemically. These analgesics fall into four main categories:

- opioids;
- non-steroidal anti-inflammatory drugs (NSAIDs);
- paracetamol;
- local anaesthetic.

The first three of these analgesics are commonly taken, systemically, within two hours of the orthodontic visit and can then be re-administered over a period of time until pain resolves. Local, topical NSAIDs and anaesthetic are also commonly used for the relief of traumatic ulceration caused to the oral mucosa as a result of irritation by orthodontic appliances. As a result, these topical forms of analgesia are more commonly used to relieve the symptoms of pain, rather than as preventive measures.

Analgesics for the relief of orthodontic pain are readily available, have a low cost, are easily administered and are generally harmless (in terms of a lack of side effects).

How the intervention might work

The mechanism of action for pain relief differs according to the analgesic being used.

Opioids

Opioids, which are also referred to as narcotics, include codeine sulphate, tramadol and morphine sulphate. They may be classified as agonistic, agonist-antagonistic or partial agonist depending on their specific mode of action but they act on large A- δ fibres in the dorsal horn of the spinal cord. They bind to G-protein-

coupled opiate receptors on inhibitory fibres, preventing stimulus of the gate and therefore prevent pain transmission to the brain (Pleuvry 1993). However, the specific mechanism of action differs slightly when considering tramadol. In addition to the mechanism described, tramadol can act to inhibit the reuptake of monamines, causing an analgesic effect, but limiting the osteoporotic changes seen with other opioids at a histological level. By acting in this non-opioid way, it has been hypothesised that the effect on the rate of orthodontic tooth movement will be less with tramadol than that experienced with other, traditional opioids; however, under experimental situations this has not been the case (Rashidpour 2012).

NSAIDs

Non-steroidal anti-inflammatory drugs are the most popular method of pain control used during orthodontic treatment (Krishnan 2007). These include drugs like ibuprofen and aspirin, which function by inhibiting the activity of the enzyme cyclooxygenase (COX), which modulates the transformation of prostaglandins from arachidonic acid in the cellular plasma membrane (De Carlos 2006). Prostaglandins are responsible for causing pain; inhibition of COX suppresses prostaglandin production and so reduces pain. However, prostaglandins, including PGE1 and PGE2, are important mediators of bone resorption, and it has been suggested that suppression of their activity with NSAIDs may affect the rate of orthodontic tooth movement (Krishnan 2006). Kehoe 1996 found a significant difference in the rate of tooth movement achieved with elastic separators in guinea pigs when comparing treatment with misoprostol (a prostaglandin analogue) or ibuprofen to a control group. However, the significance of this on a clinical level is negligible: there was a 1 mm average difference between intervention and control groups, and the doses used experimentally differed from those routinely used in practice.

Paracetamol

Paracetamol, known as acetaminophen in the USA, has been available in the UK as an analgesic on prescription since 1956, and over-the-counter since 1963 (Shenoy 2013). The primary mechanism of action of paracetamol is similar to that of NSAIDs. It is believed to inhibit COX, with a predominant effect on COX-2; however, unlike NSAIDs, it is thought to act at a central nervous system level rather than acting across cell membranes (Karthi 2012). As a result, inhibition of prostaglandins is minimal and therefore it is thought that its use has no effect on the rate of tooth movement. However, although useful as an antipyretic and analgesic, it lacks an anti-inflammatory action and is therefore often used in combination with NSAIDs for management of pain.

Local anaesthetic

It has been suggested that local anaesthetics, in the form of topical gels, might be safer alternatives to systemic analgesics as a method of pain management before or during orthodontic procedures (Shenoy 2013). Gels provide localised delivery of the anaesthetic into the gingival crevice, and because of this, their use has been proposed for local orthodontic procedures such as band placement, archwire ligation and bracket removal (Keim 2005).

Why it is important to do this review

There is currently a lack of evidence regarding the best pharmacological intervention for pain relief during orthodontic pain. The recently published Cochrane Review exploring the evidence for non-pharmacological management of orthodontic pain found low-quality evidence suggesting that laser irradiation may help reduce pain during orthodontic treatment and for up to seven days following treatment, however, overall the results were inconclusive, suggesting further prospective research is required (Fleming 2016). We hope that this review will help produce evidence-based recommendations for managing orthodontic pain and can be used alongside the Fleming 2016 review.

OBJECTIVES

The objectives of this review are to determine:

- the effectiveness of drug interventions for pain relief during orthodontic treatment; and
- whether there is a difference in the analgesic effect provided by different types, forms and doses of analgesia taken during orthodontic treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials (RCTs) of orthodontic treatments where a pharmacological intervention for pain relief was compared to a placebo, or no intervention, or another pharmacological intervention. We excluded split-mouth studies, as we consider them to be an inappropriate study design.

If an RCT compared pharmacological and non-pharmacological interventions to a placebo or no intervention, we included the study, but used only the data for the pharmacological intervention compared to placebo or no intervention.

Types of participants

Inclusion criteria

We included trials that recruited participants of any age who were receiving any type of orthodontic treatment.

Exclusion criteria

We excluded trials that recruited participants who had undergone surgical interventions, placement of temporary anchorage devices or dental extractions in combination with orthodontic treatment.

Types of interventions

Active interventions

We assessed the following active interventions to alleviate pain:

- opioid analgesics;
- any non-steroidal anti-inflammatory drug (NSAID);
- paracetamol;
- local anaesthetic.

We evaluated any intervention taken by any route, dose, form or combination, at any time during treatment. Interventions could be

given at any time following treatment, or up to two hours before treatment.

Controls

Interventions could be compared to each other, a placebo or the same intervention at a different dose, intensity or time interval.

Types of outcome measures

Primary outcomes

- Participant-reported pain intensity, or relief, measured on a visual analogue scale (VAS), numerical rating scale (NRS) or any categorical scale

Secondary outcomes

- Rescue analgesia (alternative pain relief taken or prescribed, including dose and time, following last orthodontic treatment)
- Adverse effects (harms) of pain treatment, for example, total gastrointestinal side effects. We recorded and reported harms in descriptive terms.
- Quality of life or participant satisfaction
- Time off school or work
- Failure to complete orthodontic treatment due to the pain experienced

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomized controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions:

- the Cochrane Oral Health Trials Register (searched 19 June 2017) (Appendix 1);
- Cochrane Central Register of Controlled Trials in the Cochrane Library (CENTRAL; 2016, Issue 7; searched 19 June 2017) (Appendix 2);
- MEDLINE Ovid (1946 to 19 June 2017) (Appendix 3);
- Embase Ovid (1980 to 19 June 2017) (Appendix 4);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 19 June 2017) (Appendix 5).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

The following trial registries were searched for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 19 June 2017) (Appendix 6);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 19 June 2017) (Appendix 7).

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

We checked the bibliographies of the clinical trials identified for references to trials.

Language

We searched databases to include papers and abstracts published in all languages and every effort was made to translate non-English papers.

Unpublished studies

We contacted the first named authors of all trial reports in an attempt to identify unpublished studies and to obtain any further information about the trials.

Data collection and analysis

Selection of studies

Two review authors (Aoife Monk (AM) and Jayne Harrison (JH) or Annabel Teague (AT)) assessed the titles and abstracts (when available) of all reports that were identified by the search strategy. This was carried out independently and in duplicate. The review authors were not blinded to trial author(s), institution or site of publication.

When we found insufficient information in the title and abstract to make a clear decision to exclude, or when there was disagreement between the review authors about eligibility, we obtained the full text of the paper. These full texts were then assessed independently and in duplicate by two review authors (AM and JH or AT) to establish whether or not the studies met the inclusion criteria.

We resolved disagreements through discussion between AM and JH. We consulted a third review author if we could not resolve disagreements. We kept a record of all decisions made about the potentially eligible studies. We obtained full texts for all studies that were ultimately included in this review.

Data extraction and management

Two review authors (AM and JH or AT) carried out data extraction independently and in duplicate, using a predesigned and piloted data collection form, which was stored electronically. We contacted study authors for clarification of missing data where necessary and feasible. We resolved any disagreements through discussion, consulting a third review author to achieve a consensus where necessary. We recorded the following key data for each included study in the Characteristics of included studies tables.

- Trial design, source of participants, method of recruitment, recruitment period and study duration
- Inclusion and exclusion criteria; age, gender and ethnicity of participants; number selected, excluded, randomized and analyzed
- Detailed description of the invention and comparison including time, dose and route. We noted information relating to compliance, where available.
- Details of the outcomes reported, including method of assessment and time(s) assessed

- Details of sample size calculations, adverse effects, funding sources, declarations or conflicts of interest

The primary outcome was the relief of pain. We recorded adverse events or harms (e.g. total gastrointestinal side effects) narratively where these were reported.

We extracted all outcome data. We then grouped data into the time points that we felt were the most clinically relevant: that is, 2 hours, 6 hours and 24 hours following the orthodontic procedure (placement or adjustment of appliance). If outcome data were reported at other time points, we considered examining those as well.

Assessment of risk of bias in included studies

Independently and in duplicate, two review authors (AM and JH) undertook an assessment of the risk of bias in the studies as a part of the data extraction process. We used the Cochrane domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Inteventions* (Higgins 2008), which investigates seven domains:

- method of sequence generation;
- method of allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

We assessed sequence generation, allocation concealment and selective outcome reporting for the study as a whole. We assessed blinding and incomplete outcome data on the level of the study and for each outcome as appropriate. We assigned each domain a risk of bias judgement of high, low or unclear risk of bias. We also assessed the overall risk of bias as:

- low risk of bias (plausible bias that is unlikely to alter the results seriously), if all domains were at a low risk of bias;
- high risk of bias (plausible bias that seriously weakens confidence in the results), if one or more domains were at a high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results), if one or more domains were at an unclear risk of bias.

We presented our 'Risk of bias' judgements in tables and in two summary diagrams (Figure 1; Figure 2).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

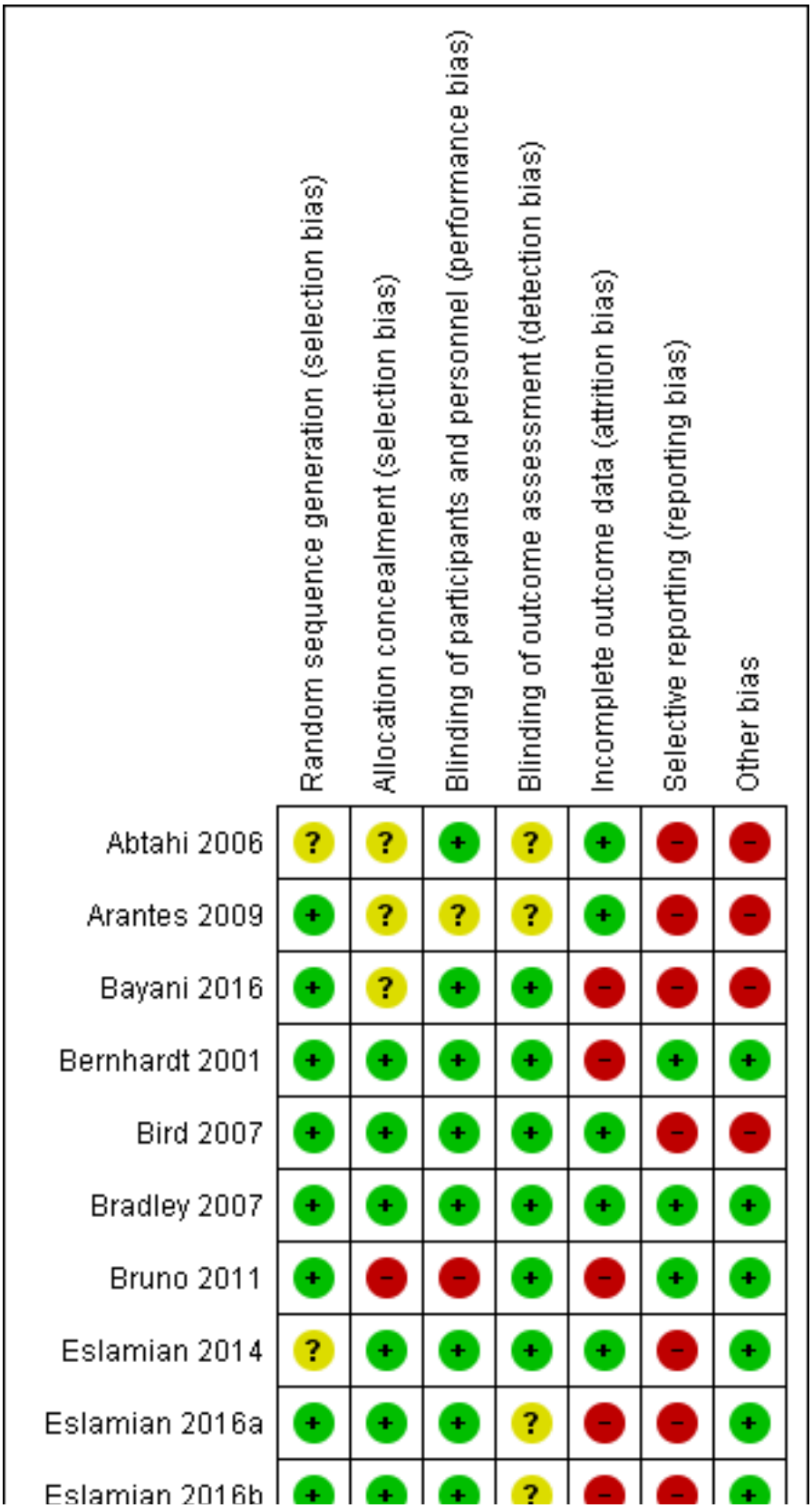


Figure 1. (Continued)

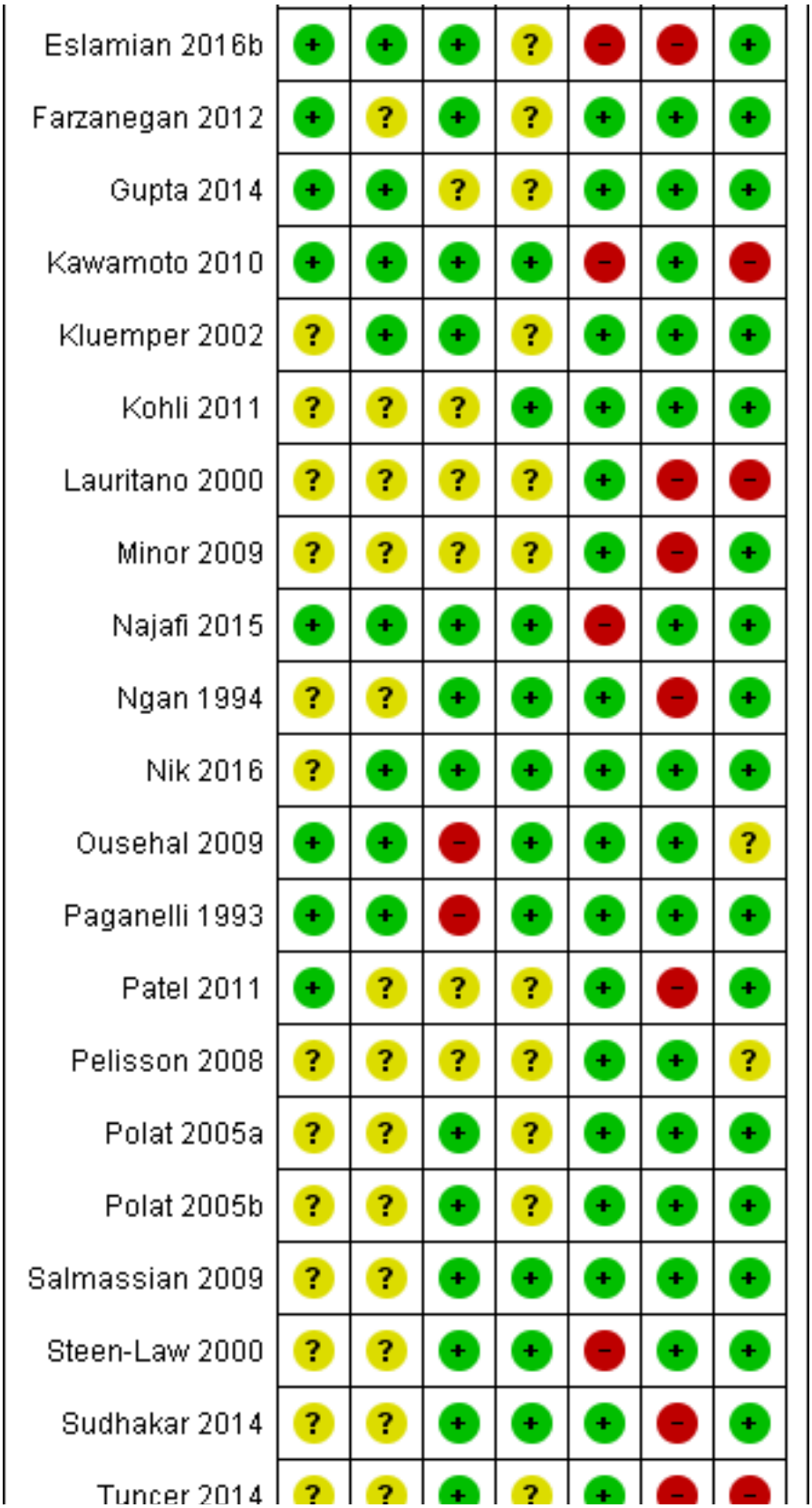


Figure 1. (Continued)

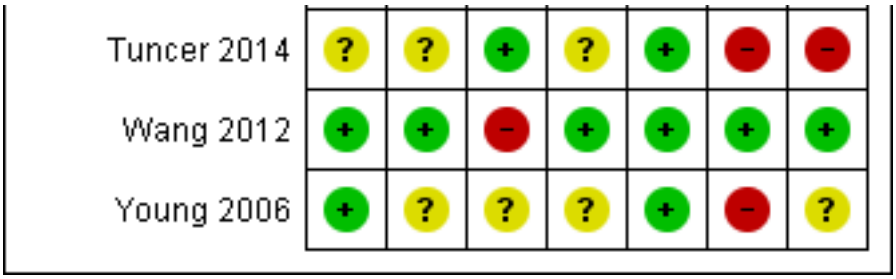
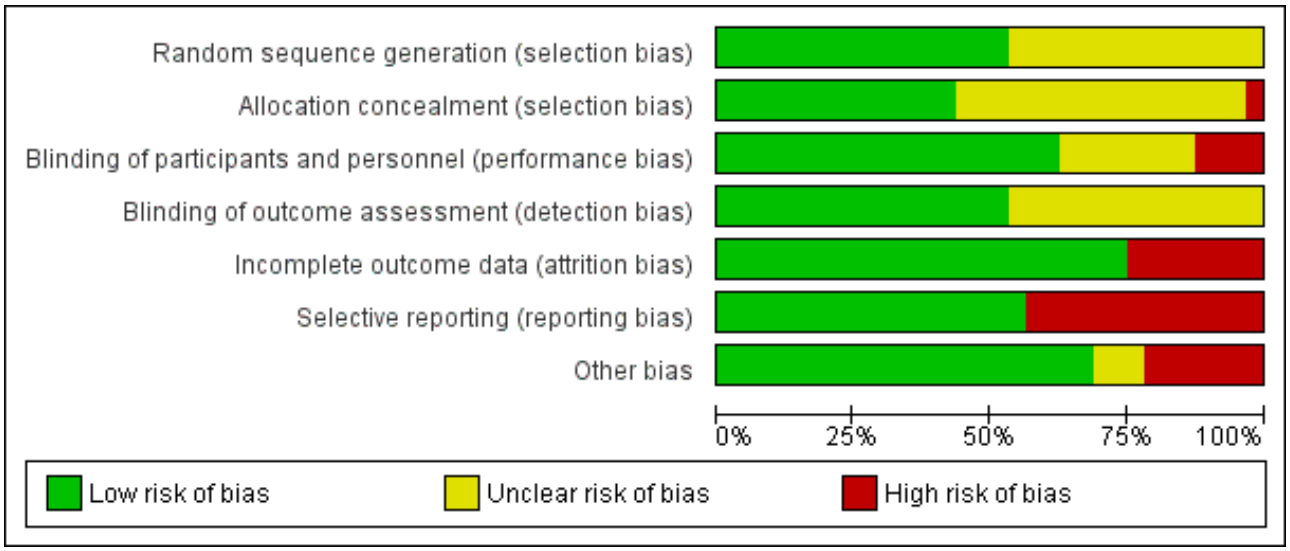


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Measures of treatment effect

For continuous outcomes (e.g. pain measured on a VAS) where studies used the same scale, we used the mean values and standard deviations (SDs) reported in the studies in order to express the estimate of effect as mean difference (MD) with 95% confidence interval (CI). If different scales had been used to assess an outcome, we would have considered expressing the treatment effect as a standardised mean difference (SMD) with 95% CI. We calculated risk ratios (RR) and corresponding 95% CI for dichotomous data where possible.

For trials with multiple arms, the sample sizes of any shared groups were split for purposes of independent comparison.

Unit of analysis issues

The participant was the unit of analysis.

The treatment effects from crossover trials were combined with those from parallel group trials where appropriate. We used data from the first round of the trial only and treated it as a parallel trial.

Dealing with missing data

We attempted to contact the author(s) of all included studies, where feasible, for clarification, missing data, and details of any outcomes that may have been measured but not reported. We were unable to use the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing SDs due to unclear or unavailable data (Higgins 2008). We did not use any other statistical methods, or perform any further imputation to account for missing data.

Assessment of heterogeneity

When a sufficient number of studies were included in any meta-analyses, we assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes. We also assessed heterogeneity statistically using a Chi^2 test, where a P value of less than 0.1 indicated statistically significant heterogeneity. We quantified heterogeneity using the I^2 statistic. A guide to interpretation of the I^2 statistic given in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* reads as follows (Higgins 2008):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

Assessment of reporting biases

If we had included at least 10 studies in a meta-analysis, we would have assessed publication bias by testing for funnel plot asymmetry, as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). If asymmetry had been identified, we would have examined possible causes. It was not possible to assess publication bias in this way because, although we had a sufficient number of studies in our meta-analyses for the primary outcome, they were split into subgroups of less than 10 studies.

Data synthesis

We only carried out meta-analyses where there were studies of similar comparisons reporting the same outcomes. We combined MDs for continuous data, and would have combined RRs for dichotomous data, had any been reported. Our general approach was to use a random-effects model. With this approach, the CIs for the average intervention effect were wider than those that would have been obtained using a fixed-effect approach, leading to a more conservative interpretation. We used an additional table to report the results from studies that were not suitable for inclusion in a meta-analysis, including data analyzed by intervention.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to type of pharmacological intervention and timing of intervention. We carried our further subgroup analysis according to type of orthodontic intervention where possible.

Sensitivity analysis

As all studies except Bruno 2011 were at high risk of both performance and detection bias, it was not possible to test the robustness of our results by performing sensitivity analyses based on excluding studies judged to be at unclear or high risk of bias from the analyses. If any meta-analyses had included several small studies and a single very large study, we would have undertaken a sensitivity analysis to compare the effect estimates from both random-effects and fixed-effect models. If these had been different, we would have reported on both analyses as part of the results section, and we would have considered possible interpretations.

RESULTS

Description of studies

Results of the search

The electronic database search identified 721 references to studies and four additional articles were identified from additional sources (authors of this review); 360 of the records were duplicates, leaving 361 references. We discarded 315 of these as a result of screening the titles and abstracts. We obtained full-text articles of the remaining 46 articles, where possible, and excluded nine of the references at this stage. The remaining 37 references appeared to meet our inclusion criteria and we were able to include 33 references relating to 32 studies. We made attempts to contact the authors of the four remaining studies for further information. One of the studies is ongoing and the other three studies are awaiting classification. This selection process is presented as a flow chart in Figure 3.

Figure 3. Study flow diagram

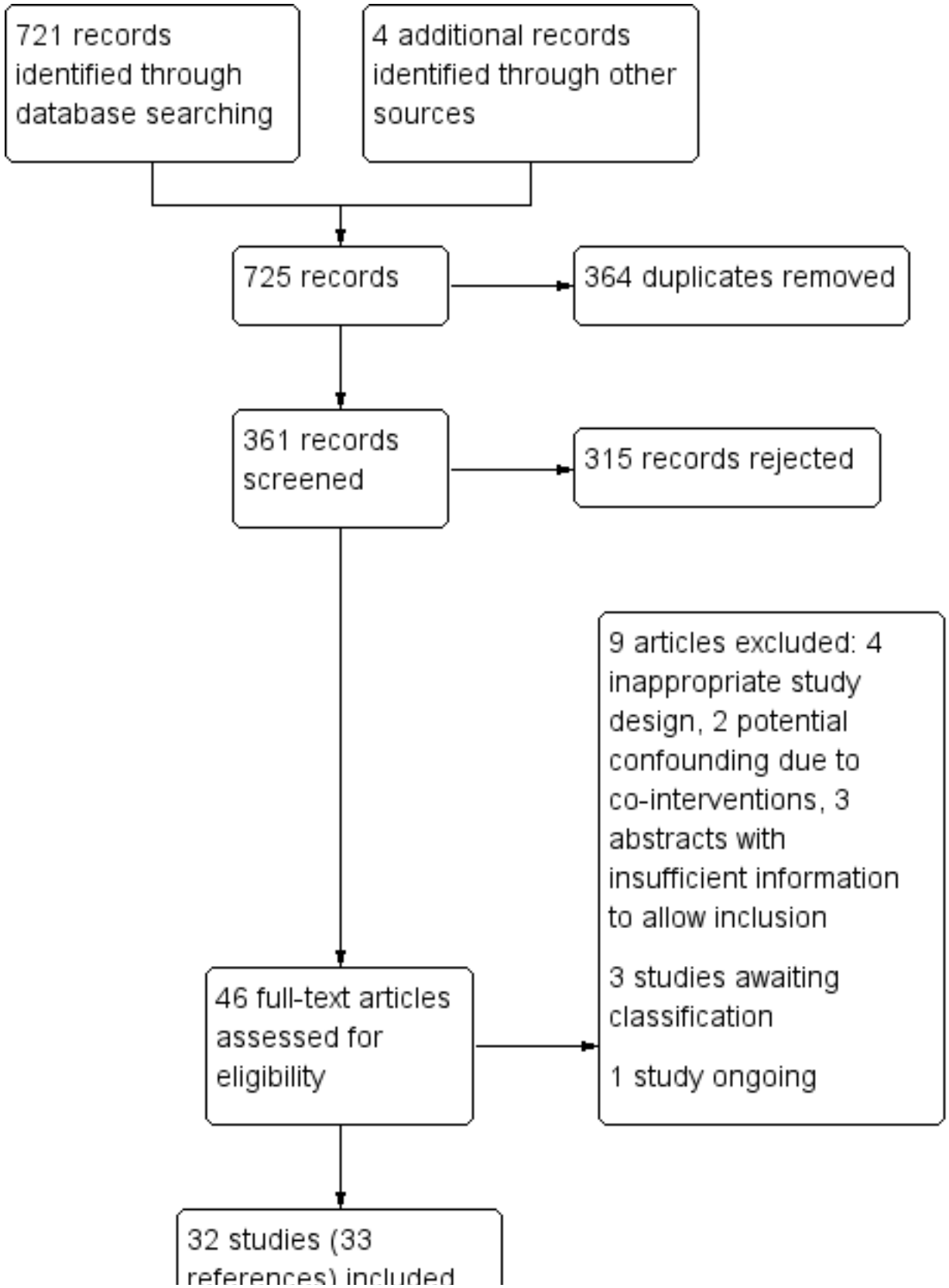
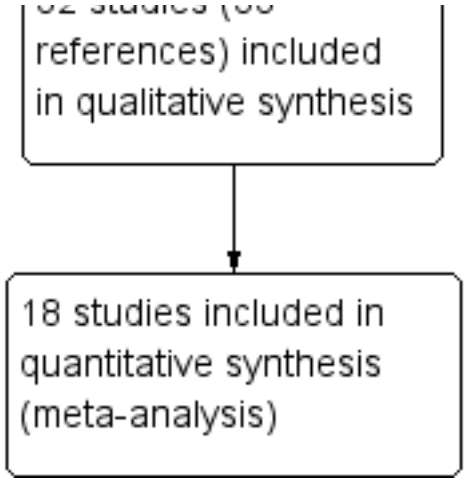


Figure 3. (Continued)



Included studies

We included 32 studies, which randomized a total of 3110 participants and analyzed 2348 participants (see Characteristics of included studies tables).

Characteristics of the trial designs and settings

Design

Twenty-eight studies were of parallel design, and the remaining four studies used a cross-over design (Arantes 2009; Eslamian 2014; Eslamian 2016a; Eslamian 2016b).

Studies had between two and six arms:

- five studies had two arms (Bird 2007; Bradley 2007; Kluemper 2002; Lauritano 2000; Ousehal 2009);
- 20 studies had three arms, but five of these studies had one arm excluded from this review because it involved a non-pharmacological intervention (Wang 2012), or non-comparable data (that is, mean and SD pain data were not available) (Bernhardt 2001; Minor 2009; Steen-Law 2000; Young 2006);
- two studies had four arms (Patel 2011; Sudhakar 2014);
- two studies had five arms; however, both had three arms excluded from this review because they involved data from non-pharmacological interventions (Bayani 2016; Farzanegan 2012);
- three studies had six arms (Pelisson 2008; Polat 2005a; Polat 2005b); however, one arm from Pelisson 2008 was excluded from this review because it involved non-comparable data.

Setting

Ten studies were conducted in the USA (Bernhardt 2001; Bird 2007; Kawamoto 2010; Kluemper 2002; Minor 2009; Ngan 1994; Patel 2011; Salmassian 2009; Steen-Law 2000; Young 2006); eight in Iran (Abtahi 2006; Bayani 2016; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Farzanegan 2012; Najafi 2015; Nik 2016); three in Turkey (Polat 2005a; Polat 2005b; Tuncer 2014); three in India (Gupta 2014; Kohli 2011; Sudhakar 2014); three in Brazil (Arantes 2009; Bruno 2011; Pelisson 2008); and one in each of China (Wang 2012), Italy (Paganelli 1993), Morocco (Ousehal 2009), Spain (Lauritano 2000), and the UK (Bradley 2007).

There were 25 single-centre studies, two studies with two centres (Eslamian 2014; Kawamoto 2010), and one study with three centres (Bradley 2007). Five studies were unclear about how many centres were involved (Kluemper 2002; Polat 2005a; Polat 2005b; Tuncer 2014; Young 2006).

Funding

Four studies reported their funding source (Arantes 2009; Bradley 2007; Najafi 2015; Wang 2012), all of which were in the form of independent funding from government, charities or universities. The remaining 28 studies did not report any funding source.

Conflict of interest

Six studies declared that there were no conflicts of interest (Bruno 2011; Gupta 2014; Najafi 2015; Salmassian 2009; Sudhakar 2014; Wang 2012), while the other 26 did not mention conflicts of interest.

Characteristics of the participants

There were 3110 participants randomized to interventions (in the intervention groups relevant to this review), of which 2348 were included in the studies' analyses. Participant age ranged from 9 to 34 years. In general, there were comparable numbers of males and females in the studies, however, one study recruited only female participants (Farzanegan 2012), and nine studies reported large variation between male and female numbers at baseline (Abtahi 2006; Bradley 2007; Bruno 2011; Eslamian 2016b; Kawamoto 2010; Najafi 2015; Ousehal 2009; Tuncer 2014; Wang 2012).

Orthodontic intervention

In 14 studies, participants had separators placed (Abtahi 2006; Bernhardt 2001; Bird 2007; Bradley 2007; Bruno 2011; Kawamoto 2010; Kohli 2011; Minor 2009; Najafi 2015; Ngan 1994; Nik 2016; Patel 2011; Steen-Law 2000; Sudhakar 2014). In 12 studies, participants had placement of an initial aligning archwire (Bayani 2016; Farzanegan 2012; Gupta 2014; Lauritano 2000; Ousehal 2009; Pelisson 2008; Polat 2005a; Polat 2005b; Salmassian 2009; Tuncer 2014; Wang 2012; Young 2006). Five studies included participants who were in the middle of treatment (Arantes 2009; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Paganelli 1993). One study included participants who had only brackets placed, without placement of an archwire (Kluemper 2002).

Characteristics of the interventions and comparisons

Opioid

One study compared tramadol with a control group that received a placebo (Abtahi 2006). This study also compared ibuprofen with tramadol (Abtahi 2006).

Paracetamol

Eight studies compared paracetamol with a control group that received a placebo (Gupta 2014; Kawamoto 2010; Nik 2016; Patel 2011; Polat 2005a; Salmassian 2009; Sudhakar 2014; Tuncer 2014). Twelve studies compared NSAIDs with paracetamol (Bird 2007; Bradley 2007; Gupta 2014; Kawamoto 2010; Najafi 2015; Nik 2016; Ousehal 2009; Patel 2011; Polat 2005a; Salmassian 2009; Sudhakar 2014; Tuncer 2014). Eleven of these studies compared ibuprofen with paracetamol, either independently or in addition to other classes of NSAID (Bird 2007; Bradley 2007; Kawamoto 2010; Najafi 2015; Nik 2016; Ousehal 2009; Patel 2011; Polat 2005a; Salmassian 2009; Sudhakar 2014; Tuncer 2014). One study compared etoricoxib with paracetamol (Gupta 2014).

NSAIDs

Twenty-one studies compared NSAIDs with a control group (Abtahi 2006; Bayani 2016; Bruno 2011; Eslamian 2014; Eslamian 2016a; Farzanegan 2012; Gupta 2014; Kawamoto 2010; Kohli 2011; Minor 2009; Ngan 1994; Nik 2016; Paganelli 1993; Patel 2011; Pelisson 2008; Polat 2005a; Polat 2005b; Salmassian 2009; Sudhakar 2014; Tuncer 2014; Wang 2012). Sixteen of these studies compared ibuprofen to a control group, either independently or in addition to other classes of NSAID (Abtahi 2006; Bayani 2016; Farzanegan 2012; Kawamoto 2010; Kohli 2011; Minor 2009; Ngan 1994; Nik 2016; Patel 2011; Pelisson 2008; Polat 2005a; Polat 2005b; Salmassian 2009; Sudhakar 2014; Tuncer 2014; Wang 2012). Eight studies compared ibuprofen with another form of NSAID (Kohli 2011; Najafi 2015; Ngan 1994; Patel 2011; Pelisson 2008; Polat 2005a; Polat 2005b; Sudhakar 2014). Two studies compared ibuprofen taken pre-emptively with ibuprofen taken postoperatively (Bernhardt 2001; Steen-Law 2000). One study compared valdecoxib taken pre-emptively with valdecoxib taken postoperatively (Young 2006). One study compared tenoxicam taken pre-emptively with tenoxicam taken postoperatively (Arantes 2009). One study compared a topical NSAID (benzidamine hydrochloride) with another topical NSAID (ketoprofen lysinate) (Lauritano 2000).

Local anaesthetic

Four studies compared benzocaine local anaesthetic with a control. One of these studies had the benzocaine intervention in chewing gum form (Eslamian 2014), two had the benzocaine intervention in gel form (Eslamian 2016a; Eslamian 2016b), and one had the benzocaine intervention in wax form for the management of orthodontic related ulceration (Kluemper 2002). Two studies compared NSAIDs with local anaesthetic (Eslamian 2014; Eslamian 2016a).

Duration

The duration of treatment varied between studies, from one dose one hour before treatment to seven days of treatment.

Characteristics of the outcomes

Primary outcome

For the primary outcome of pain, we were interested in either pain relief or pain intensity, and also different levels of severity. All included studies measured pain intensity using a 100 mm visual analogue scale (VAS), reported in either centimetres or millimetres. For the purposes of this review, we analyzed VAS data relating to the primary outcome in millimetres. Therefore, for studies that recorded results in centimetres, we converted the data to millimetres. Most studies recorded this value on the basis of an overall summary of the participant's pain experience, however, some studies reported pain intensity for additional specified activities. Ten studies recorded pain intensity during chewing, biting, fitting front teeth together, and fitting posterior teeth together (Bayani 2016; Bernhardt 2001; Farzanegan 2012; Kohli 2011; Minor 2009; Ngan 1994; Pelisson 2008; Polat 2005a; Polat 2005b; Steen-Law 2000). Four studies recorded pain intensity during chewing, rest, and fitting posterior teeth together (Bird 2007; Kawamoto 2010; Najafi 2015; Sudhakar 2014), and one study recorded pain intensity during chewing, fitting front teeth together, and fitting back teeth together (Tuncer 2014). For the purposes of this review, we included only data for chewing in our analyses of these studies. One study also measured pain using a verbal descriptive scale (VDS) consisting of a group of words that described pain intensity. The participants were asked to mark the word that best described what they were feeling.

The studies recorded a total of 23 time points. These ranged from one hour pre-treatment to 30 days post-treatment. We analyzed data from 2 hours, 6 hours and 24 hours, as we felt these were the most important time points from a clinical perspective, in addition to being some of the time points reported most commonly across the studies. It was also evident from the data that the peak in pain intensity occurred at 24 hours, after which it rapidly reduced regardless of intervention and, therefore, we felt that analysing data beyond this point would provide little valuable information. As a result, data from Kluemper 2002; Lauritano 2000 and Paganelli 1993 did not contribute to the overall analyses due to variations in time points used to measure their primary outcome.

Although all studies reported mean VAS measurements for pain intensity in addition to standard deviation, a number of studies did not contribute data to the analyses because the data relating to the primary outcome were not presented clearly, lacked a standard deviation, or were presented in median and interquartile format, and attempts to contact the authors produced no response or no answers (Abtahi 2006; Arantes 2009; Bayani 2016; Bird 2007; Ngan 1994; Patel 2011; Sudhakar 2014; Young 2006). Data for these studies have been reported descriptively. We converted data presented in a standard error format appropriately to present standard deviation.

Secondary outcomes

Rescue analgesia

Use of rescue analgesia was reported in seven studies (Arantes 2009; Bernhardt 2001; Bradley 2007; Bruno 2011; Najafi 2015; Steen-Law 2000; Tuncer 2014). However, data relating to class and dose were not reported in any study, and timing was reported in only one study (Bradley 2007), although all studies stated that participants were asked to record this information on the VAS questionnaires.

Adverse events

Adverse events were reported in two studies (Abtahi 2006; Bradley 2007). We decided to report this outcome in narrative form.

Quality of life or participant satisfaction

Patient satisfaction was not reported for any study. The authors of one study reported quality of life assessed by the Short Form-36 Health Survey (SF-36) at baseline and 30 days, and the Self-Rating Anxiety Scale (SAS) at baseline and 30 days (Wang 2012). One study reported affective states assessed with the State and Trait Anxiety Inventory (STAI) and the Positive Affect Negative Affect Schedule (PANAS) (Minor 2009).

Time off school or work

No studies reported this outcome.

Failure to complete orthodontic treatment due to the pain experienced

No studies reported this outcome.

Excluded studies

We excluded nine studies from this review for the following reasons:

- confounding due to co-interventions and therefore not possible to attribute effect to specific analgesic (Ireland 2016; Murdock 2010);
- inappropriate study design (Al-Melh 2017; Eslamian 2013; Eslamian 2017a; Soheilifar 2016);
- abstract with insufficient information (Cherubini 2003; Ogata 1999; Parks 2001).

In addition, three studies had insufficient information in the trial registration record to allow inclusion and are therefore awaiting classification (Eslamian 2017b; Moradinejad 2014; Rooke 2012). One study is ongoing (Mohammed 2016). See Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

Risk of bias in included studies

Allocation

Random sequence generation

Seventeen studies described an adequate method of random sequence generation in the papers or in further information received via correspondence with the authors (Arantes 2009; Bayani 2016; Bernhardt 2001; Bird 2007; Bradley 2007, Bruno 2011; Eslamian 2016b; Eslamian 2016a; Farzanegan 2012; Gupta 2014; Kawamoto 2010; Najafi 2015; Ousehal 2009; Paganelli 1993; Patel 2011; Wang 2012; Young 2006). We assessed these 17 trials as being at low risk of bias for this domain. The remaining 15 studies simply stated that participants were randomized. Since their methods were not described, or remained unclear, we assessed them as being at unclear risk of bias for this domain.

Allocation concealment

Fourteen studies described an adequate method of allocation concealment in the papers or through further information received via correspondence with the authors (Bernhardt 2001; Bird 2007; Bradley 2007; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Gupta 2014; Kawamoto 2010; Kluemper 2002; Najafi 2015; Nik 2016; Ousehal 2009; Paganelli 1993; Wang 2012). Therefore, we assessed these 14 trials as being at low risk of bias for this domain. Seventeen of the remaining studies did not mention any methods used to conceal the random sequence, so we assessed them as being at unclear risk of bias. One trial author, in correspondence, stated that the allocation was not concealed in his study, so we assessed it as being at high risk of bias for this domain (Bruno 2011).

We assessed 11 studies as being at low risk of bias for both random sequence generation and allocation concealment, and, therefore, at overall low risk of selection bias (Bernhardt 2001; Bird 2007; Bradley 2007; Eslamian 2016b; Eslamian 2016a; Gupta 2014; Kawamoto 2010; Najafi 2015; Ousehal 2009; Paganelli 1993; Wang 2012).

Blinding

Blinding of participants and personnel (performance bias)

Twenty studies described adequate methods of blinding of participants and personnel, and, therefore, were assessed as being at low risk of bias for this domain (Abtahi 2006; Bayani 2016; Bernhardt 2001; Bird 2007; Bradley 2007; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Farzanegan 2012; Kawamoto 2010; Kluemper 2002; Najafi 2015; Ngan 1994; Nik 2016; Polat 2005a; Polat 2005b; Salmassian 2009; Steen-Law 2000; Sudhakar 2014; Tuncer 2014). It was not possible to blind participants to the type of intervention in four studies (Bruno 2011; Ousehal 2009; Paganelli 1993; Wang 2012). Therefore, we assessed these four studies as being at a high risk of performance bias. The remaining eight studies stated that blinding was achieved, but did not describe their methods, and so we assessed them as being at unclear risk of performance bias.

Blinding of outcome assessment (detection bias)

Seventeen studies described an adequate method of blinding of outcome assessment (Bayani 2016; Bernhardt 2001; Bird 2007; Bradley 2007; Bruno 2011; Eslamian 2014; Kawamoto 2010; Kohli 2011; Najafi 2015; Ngan 1994; Nik 2016; Ousehal 2009; Paganelli 1993; Salmassian 2009; Steen-Law 2000; Sudhakar 2014; Wang 2012). Therefore, we assessed them as being at low risk of detection bias. The remaining 15 studies stated that blinding was achieved, but did not describe their methods, so we assessed them as being at unclear risk of performance bias.

Incomplete outcome data

We assessed eight studies as being at high risk of attrition bias due to high numbers of dropouts (Bayani 2016; Bernhardt 2001; Bruno 2011; Eslamian 2016b; Eslamian 2016a; Kawamoto 2010; Najafi 2015; Steen-Law 2000). The remaining 24 studies had negligible, or no attrition, and, therefore, we assessed them as being at low risk of attrition bias.

Selective reporting

We assessed 13 studies as being at a high risk of selective reporting bias. Eleven of these studies did not report the outcomes appropriately and we were unable to use the data for pooling (Abtahi 2006; Arantes 2009; Bayani 2016; Bird 2007; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Ngan 1994; Patel 2011; Sudhakar 2014; Young 2006). One study did not report outcomes for all time points investigated (Lauritano 2000). Another did not report on the outcome of bite efficiency as measured with a modified mastication

performance index (Minor 2009). The remaining 19 studies reported appropriately on all outcomes, and, therefore, we assessed them as being at low risk of reporting bias.

Other potential sources of bias

We assessed six studies as being at high risk of other sources of bias. Four of these studies provided no baseline characteristics of groups, or sample sizes for the final numbers included in the analysis (Arantes 2009; Bayani 2016; Bird 2007; Lauritano 2000). There was an imbalance between numbers of males and females at baseline in two studies (Abtahi 2006; Tuncer 2014). Two further studies failed to report gender or age at baseline by study group, and we assessed these as being at unclear risk of bias (Ousehal 2009; Pelisson 2008; Young 2006). We did not consider the remaining 23 studies to have any other potential sources of bias, and, therefore, we assessed them as being at low risk of bias for this domain.

Overall risk of bias

We assessed only one study as being at low risk of bias overall (Bradley 2007). We assessed 10 studies as being at unclear risk of bias overall (Farzanegan 2012; Gupta 2014; Kluemper 2002; Kohli 2011; Nik 2016; Patel 2011; Pelisson 2008; Polat 2005a; Polat 2005b; Salmassian 2009). We assessed the remaining 21 studies as being at high risk of bias overall. This is summarised in Figure 1 and Figure 2.

Effects of interventions

See: **Summary of findings for the main comparison** Analgesic compared to control (placebo or no treatment) for pain relief during orthodontic treatment; **Summary of findings 2** NSAID compared to paracetamol for pain relief during orthodontic treatment; **Summary of findings 3** Pre-emptive ibuprofen compared to ibuprofen post-treatment for pain relief during orthodontic treatment; **Summary of findings 4** NSAID compared to local anaesthetic for pain relief during orthodontic treatment

Comparison 1: Analgesic versus control (placebo or no treatment)

Pain

We combined data from 10 studies (685 participants) that measured pain at two hours. Four of these studies were at a high risk of bias (Bruno 2011; Farzanegan 2012; Kawamoto 2010; Minor 2009); whilst the remaining six were at unclear risk of bias (Gupta 2014; Kohli 2011; Nik 2016; Pelisson 2008; Polat 2005a; Polat 2005b). All except Pelisson 2008 also provided data at six hours (535 participants).

These 10 studies measured pain at 24 hours, but Minor 2009 did not provide data. Three additional studies measured pain at 24 hours: one study had an unknown risk of bias (Salmassian 2009), and the other two studies were at a high risk of bias (Tuncer 2014; Wang 2012). This resulted in a total of 12 studies (1012 participants) being combined in a meta-analysis for pain at 24 hours.

The meta-analyses showed that analgesics reduced mean pain intensity during orthodontic treatment at:

- 2 hours (mean difference (MD) -11.66 mm, 95% confidence interval (CI) -16.15 to -7.17, P < 0.00001; 10 studies; Analysis 1.1);
- 6 hours (MD -24.27 mm, 95% CI -31.44 to -17.11, P < 0.001; 9 studies; Analysis 1.2); and
- 24 hours (MD -21.19 mm, 95% CI -28.31 to -14.06, P < 0.001; 12 studies; Analysis 1.3), when compared to a placebo or no-treatment control.

However, there was substantial heterogeneity at all three time points (I^2 statistic between 70% and 85%), which may be related in part to variations in orthodontic treatment method, or to different interventions at different doses. Data for all time points was deemed to provide evidence of moderate quality.

We were unable to use the data from 11 studies that also compared analgesics with control. The reported results for 10 of these studies (Abtahi 2006; Arantes 2009; Bayani 2016; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Ngan 1994; Patel 2011; Sudhakar 2014; Young 2006), plus extra narrative is given in Analysis 1.4. In general, these findings agreed with the meta-analyses presented above. Paganelli 1993 compared an NSAID mouthwash with placebo, but only reported data at baseline, three and seven days after separator placement, so did nor report pain at the time points of interest to this review.

Subgroup analysis and heterogeneity

We included two subgroups for paracetamol and NSAID in the pooled estimate for any analgesic versus control (placebo or no treatment) at each time point. There was no evidence of a difference between the subgroups.

Although no difference was found between the subgroups, the effect estimates for ibuprofen are given below as this is the most common analgesic:

- 2 hours (MD -16.10, 95% CI -17.63 to -10.99, P < 0.001; 8 studies, 265 participants)
- 6 hours (MD -22.96, 95% CI -35.42 to -10.49, P < 0.001; 7 studies, 227 participants)
- 24 hours (MD -17.95, 95% CI -28.64 to -7.27, P < 0.001; 10 studies, 588 participants)

There were insufficient trials comparing the same NSAID to make subgroup comparisons between them.

For each meta-analysis, there was substantial heterogeneity. This may have been due in part to the type of orthodontic intervention, which we explored in a subgroup analysis of pain following separator placement and pain following placement of an initial archwire.

For separator placement, paracetamol was more effective than a control at reducing pain at 2 and 6 hours, however, there was no difference at 24 hours. There was no heterogeneity at 2 or 6 hours (I^2 = 0%), however, there was considerable heterogeneity at 24 hours (I^2 = 65%) (Table 1).

For archwire placement, paracetamol was more effective than a control at reducing pain at 2, 6 and 24 hours. There was no heterogeneity at 2 hours (I^2 = 0%), and low heterogeneity - which may not be important - at 6 hours (I^2 = 6%), but there was considerable heterogeneity at 24 hours (I^2 = 85%) (Table 2).

For separator placement, NSAIDs were more effective than a control at reducing pain at 2, 6 and 24 hours. The results for heterogeneity improved, with low heterogeneity - which may not be important - at 2 hours (I^2 = 23%), no heterogeneity at 6 hours (I^2 = 0%), and moderate heterogeneity at 24 hours (I^2 = 42%) (Table 3).

For archwire placement, NSAIDs were more effective than a control at reducing pain at 2, 6 and 24 hours. However, there was moderate heterogeneity at 2 hours (I^2 = 47%), low heterogeneity at 6 hours (I^2 = 10%), and considerable heterogeneity at 24 hours (I^2 = 85%) (Table 4).

For participants who were mid-treatment, NSAIDs, in the form of ketoprofen chewing gum, were more effective than a control at reducing pain at 2, 6 and 24 hours (Table 5).

Rescue analgesia

Use of rescue analgesia was recorded in seven studies (Arantes 2009; Bernhardt 2001; Bradley 2007; Bruno 2011; Najafi 2015; Steen-Law 2000; Tuncer 2014). Only two of these studies reported data on the number of participants who required rescue medication during the study (Bruno 2011; Tuncer 2014). Tuncer 2014 reported that two participants required rescue medication, whilst Bruno 2011 reported that six participants required the use of analgesic medication during the study. No further information was available relating to class, dose or timing of this medication.

Adverse events

No studies in this comparison reported any adverse events.

Quality of life or participant satisfaction

One study reported quality of life assessed using SF-36 and found that, at 30 days, there was a significant reduction in the scale of bodily pain compared to baseline results, however, there were no significant differences in other variables of the SF-36 among the three treatment groups (Wang 2012). The study also recorded SAS scores and found that these were not significantly different between the three treatment groups.

One study reported quality of life assessed using STAI and PANAS, and found that there were no significant differences between the treatment groups (Minor 2009).

Time off school or work

No studies in this comparison reported this outcome.

Failure to complete orthodontic treatment due to the pain experienced

No studies reported this outcome.

Comparison 2: NSAID versus paracetamol

Pain

We combined seven studies in a meta-analysis for pain at 2 hours and at 6 hours. Three of these studies were at a high risk of bias (Kawamoto 2010; Najafi 2015; Ousehal 2009); three studies were at an unclear risk of bias (Gupta 2014; Nik 2016; Polat 2005a); and one study was assessed as being at a low risk of bias (Bradley 2007). In total, 664 participants were analyzed at these time points (Analysis 2.1; Analysis 2.2).

For the outcome at 24 hours, we combined nine studies in a meta-analysis (Analysis 2.3). Four of these studies were at a high risk of bias (Kawamoto 2010; Najafi 2015; Ousehal 2009; Tuncer 2014); four studies were at an unclear risk of bias (Gupta 2014; Nik 2016; Polat 2005a; Salmassian 2009); and one study was assessed as being at a low risk of bias (Bradley 2007). In total, 734 participants were analyzed for pain at 24 hours.

Six different classes of NSAIDs were investigated across the nine studies. Eight studies investigated ibuprofen (Bradley 2007; Kawamoto 2010; Najafi 2015; Nik 2016; Ousehal 2009; Polat 2005a; Salmassian 2009; Tuncer 2014). One study also investigated each of the following: aspirin (Polat 2005a), etoricoxib (Gupta 2014), flurbiprofen (Polat 2005a), meloxicam (Najafi 2015), and naproxen sodium (Polat 2005a).

The meta-analysis showed no evidence of a difference in mean pain intensity during orthodontic treatment between NSAID and paracetamol at 2, 6 or 24 hours.

- 2 hours (MD -2.92, 95% CI -8.48 to 2.65, P = 0.30; 7 studies, 664 participants; Analysis 2.1)
- 6 hours (MD -5.17, 95% CI -11.71 to 1.37, P = 0.12; 7 studies, 664 participants; Analysis 2.2)
- 24 hours (MD -0.51, 95% CI -8.93 to 7.92, P = 0.91; 9 studies, 734 participants; Analysis 2.3), when compared to paracetamol.

A further study compared NSAID versus paracetamol and the findings support those presented above (Sudhakar 2014) (Analysis 2.4).

For separator placement, NSAIDs were no more effective than paracetamol for reducing pain at 2, 6 and 24 hours. The results for heterogeneity improved, with low heterogeneity - which may not be important - at 2 hours (I^2 = 6%), moderate heterogeneity at 6 hours (I^2 = 40%), and no heterogeneity at 24 hours (I^2 = 0%) (Table 6). We considered the data for all time points to be of low quality.

Again, for archwire placement, NSAIDs were no more effective than paracetamol for reducing pain at 2, 6 and 24 hours. Heterogeneity in these results remained, with substantial heterogeneity at 2 hours (I^2 = 73%) and 6 hours (I^2 = 63%), and considerable heterogeneity at 24 hours (I^2 = 82%) (Table 7).

Rescue analgesia

Two studies in this comparison reported that participants required rescue medication during the study (Bradley 2007; Najafi 2015). Bradley 2007 reported that 18 participants required rescue medication. The percentages of participants who took additional analgesia were 9% (7 participants) in the paracetamol group and 14% (11 participants) in the ibuprofen group (relative risk (RR) 1.5, 95% CI 0.60 to 3.60). The study stated that "the additional analgesics were most often taken at bedtime or on day one after separator placement"; however, no additional information was available regarding class, dose or specific timing of medication. Najafi 2015 reported 18 participants used other analgesics during the study, again, no further information was available relating to class, dose or timing.

Adverse events

One study reported that one participant (< 1%) experienced a suspected adverse reaction (Bradley 2007). Further information

was provided in an additional paper that detailed an incident involving a 12-year-old boy with no relevant medical history and no history of drug allergy (McAlinden 2005): "Following 2 doses of the intervention analgesia, the patient was still experiencing discomfort and self-medicated with 1000 mg of paracetamol. Several hours later he suddenly developed a rash on all parts of his body described as 'red, blotchy and itchy'. There were no other symptoms. The patient attended his GMP [general medical practitioner] the following day and was prescribed a course of anti-histamines. He did not report the adverse reaction to the trial coordinators until 1 week after the trial drugs were given, at which time the rash had completely resolved and the patient was symptom-free. A provisional diagnosis of drug hypersensitivity to either the trial drug or to the paracetamol was made. Since one of the trial drugs was also paracetamol we decided to break the randomisation code for this patient to determine which drug the patient had received. The trial drug given was found to be paracetamol, suggesting a drug hypersensitivity reaction to paracetamol. Before a controlled Drug Provocation Test (DPT) could be organized, the patient took another dose of paracetamol on the advice of his GMP. On this occasion there was no reaction to the drug, suggesting a previous false positive result. Since the patient had already taken paracetamol without event, the DPT was deemed unnecessary."

Quality of life or participant satisfaction

No studies in this comparison reported this outcome.

Time off school or work

No studies in this comparison reported this outcome.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this comparison reported this outcome.

Comparison 3: one type of NSAID versus another type of NSAID

Pre-emptive NSAID versus NSAID post-treatment

Pain

One study at a high risk of bias showed that pre-emptive ibuprofen reduced mean pain intensity following separator placement at 2 hours (MD -11.30, 95% CI -16.27 to -6.33, P < 0.001; 41 participants) when compared with ibuprofen taken post-treatment (Steen-Law 2000) (Analysis 3.1). Data from a second paper did not contribute to data at this time point, as participants in the comparison group did not receive the active intervention until 6 hours post-treatment (Bernhardt 2001).

For pain at 6 hours and 24 hours, two studies at high risk of bias compared ibuprofen taken pre-emptively with ibuprofen taken post-treatment for the placement of separators, analysing 69 participants (Bernhardt 2001; Steen-Law 2000). This showed that there was no difference at 6 hours (MD -8.43, 95% CI -30.37 to 13.50, P = 0.45; Analysis 3.2); or 24 hours (MD -9.74, 95% CI -47.88 to 28.40, P = 0.62; Analysis 3.3). Additionally, although there was no heterogeneity at 2 hours (I^2 = 0%), there was substantial heterogeneity at 6 hours (I^2 = 72%), and considerable heterogeneity at 24 hours (I^2 = 87%). We considered data for all time points to be of very low quality.

Rescue analgesia

Two studies in this comparison reported on the need for rescue medication during the study. One study reported that 22 participants required additional analgesics during the study (Bernhardt 2001). These 22 participants were evenly distributed among the three groups in the study, but no further information was available relating to class, dose or timing of the medication, and participants from one group who received pre-emptive and post-treatment ibuprofen did not contribute to the analysis in this review.

One study reported that 17 participants required additional analgesics during the study, four in the pre-emptive ibuprofen group; six in the post-treatment ibuprofen group and seven in the control group, who did not contribute to the analysis in this review (Steen-Law 2000). No further information was available relating to class, dose or timing of medication. When these results were combined, we did not find evidence of a difference in risk of requiring rescue analgesia when ibuprofen was taken pre-emptively compared to after treatment (RR 0.8, 95% CI 0.30 to 1.90).

Adverse events

No studies in this comparison reported any adverse events.

Quality of life and/or participant satisfaction

No studies in this comparison reported this outcome.

Time off school/work

No studies in this comparison reported this outcome.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this comparison reported this outcome.

One NSAID versus another NSAID: ketoprofen (160 mg) versus benzidamine chloride (22.5 mg)

Pain

One further study compared ketoprofen versus benzidamine chloride mouthwashes (Lauritano 2000). It presented data at four days only so we were unable to include the data in this review.

Adverse events

The study did not report any adverse events.

Quality of life and/or participant satisfaction

The study did not report this outcome.

Time off school or work

The study did not report this outcome.

Failure to complete orthodontic treatment due to the pain experienced

The study did not report this outcome.

Comparison 4: NSAID versus local anaesthetic

Pain

One study at unclear risk of bias, compared ketoprofen chewing gum with benzocaine chewing gum, for the relief of pain mid-treatment, and analyzed 48 participants (Eslamian 2014). We were

unable to use the data from this cross-over study as the mean and standard deviation results were unclearly reported; however, the results showed no evidence of a difference between the interventions. We judged the data for this comparison to be of very low quality.

Adverse events

The study did not report any adverse events.

Quality of life or participant satisfaction

The study did not report this outcome.

Time off school or work

The study did not report this outcome.

Failure to complete orthodontic treatment due to the pain experienced

The study did not report this outcome.

Comparison 5: one type of NSAID versus another type of NSAID

Pain

One study at high risk of bias, compared ketoprofen chewing gum with benzocaine chewing gum, for the relief of pain mid-treatment, and analyzed 48 participants (Eslamian 2014). We were unable to use the data from this cross-over study as the mean and standard deviation results were unclearly reported; however, the results failed to show a benefit for either intervention.

Adverse events

The study did not report any adverse events.

Quality of life or participant satisfaction

The study did not report these outcomes.

Time off school or work

The study did not report this outcome.

Failure to complete orthodontic treatment due to the pain experienced

The study did not report this outcome.

DISCUSSION

Summary of main results

Thirty-two randomized controlled trials (RCTs) met our eligibility criteria and were included in this review. We performed a meta-analysis where appropriate for the main outcome of pain intensity at 2 hours, 6 hours and 24 hours after orthodontic treatment. All data were measured using a visual analogue scale (VAS), with most studies comparing the effectiveness of drug interventions following either placement of separators or placement of an initial aligning archwire. We assessed the quality of the body of evidence for each comparison and outcome.

Analgesic versus control

We found moderate-quality evidence that analgesics were effective at reducing pain intensity at 2 hours, 6 hours and 24 hours following orthodontic treatment.

Subgroup analysis by drug type found that both paracetamol and NSAIDs were effective at reducing pain intensity at 2 hours, 6 hours and 24 hours after treatment compared with a placebo or no treatment group, and there was no evidence of a difference between the subgroups.

We performed further subgroup analyses, grouping data according to the orthodontic intervention carried out, and found the following.

- Non-steroidal anti-inflammatories (NSAIDs) were significantly more effective at reducing pain intensity than a control intervention at all time points, regardless of the orthodontic intervention.
- Paracetamol was significantly more effective at reducing pain intensity than a control intervention at all time points when an initial archwire was placed, however, it was effective only at 2 hours and 6 hours following placement of separators. By 24 hours, there was no significant difference between the effectiveness of paracetamol or a control intervention on pain intensity.

NSAID versus paracetamol

There was insufficient evidence to claim that either NSAIDs or paracetamol were better at reducing pain intensity at 2 hours, 6 hours or 24 hours following either the placement of separators or placement of an initial aligning archwire (low-quality evidence).

Pre-emptive NSAID versus post-treatment NSAID

We found some very low-quality evidence that ibuprofen taken one hour prior to separator placement significantly reduced pain intensity at 2 hours after treatment when compared to ibuprofen taken post-treatment. However, it is worth noting that this effect was seen at 2 hours, even when ibuprofen was taken immediately after treatment. However, at 6 hours and 24 hours, there was no significant difference detected.

NSAID versus local anaesthetic

One study compared the use of topical ketoprofen chewing gum (NSAID) with benzocaine chewing gum (local anaesthetic). This small study did not show evidence of a difference between ketoprofen or benzocaine in terms of pain intensity following treatment, and, therefore, no recommendation can be made to support one intervention over the other (very low-quality evidence).

Overall completeness and applicability of evidence

Overall, we found 32 studies that investigated interventions to treat pain associated with orthodontic treatment. The studies measured multiple outcomes. Six studies compared paracetamol with a control group receiving either no treatment or a placebo; 14 studies compared NSAIDs with a control group receiving either no treatment or a placebo; nine studies compared NSAIDs with paracetamol and five studies compared different classes of NSAIDs with one another. Two studies compared ibuprofen taken pre-emptively with ibuprofen taken postoperatively. Two studies compared benzocaine local anaesthetic with a control group receiving a placebo, and one study compared NSAIDs with a local anaesthetic. The current evidence allowed us to assess if any of the interventions succeed in providing pain relief during the first 24 hours of orthodontic treatment.

Most studies carried out an a priori sample size calculation; however, due to high levels of attrition, it is likely that five studies were underpowered to find a difference between their analgesic and control groups (Bernhardt 2001; Bruno 2011; Kawamoto 2010; Najafi 2015; Steen-Law 2000).

There was a lack of clear reporting, especially with respect to methodology, as well as some cases of inappropriate or missing statistical data. In particular, presentation of the results for cross-over studies was problematic. Some of the evidence was moderate quality, but much of it was of low or very low quality and the results must be interpreted with caution.

Quality of the evidence

We describe the overall quality of the evidence in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4). We graded the evidence for all comparisons and outcomes as moderate, low, or very low quality. The reasons for our gradings included the small number of studies and participants, the high or unclear risk of bias in these studies, and the high level of heterogeneity in the meta-analyses.

Potential biases in the review process

We minimised bias in this review by using a broad, sensitive search of multiple databases with no restrictions on language. We also searched for unpublished studies and data, and included studies reported in all languages. However, numerous potential biases have been detected, both within and between, individual studies included in this review.

We were unable to pool data from 10 studies in the meta-analyses due to inconsistencies or inappropriate presentation of the data (Abtahi 2006; Arantes 2009; Bayani 2016; Eslamian 2014; Eslamian 2016b; Eslamian 2016a; Ngan 1994; Patel 2011; Sudhakar 2014; Young 2006).

Data were not presented in any study according to the class, dose or specific timing of rescue analgesia taken, despite six studies recording these medications. This presents a potential bias and limitation, as it may be that one intervention required more additional analgesics than another, ultimately influencing the pain intensity experienced, and this effect may have been attributed to the trial intervention.

A number of included studies had small sample sizes, which in some cases did not reach the minimum number required to detect a difference based on the studies' sample size calculations. Additionally, multiple studies with three or more arms required the sample sizes to be split for the purpose of comparison. The control arm sample size was split for the comparison of analgesics versus control in 10 studies (Bruno 2011; Eslamian 2014; Gupta 2014; Kawamoto 2010; Kohli 2011; Nik 2016; Polat 2005a; Polat 2005b; Salmassian 2009; Tuncer 2014). The paracetamol arm sample size was split for the head-to-head comparison of NSAIDs versus paracetamol in two studies (Najafi 2015; Polat 2005a). This resulted in small numbers of participants and wide confidence intervals in the final analysis, which may have had an impact on the overall outcome.

Another limitation of the studies was heterogeneity, which was identified to varying degrees across all comparisons. We considered this to be caused by clinical heterogeneity, such as individual variations in participant responses to pain, differences in orthodontic treatments, and different doses, classes and timings of the analgesics. We carried out further subgroup analyses, by orthodontic intervention, to determine if this was the cause of the heterogeneity. Our results showed that, although it did account for some heterogeneity, and reduced the I^2 statistic to some extent in most cases, heterogeneity still remained. We did not feel that further subgroup analysis to try to account for this remaining element of heterogeneity, for example by reanalyzing according to timing of intervention, was appropriate due to the small number of studies. Therefore, we allowed for the heterogeneity by using a random-effects model.

Agreements and disagreements with other studies or reviews

We found three other reviews that reported on comparisons and outcomes similar to those in this review (Angelopoulou 2012; Ashley 2016; Xiaoting 2010). Angelopoulou 2012 and Xiaoting 2010 reported the efficacy of ibuprofen with lower confidence than we have reported. Although each of these reviews found a significant difference between ibuprofen and a control group receiving a placebo or no treatment, Angelopoulou 2012 found there was only a significant difference at two hours and six hours following placement of separators or an initial aligning archwire, whilst Xiaoting 2010 reported the difference as significant only at six hours and 24 hours following placement an initial aligning archwire. We are able to be more confident in the findings than previous reviews, because we have included several additional studies that were published subsequent to the other reviews.

Additionally, Xiaoting 2010 reported that there was no difference in pain control between ibuprofen and paracetamol, which supports the findings of this review.

The Ashley 2016 Cochrane Review reported the efficacy of pre-emptive ibuprofen at two hours, which supports our conclusion that pre-emptive ibuprofen is effective at reducing pain following treatment. However, unlike this review, they did not investigate the effectiveness at any time points beyond two hours.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-quality evidence that the use of analgesics reduces the pain associated with orthodontic treatment.

Due to a lack of evidence, we remain uncertain whether the systemic non steroidal anti-inflammatories (NSAIDs) are more effective than paracetamol, and whether topical NSAIDs are more effective than local anaesthetic, at reducing pain associated with orthodontic treatment.

There is very low-quality evidence that the use of pre-emptive ibuprofen, taken one hour before orthodontic treatment, significantly reduces pain up to two hours after treatment; however, the effect appears to reduce over time, with no evidence of a difference at six hours and beyond.

Implications for research

In view of the quality of the available evidence, it is difficult to draw definitive conclusions regarding the relative effectiveness of different drugs, and whether taking an analgesic before treatment is effective.

The results of this review imply that there is a need for more long-term, well designed and reported randomized controlled clinical studies to assess the efficacy of drug interventions with relation to NSAIDs and paracetamol.

The design of future studies should consider the following.

- Clear inclusion and exclusion criteria should be set, taking into consideration factors that can effect participant perception of pain, particularly gender.
- An a priori sample size calculation should be carried out.
- Presentation and analysis of data should be appropriate, especially for cross-over studies.
- There should be adequate reporting of rescue analgesics taken by participants in each arm of the trial. We recommend that the following be reported:
  * type of drug taken;
  * dose of drug taken;
  * time at which drug was taken
  * intervention group of person taking the drug.
- Adverse effects should be reported; and if none were encountered, this should be recorded.
- Reports of clinical trials would be improved by following the guidelines produced by the CONSORT group to ensure that all relevant information is provided.

ACKNOWLEDGEMENTS

We would like to thank James E. Cooper for his work on the protocol. We would like to thank Anne Littlewood (Information Specialist, Cochrane Oral Health) for developing the search strategy; Laura MacDonald for editorial management of the review; Jo Weldon for entering study characteristics to tables; Scott Deacon, Tanya Walsh and Ruth Floate for editorial comments; Soodabeh Behboodi and Greg Herbert for external referee feedback; and Elizabeth Royle for final copy editing.

We are grateful to Dr Sepideh Banava for translating Abtahi 2006 from Farsi, and to Janet Lear for arranging this.

We would also express our sincere thanks to the following study authors who provided extra information on their studies.

- Marcella Bruno: provided mean and standard deviation data relating to VAS measurements of pain intensity, as well as details of random sequence generation and allocation concealment (Bruno 2011).
- Melissa Bernhardt: provided details of random sequence generation and allocation concealment (Bernhardt 2001).
- Sarvraj Kohli: provided details of random sequence generation, allocation concealment and blinding (Kohli 2011).
- Sara Yousefinia: provided details of random sequence generation, allocation concealment and orthodontic intervention (Eslamian 2014).

REFERENCES

References to studies included in this review

Abtahi 2006 *{published and unpublished data}*

Abtahi SM, Zeraati F, Shirinzad M, Adabi F. A comparison on the analgesic efficacy of ibuprofen 400 mg with tramadol 50 mg in the reduction of pain caused by orthodontic treatment. *Journal of Islamic Dental Association of IRAN (JIDA)* 2006;**18**(1):78-84.

Arantes 2009 *{published data only (unpublished sought but not used)}*

Arantes G, Arantes V, Ashmawi H, Posso I. Tenoxicam controls pain without altering orthodontic movement of maxillary canines. *Orthodontics & Craniofacial Research* 2009;**12**:14-9.

Bayani 2016 *{published data only}*

Bayani S, Rostami S, Ahrari F, Saeedipouya I. A randomized clinical trial comparing the efficacy of bite wafer and low level laser therapy in reducing pain following initial arch wire placement. *Laser Therapy* 2016;**25**(2):121-9.

Bernhardt 2001 *{published data only (unpublished sought but not used)}*

Bernhardt MK, Southard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 2001;**120**(1):20-7.

Bird 2007 *{published data only (unpublished sought but not used)}*

Bird SE, Williams K, Kula K. Preoperative acetaminophen vs ibuprofen for control of pain after orthodontic separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics* 2007;**132**(4):504-10.

Bradley 2007 *{published data only (unpublished sought but not used)}*

* Bradley RL, Ellis PE, Thomas P, Bellis H, Ireland AJ, Sandy JR. A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 2007;**132**(4):511-7.

McAlinden RL, Ellis PE, Sandy JR. Report of an adverse incident in a randomized clinical trial. *Journal of Orthodontics* 2005;**32**(3):203-5.

Bruno 2011 *{published and unpublished data}*

Bruno MB, Bruno MA, Krymchantowski AV, da Motta AF, Mucha JN. A double-blind, randomized clinical trial assessing the effects of a single dose of preemptive anti-inflammatory treatment in orthodontic pain. *Progress in Orthodontics* 2011;**12**:2-7.

Eslamian 2014 *{published and unpublished data}*

Eslamian L, Youssefinia S, Ameli N. Efficacy of ketoprofen and benzocaine chewing gums for reducing orthodontic pain. *Journal of Islamic Dental Association of IRAN* 2014;**26**(3):133-8.

Eslamian 2016a *{published data only}*

Eslamian L, Borzabadi-Farahani A, Gholami H. The effect of benzocaine and ketoprofen gels on pain during fixed orthodontic appliance treatment: a randomised, double-blind, crossover trial. *Australian Orthodontic Journal* 2016;**32**(1):64-72.

Eslamian 2016b *{published data only}*

Eslamian L, Gholami H, Mortazavi SA, Soheilifar S. Effect of 5% benzocaine gel on relieving pain caused by fixed orthodontic appliance activation. A double-blind randomized controlled trial. *Orthodontics and Craniofacial Research* 2016;**19**:190-7.

Farzanegan 2012 *{published data only (unpublished sought but not used)}*

Farzanegan F, Zebarjad SM, Alizadeh S, Ahrari F. Pain reduction after initial archwire placement in orthodontic patients: a randomized clinical trial. *American Journal of Orthodontics and Dentofacial Orthopedics* 2012;**141**(2):169-72.

Gupta 2014 *{published data only (unpublished sought but not used)}*

Gupta M, Kandula S, Laxmikanth SM, Vyavahare SS, Reddy SB, Ramachandra CS. Controlling pain during orthodontic fixed appliance therapy with non-steroidal anti-inflammatory drugs (NSAID): a randomized, double-blinded, placebo-controlled study. *Journal of Orofacial Orthopedics* 2014;**75**(6):471-6.

Kawamoto 2010 *{published data only}*

Kawamoto SA. Acetaminophen versus ibuprofen for the control of immediate and delayed pain following orthodontic separator placement. ProQuest - Dissertations & Theses 2010.

Kluemper 2002 *{published data only (unpublished sought but not used)}*

Kluemper GT, Hiser DG, Rayens MK, Jay MJ. Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. *American Journal of Orthodontics and Dentofacial Orthopedics* 2002;**122**(4):359-65.

Kohli 2011 *{published data only (unpublished sought but not used)}*

Kohli SS, Kohli VS. Effectiveness of piroxicam and ibuprofen premedication on orthodontic patients' pain experiences. *Angle Orthodontist* 2011;**81**(6):1097-102.

Lauritano 2000 *{published and unpublished data}*

Lauritano D, Spadari F, Salvato A. Efficacy of and tolerance to topical ketoprofen lysinate solution in acute inflammation of the mouth in orthodontic therapy. Randomized single blind study, with parallel groups, versus benzidamine hydrochloride. Minerva Stomatologica 2000; Vol. 49, issue 11-12:561-8.

Minor 2009 *{published data only (unpublished sought but not used)}*

Minor V, Marris CK, McGorray SP, Yezierski R, Fillingim R, Logan H, et al. Effects of preoperative ibuprofen on pain after separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics* 2009;**136**(4):510-7.

Najafi 2015 *{published data only (unpublished sought but not used)}*

Najafi HZ, Oshagh M, Salehi P, Babanouri N, Torkan S. Comparison of the effects of preemptive acetaminophen, ibuprofen, and meloxicam on pain after separator placement: a randomized clinical trial. *Progress in Orthodontics* 2015;**16**:34.

Ngan 1994 *{published data only (unpublished sought but not used)}*

Ngan P, Wilson S, Shanfeld J, Amini H. The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *American Journal of Orthodontics and Dentofacial Orthopedics* 1994;**106**(1):88-95.

Nik 2016 *{published data only (unpublished sought but not used)}*

Nik TH, Shahsavari N, Ghadirian H, Ostad SN. Acetaminophen versus liquefied ibuprofen for control of pain curing separation in orthodontic patients: a randomized triple blinded clinical trial. *Acta Medica Iranica* 2016;**54**(7):418-21.

Ousehal 2009 *{published and unpublished data}*

Ousehal L, Lakhdar A, Elquars F. Comparison of the effect of paracetamol and ibuprofen on orthodontic pain [Comparaison de l'effet du paracétamol et de l'ibuprofène sur la douleur orthodontique]. *International Orthodontics [Collège européen d'orthodontie]* 2009;**7**(2):193-206.

Paganelli 1993 *{published and unpublished data}*

Paganelli C. Pharmacological support during orthodontic therapy with a topical anti-inflammatory. *Minerva Stomatologica* 1993;**42**(6):271-4.

Patel 2011 *{published data only (unpublished sought but not used)}*

Patel S, McGorray SP, Yezierski R, Fillingim R, Logan H, Wheeler TT. Effects of analgesics on orthodontic pain. *American Journal of Orthodontics and Dentofacial Orthopedics* 2011;**139**(1):e53-8.

Pelisson 2008 *{published data only}*

Pelisson CJ. Assessment of Pain Control After Mounting Brackets Orthodontic [Thesis] [Avaliação do controle da dor após a fixação de brackets ortodônticos]. Library catalogue of Sao Leopoldo Medic, 2008.

Polat 2005a *{published data only}*

Polat O, Karaman AI. Pain control during fixed orthodontic appliance therapy. *Angle Orthodontist* 2005;**75**(2):214-9.

Polat 2005b *{published data only}*

Polat O, Karaman AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. *Angle Orthodontist* 2005;**75**(5):791-6.

Salmassian 2009 *{published data only (unpublished sought but not used)}*

Salmassian R, Oesterle LJ, Shellhart WC, Newman SM. Comparison of the efficacy of ibuprofen and acetaminophen in controlling pain after orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics* 2009;**135**(4):516-21.

Steen-Law 2000 *{published data only (unpublished sought but not used)}*

Steen Law SL, Southard KA, Law AS, Logan HL, Jakobsen JR. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. *American Journal of Orthodontics and Dentofacial Orthopedics* 2000;**118**(6):629-35.

Sudhakar 2014 *{published data only (unpublished sought but not used)}*

Sudhakar V, Vinodhini TS, Mohan AM, Srinivasan B, Rajkumar BK. The efficacy of different pre- and post-operative analgesics in the management of pain after orthodontic separator placement: a randomized clinical trial. *Journal of Pharmacy and Bioallied Sciences* 2014;**6**(Suppl 1):S80-4.

Tuncer 2014 *{published data only}*

Tunçer Z, Polat-Ozsoy O, Demirbilek M, Bostanoglu E. Effects of various analgesics on the level of prostaglandin E2 during orthodontic tooth movement. *European Journal of Orthodontics* 2014;**36**(3):268-74.

Wang 2012 *{published data only}*

Wang J, Jian F, Chen J, Ye NS, Huang YH, Wang S, et al. Cognitive behavioral therapy for orthodontic pain control: a randomized trial. *Journal of Dental Research* 2012;**9**(6):580-5.

Young 2006 *{published data only (unpublished sought but not used)}*

Young AN, Taylor RW, Taylor SE, Linnebur SA, Buschang PH. Evaluation of preemptive valdecoxib therapy on initial archwire placement discomfort in adults. *Angle Orthodontist* 2006;**76**(2):251-9.

References to studies excluded from this review

Al-Melh 2017 *{published data only}*

Al-Melh MA, Andersson L. The effect of a lidocaine/prilocaine topical anesthetic on pain and discomfort associated with orthodontic elastomeric separator placement. *Progress in Orthodontics* 2017;**18**(1):1-9. [DOI: 10.1186/s40510-016-0156-7]

Cherubini 2003 *{unpublished data only}*

Cherubini ML. Rofecoxib, a cyclooxygenase-2 inhibitor, and its analgesic efficacy in orthodonti-cally induced pain: a randomized, controlled trial. *Journal of Dental Research* 2003;**82**:B13-B398.

Eslamian 2013 *{published data only}*

Eslamian L, Borzabadi-Farahani A, Edini H, Badiee MR, Lynch L, Mortazavi A. The analgesic effect of benzocaine mucoadhesive patches on orthodontic pain caused by elastomeric separators, a preliminary study. *Acta Odontologica Scandinavica* 2013;**71**(5):1168-73.

Eslamian 2017a *{published data only}*

Eslamian L, Kianipour A, Mortazavi SA. The analgesic efficacy of 5% maproxen gel for pain associated with orthodontic separator placement: a randomized double-blind controlled trial [The comparison of the effect of 5% naproxen gel and

the placebo gel on reduction of fixed orthodontic pain after elastic separator placement; a randomized clinical trial study]. Anaesthesiology and Pain Medicine 2017; Vol. 7, issue 2:In press.

Ireland 2016 *{published data only}*

Ireland AJ, Ellis P, Jordan A, Bradley R, Ewings P, Atack NE, et al. Comparative assessment of chewing gum and ibuprofen in the management of orthodontic pain with fixed appliances: a pragmatic multicenter randomized controlled trial. *American Journal of Orthodontics and Dentofacial Orthopaedics* 2016;**150**(2):220-7. [DOI: 10.1016/j.ajodo.2016.02.018]

Murdock 2010 *{published data only}*

Murdock S, Phillips C, Khondker Z, Hershey HG. Treatment of pain after initial archwire placement: a noninferiority randomized clinical trial comparing over-the-counter analgesics and bite-wafer use. *American Journal of Orthodontics and Dentofacial Orthopedics* 2010;**137**(3):316-23.

Ogata 1999 *{unpublished data only}*

Ogata GY, Killiany DM, Ferguson DJ, Starnes HB. Efficacy of three analgesics in reducing discomfort during the initial treatment of orthodontic patients [abstract]. Journal of Dental Research. 1999; Vol. 78:198.

Parks 2001 *{unpublished data only}*

Parks CT, Runck LA, Miranda LS, Southard KA, Baker KA, Jakobsen JR. A comparison of ibuprofen and acetaminophen for orthodontic pain. *Journal of Dental Research* 2001;**80**:128.

Soheilifar 2016 *{unpublished data only}*

Soheilifar S. Comparison of pain perception from two type of elastomeric and brass wire separators and utilizing menthol patch and benzocaine patch in orthodontic patients: a randomized clinical trial. Iranian Registry of Clinical Trials 2016.

References to studies awaiting assessment

Eslamian 2017b *{unpublished data only}*

Eslamian L, Dehghani F. Comparative effect of ketoprofen chewing gums and ketoprofen gel in reducing orthodontic pain. Iranian Registry of Clinial Trials 2017.

Moradinejad 2014 *{unpublished data only}*

Moradinejad M, Kazemi P. Comparison of acetaminophen and ibuprofen before orthodontic treatment in reducing pain-clinical trial. Iranian Registry of Clinical Trials 2014.

Rooke 2012 *{unpublished data only}*

Rooke J. A randomised prospective study of analgesic protocols involving ibuprofen and acetaminophen (paracetamol) for the management of orthodontic pain and discomfort in relation to fitting of fixed appliances in patients aged 14-19. Australian New Zealand Clinical Trials Registry 2012.

References to ongoing studies

Mohammed 2016 *{unpublished data only}*

Mohammed H. Effectiveness of a preemptive Ibuprofen on the control of pain before orthodontic separator placement in children and adolescents: a single centre randomised controlled trial. Pan African Clinical Trials Registry 2004.

Additional references

Angelopoulou 2012

Angelopoulou M, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment:a meta-analysis. *Orthodontics and Craniofaial Research* 2012;**15**:71-83.

Ashley 2016

Ashley PF, Parekh S, Moles DR, Anand P, MacDonald LC. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. *Cochrane Database of Systematic Reviews* 2016, Issue 8. [DOI: 10.1002/14651858.CD008392]

British Orthodontic Society

British Orthodontic Society. Treatment and Brace Types. Available at URL: http://www.bos.org.uk/public-patients-home/orthodontics-for-children-and-teens/treatment-types..

Buttke 1999

Buttke TM, Proffit WR. Referring adult patients for orthodontic treatment.. *Journal of the American Dental Association* 1999;**130**:73-79.

De Carlos 2006

De Carlos F, Cobo J, Diaz-Esnal B, Arguelles J, Vijande M, Costales M. Orthodontic tooth movement after inhibition of cyclooxygenase-2. *American Journal of Orthodontics and Dentofacial Orthopedics* 2006;**129**(3):402-406.

Fleming 2016

Fleming PS, Strydom H, Katsaros C, MacDonald L, Curatolo M, Fudalej P, Pandis N. Non-pharmacological interventions for alleviating pain during orthodontic treatment. *Cochrane Database of Systematic Reviews* 2016, Issue 12. [DOI: 10.1002/14651858.CD010263.pub2]

Higgins 2008

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2008.

Johnson 1997

Johnson MH, Petrie SM. The effects of distraction on exercise and coldpressor tolerance for chronic low back pain sufferers. *Pain* 1997;**69**:43-8.

Jones 1992

Jones M, Chan C. Pain in the early stages of orthodontic treatment. *Journal of Clinical Orthodontics* 1992;**26**(5):311-3.

Karthi 2012

Karthi M, Anbuslevan GJ, Senthilkumar KP, Tamizharsi S, Raja S, Prabhakar K. NSAIDs in orthodontic tooth movement. *Journal of Pharmacy & Bioallied Sciences* 2012;**4**(2):304-6.

Kehoe 1996

Kehoe MJ, Cohen SM, Zarrinnia K, Cowan A. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. *The Angle Orthodontist* 1996;**66**(5):339-9.

Keim 2005

Keim RG. Managing orthodontic pain. *Journal of Clinical Orthodontics* 2005;**38**(12):641-2.

Krishnan 2006

Krishnan V, Davidovitch Z. The effect of drugs on orthodontic tooth movement. *Orthodontics and Craniofacial Research* 2006;**9**(4):163-71.

Krishnan 2007

Krishnan V. Orthodontic pain: from causes to management—a review. *European Journal of Orthodontics* 2007;**29**:170-9.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Little 1975

Little RM. The Irregularity Index: a quantitative score of mandibular anterior alignment. *American Journal of Orthodontics and Dentofacial Orthopedics* 1975;**68**(5):554-63.

McAlinden 2005

McAlinden RL, Ellis PE, Sandy JR. Report of an adverse incident in a randomized clinical trial. *Journal of Orthodontics* 2005;**32**(3):203-5.

Oliver 1985

Oliver R, Knapman Y. Attitudes to orthodontic treatment. *British Journal of Orthodontics* 1985;**12**:179-88.

Pleuvry 1993

Pleuvry BJ. Opioid receptors and their relevance to anaesthesia. *British Journal of Anaesthesia* 1993;**71**(1):119-26.

Proffit 2000

Proffit WR, Fields HW Jr. Contemporary Orthodontics. Third Edition. St Louis, Missouri, USA: Mosby-Year Book, Inc, 2000.

Rashidpour 2012

Rashidpour M, Ahmad Akhoundi MS, Hosseinzadeh Nik T, Dehpour AR, Alaeddini M, Javadi E, Noroozi H. Effect of tramadol (μ-opioid receptor agonist) on orthodontic tooth movements in a rat model. *Journal of Dentistry of Tehran University of Medical Sciences* 2012;**9**(2):83-89.

Sergl 1998

Sergl H, Klages U, Zentner A. Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. *American Journal of Orthodontics and Dentofacial Orthopaedics* 1998;**114**(6):684-91.

Shek 1993

Shek DT. The Chinese version of the State-Trait Anxiety Inventory: its relationship to different measures of psychological well-being. *Journal of Clinical Psychology* 1993;**49**:349-58.

Shenoy 2013

Shenoy N, Shetty S, Ahmed J, Shenoy KA. The pain management in orthodontics. *Journal of Clinical and Diagnostic Research* 2013;**7**(6):1258-60.

Xiaoting 2010

Xiaoting L, Yin T, Yangxi C. Interventions for pain during fixed orthodontic appliance therapy: A systematic review. *The Angle Orthodontist* 2010;**80**(5):925-32.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abtahi 2006

Methods	**Setting:** orthodontics private offices (in Hamedan, Iran) **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** people who were not experiencing any kind of pain before treatment, or using any kind of analgesic; and who did not have any kidney or liver disease or other contraindication for using the medications being tested in the study **Exclusion criteria:** people who had not completed the questionnaires in different times [sic]; people who consumed other analgesics during the study **Orthodontic intervention:** separator placement

Abtahi 2006 *(Continued)*

	Participant sampling: n = 60 recruited and randomized n = 0 lost to follow-up n = 60 data analyzed (18 male:42, female, mean age 15.43 years ± 3.7) **Group 1** (n = 20): 10 male:3 female, mean age 15.75 ± 3.95 years **Group 2** (n = 20): 4 male:10 female, mean age 15.05 ± 3.49 years **Group 3** (n = 20): 6 male:8 female, mean age 15.5 ± 3.98 years
Interventions	**Comparison: NSAID vs placebo, opioid vs placebo, NSAID vs opioid** **Ibuprofen (800 mg) vs tramadol (100 mg) vs placebo (500 mg starch)** provided pre-emptively and postoperatively following insertion of separators **Group 1:** 400 mg ibuprofen 1 h before and 5 h after insertion of separators **Group 2:** 50 mg tramadol 1 h before and 5 h after insertion of separators **Group 3:** placebo 1 h before and 5 h after insertion of separators
Outcomes	Pain score (VAS) recorded at 2 h, 6 h, 24 h, 2 days, 3 days and 7 days after separator placement
Notes	**Conflict of interests/funding:** no source of funding or conflict of interest reported **Adverse events/harm:** participants in the tramadol group reported dizziness, drowsiness, nausea and headache. **Data handling by review authors:** study reported Group 2 as placebo arm and Group 3 as tramadol; for the purposes of the review, Groups 2 and 3 have been inverted to present tramadol as an intervention and placebo as its control **Other information:** the paper has been translated from Farsi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The patients who met the inclusion criteria randomly allocated in one of the three groups and received the medication". **Comment:** inadequate information regarding method of randomisation therefore unable to make a judgement on appropriateness
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding allocation concealment was carried out therefore unable to make a judgement on appropriateness
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were not aware of the medication to which they or others had been allocated, as they received similar sealed pockets with A, B or C stickers on them **Comment:** blinding appears to have been adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** inadequate information regarding method of blinding of assessors, therefore unable to make a judgement on appropriateness
Incomplete outcome data (attrition bias)	Low risk	0/60 dropouts = 0% attrition (100% completed)

Abtahi 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	The data for outcomes in this study were not reported appropriately. We were unable to extract data for use in pooled analysis.
Other bias	High risk	There was large variation in the gender balance of the groups at baseline, which could indicate selection bias.

Arantes 2009

Methods	**Setting:** private clinic, Brazil **Design:** cross-over (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** people of both sexes; aged 16 to 25 years; orthodontic indication for bilateral retraction of the canine teeth **Exclusion criteria:** not reported **Orthodontic intervention:** activation of canine retraction using NiTi springs **Participant sampling:** n = 36 recruited, randomized and analyzed (Group A = 36, Group B = 36, Group C = 36)
Interventions	**Comparisons: NSAID vs placebo, and pre-emptive vs post-treatment analgesia** **Tenoxicam (20 mg) pre-emptive vs placebo (lactose placebo) vs tenoxicam post-treatment**; provided to combat pain from canine activation **Group A:** tenoxicam 45 minutes before treatment, placebo just after, tenoxicam 24 h and 48 h after activation **Group B:** placebo 45 minutes before treatment, tenoxicam just after, tenoxicam 24 h and 48 h after activation **Group C:** placebo 45 minutes before treatment, just after treatment, 24 h and 48 h after activation
Outcomes	• Pain score (VAS) recorded at 12 h, 24 h, 48 h and 72 h after each activation • Pain score (VDS) recorded at 12 h, 24 h, 48 h and 72 h after each activation • Amount of tooth movement (mm) recorded at 4 weeks after each activation (not an outcome of this review) • Rescue medication paracetamol up to 750 mg 3 times per day
Notes	**Conflict of interests/funding:** "This study was supported by a grant-in-aid for scientific research from FAPESP - Fundacao dr Arparo a Pesqiisa de Estado de Sao Paolo." **Adverse events/harm:** no rescue analgesia taken. Harm/adverse effects not reported **Data handling by review authors:** we were unable to extract any usable data from the study. **Other information:** each retraction procedure consisted of 3 activations, alternating between right and left with a 14-day wash-out interval between activations. Participants were randomised to two of the three groups for the left and right side retractions.

Risk of bias

Arantes 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The patients were initially randomized into three groups (A, B, and C) using the program for randomisation available at http://www.random.org." **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Unclear risk	**Quote:** "The drugs and administration methods had been concealed before the procedures." **Comment:** inadequate information regarding method of allocation concealment, therefore unable to make a judgement on appropriateness
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** inadequate information regarding method of blinding, therefore unable to make a judgement on appropriateness
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** inadequate information regarding method of blinding, therefore unable to make a judgement on appropriateness
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/36 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this cross-over trial were not reported appropriately. We were unable to extract data for use in pooled analysis.
Other bias	High risk	There were no data presented in the paper about baseline characteristics of the groups.

Bayani 2016

Methods	**Setting:** Department of Orthodontics, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran **Design:** parallel RCT (5 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** moderate (4 mm to 8 mm) crowding according to Little's irregularity index (Little 1975); requiring extraction of 4 first or second premolars for orthodontic reasons **Exclusion criteria:** systemic or periodontal diseases; previous orthodontic therapy; using analgesics, or medication interrupting tooth movement **Orthodontic intervention:** initial archwire placement **Participant sampling:** n = 100 recruited and randomized (34 male:66 female, aged 14 to 21 years, mean age 17.6 years); n = 90 returned their completed questionnaire; n = 90 had their data analyzed Number in each arm not reported Participant age and gender data not reported for any arm of the trial

Bayani 2016 *(Continued)*

Interventions	**Comparison: NSAID versus placebo** **Ibuprofen (400 mg) vs placebo** **Group 1:** placebo vitamin B6 40 mg tablet immediately after appliance placement and at 8-h intervals for 1 week, if pain persisted **Group 2:** ibuprofen 400 mg tablet immediately after appliance placement and at 8-h intervals for 1 week, if pain persisted **Group 3:** bite wafer to chew on immediately after appliance placement and at 8-h intervals for 1 week, if pain persisted **Group 4:** low-level red laser received as a single session irradiation from a low power indium-gallium-aluminium-phosphide diode laser immediately after appliance placement **Group 5:** low-level infrared laser received as a single session irradiation from a low-level gallium-aluminium-arsenide diode laser immediately after appliance placement Only Groups 1 and 2 are included in the comparisons for this review
Outcomes	Pain score (VAS) recorded at 2 h, 6 h, 10 h (or bedtime), 24 h, 2 days, 3 days and 7 days after archwire placement Pain was recorded during chewing, biting, fitting back teeth together and fitting front teeth together (the latter 3 not being used in this review)
Notes	**Conflict of interests/funding:** no source of funding or conflict of interest reported **Adverse events/harm:** not reported **Data handling by review authors:** data for Groups 1 and 2 have been inverted to reflect ibuprofen as an intervention and placebo as its control. Data from Groups 3, 4 and 5 did not contribute to the analyses. **Other information:** "The study protocol was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote: "**The subjects were randomly assigned to 5 groups of 20 each according to a computer-generated random assignment program." **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding method of allocation concealment, therefore unable to make a judgement on appropriateness
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The subjects assigned to the ibuprofen and placebo medication groups were blinded to their allocation. Furthermore, the investigator who assessed the outcomes and the data analyst were kept blinded to the assignments." **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The investigator who assessed the outcomes and the data analyst were kept blinded to the assignments." **Comment:** blinding appears to be adequateding

Bayani 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	59/100 dropouts = 59% attrition (41% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this study were not reported appropriately. We were unable to extract data for use in pooled analysis.
Other bias	High risk	No baseline characteristics of groups provided; no sample sizes for the final numbers included in the analysis

Bernhardt 2001

Methods	**Setting:** University of Iowa, College of Dentistry, Department of Orthodontics **Design:** parallel RCT (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** scheduled to begin comprehensive orthodontic treatment; no prophylactic antibiotic coverage required; no debilitating systemic diseases; currently not using antibiotics or analgesics; no contraindication to the use of ibuprofen; a maximum age of 16 years and a minimum weight requirement of 88 pounds (weight requirement based on Food and Drug Administration–approved over-the-counter paediatric dosage labelling guidelines) **Exclusion criteria:** none outlined in the Methods, but trialists later excluded participants who did not agree to participate or did not return a completed questionnaire, and those who took additional 'rescue' medication. **Orthodontic intervention:** separator placement **Participant sampling:** n = 114 recruited and randomized n = 63 returned their completed questionnaire n = 22 excluded from analysis for taking additional medication (evenly distributed between the 3 groups) n = 41 data analyzed for (aged 9 years 3 months to 16 years 11 months) **Group 1** (n = 13) 10 male:3 female, mean age 12.1 $\pm$ 1.6 years **Group 2** (n = 14) 4 male:10 female, mean age 13.5 $\pm$ 1.9 years **Group 3** (n =14) 6 male:8 female, mean age12.8 $\pm$ 1.5 years
Interventions	**Comparisons: NSAID vs placebo, and pre-emptive vs post-treatment** **Ibuprofen (400 mg) vs control (lactose placebo)** **Group 1:** ibuprofen 1 h before placement, followed by ibuprofen 6 h after initial dose **Group 2:** ibuprofen 1 h before placement, followed by placebo 6 h after initial dose **Group*3:*** placebo 1 h before placement, followed by ibuprofen 6 h after initial dose
Outcomes	Pain score (VAS) recorded at 2 h, 6 h, 10 h (bedtime), 17 h (awakening) and 24 h, and 2, 3 and 7 days after separator placement

Bernhardt 2001 *(Continued)*

	Pain was recorded during chewing (other measures reported in the study but not included in this review included pain during biting, when fitting back teeth together, and when fitting front teeth together).
Notes	**Conflict of interests/funding:** no source of funding or conflict of interest reported **Adverse events/harm:** 22 participants excluded from analysis for taking additional medication. No harms reported **Data handling by review authors:** data presented for analysis is based on Figure 1 in the paper, which showed mean pain scores (mean + SEM) for chewing. The SEM was used to calculate SD. Data from Group 1 did not contribute to the analyses, Groups 2 and 3 data were used for the comparison of preemptive versus post-treatment analgesia. **Other information of note:** wide variation in gender at baseline for Group 1: "a wide range of individual variation was noted in the pain levels reported, which resulted in large standard deviations. Another possible explanation is the uneven distribution of male and female patients among the groups".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quotes:** "Patients were randomly assigned to 1 of 3 experimental groups." "The randomization of which of the three experimental conditions the patients were assigned to was computer generated." **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quotes:** "Patients were randomly assigned to 1 of 3 experimental groups." "The randomization of which of the three experimental conditions the patients were assigned to was computer generated." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The ibuprofen and placebo capsules were identical in appearance. The patient, research assistant, and investigator were blinded to each subject's experimental group." **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The ibuprofen and placebo capsules were identical in appearance. The patient, research assistant, and investigator were blinded to each subject's experimental group." **Comment:** adequate method of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	73/114 dropouts = 64% attrition (36% completion). High number of dropouts, but equally distributed across the groups
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review reported appropriately
Other bias	Low risk	No other sources of bias detected.

Bird 2007

Methods	**Setting:** Postgraduate Orthodontic Clinic, Kansas City School of Dentistry, University of Missouri **Design:** parallel (2 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** starting orthodontic treatment that required separators; no orthodontic appliances in the mouth; no debilitating systemic diseases or GI problems; not currently taking analgesics or antibiotics; 9 to 19 years of age; minimum weight of 88 pounds; no prophylactic antibiotic coverage required; literate; English-speaking; able to swallow pills; and no contraindication to the use of acetaminophen or ibuprofen **Exclusion criteria:** not specified **Orthodontic intervention:** separator placement **Participant sampling:** n = 40 selected and randomized n = 7 dropouts/excluded from analysis (sought treatment elsewhere n = 1; did not complete questionnaire n = 1; excluded from analysis for not taking medication before the appointment n = 5) n = 33 data analyzed No numbers per group were provided and no sex or age data
Interventions	**Comparison: NSAID vs paracetamol** **Ibuprofen (400 mg) vs paracetamol (650 mg)**; provided pre-emptively to separator placement **Group 1:** paracetamol 1 h before placement **Group 2:** ibuprofen 1 h before placement
Outcomes	Pain score (VAS) recorded immediately after separator placement, at 2 to 3 hours, at bedtime and on rising the next day Pain was recorded during the following activities: • chewing • teeth not touching (not an outcome of this review) • biting back teeth together (not an outcome of this review)
Notes	**Conflict of interests/funding:** no source of funding or conflict of interest reported. **Adverse events/harm:** none reported **Data handling by review authors:** only pain during chewing data are reflected in this systematic review. **Other information of note:** no SD, baseline or group size data presented in the paper; no reply from authors when emailed and asked to provide further information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "A computer-generated stratified random assignment strategy was used to balance the groups with respect to sex."

Bird 2007 *(Continued)*

		Comment: method of randomisation appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "The tablets were given to the patients in sealed, coded envelopes." **Comment:** adequate method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The investigator (C.B.), the patient, and the parent were blinded to the experimental group." **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The investigator (C.B.), the patient, and the parent were blinded to the experimental group." **Comment:** adequate method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/40 dropouts = 17.5% attrition (82.5% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this study were not reported appropriately. We were unable to extract data for use in pooled analysis.
Other bias	High risk	No baseline characteristics of groups provided; no sample sizes for the final numbers included in the analysis.

Bradley 2007

Methods	**Setting:** Dorset County Hospital Dorchester; Royal United Hospitals, Bath, and, Southmead Hospital, Bristol **Design:** parallel (2 arms) **Number of centres:** 3 **Study duration:** February 2004 to December 2005 (23 months)
Participants	**Inclusion criteria:** age between 12 and 16 years; no history of peptic ulceration, or renal, hepatic, or cardiac impairment; no history of asthma requiring steroid inhalers or unstable asthma in the last year; no history of adverse reactions to ibuprofen or paracetamol; and currently not using analgesics or antibiotics **Exclusion criteria:** not specified **Orthodontic intervention:** separator placement **Participant sampling:** n = 208 selected n = 21 excluded n = 21 refused to participate n = 187 randomized (Group 1 n = 92; Group 2 n = 95) n = 28 dropouts/excluded from analysis (lost to follow-up (not returning questionnaire): Group 1 n = 6, Group 2 n = 3; did not fulfil inclusion criteria: Group 1 n = 9, Group 2 n = 10) n = 159 data analyzed

Bradley 2007 *(Continued)*

	Group 1 (n = 77): 28 male:49 female, mean age 13.7 ± 1.0 years **Group 2** (n = 82): 29 male:53 female, mean age 13.8 ± 1.2 years Age: P = 0.38 (independent-samples t test) Sex: P = 1.00 (Chi^2 test for association) male 35.8%, female 64.2%
Interventions	**Comparison: NSAID vs paracetamol** **Ibuprofen (400 mg; 2 x 200 mg caplet) vs paracetamol (1 g; 2 x 500 mg caplet)**; provided pre-emptively to separator placement, and again post-treatment **Group 1:** ibuprofen 1 h before placement, followed by ibuprofen 6 h after initial dose **Group 2:** paracetamol 1 h before placement, followed by paracetamol 6 h after initial dose
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, 10 h/bedtime (primary outcome), 24 h and 2, 3 and 7 days (secondary outcome) after separator placement
Notes	**Conflict of interests/funding:** "We thank the Clinical Trials team in the Pharmacy Production Unit at the Royal Hallamshire Hospital, Sheffield, for supplying the drugs and performing the randomization, and the patients who participated in this trial." Both ibuprofen and paracetamol supplies were cited as being produced by Boots Company, Nottingham, United Kingdom. **Adverse events/harm:** 18 participants required additional medication. **Quote:** "During this trial 1 patient experienced a suspected adverse reaction to paracetamol." This was reported in more detail in the secondary paper by McAlinden et al (Bradley 2007): "since one of the trial drugs was also paracetamol we decided to break the randomization code for this patient to determine which drug the patient had received. The trial drug given was found to be paracetamol, suggesting a drug hypersensitivity reaction to paracetamol". **Data handling by review authors:** study reported Group 1 as the paracetamol arm of trial, and Group 2 as the ibuprofen arm. In order to align with the protocol for this systematic review, the figures for Groups 1 and 2 have been inverted to reflect ibuprofen as an intervention and paracetamol as its control. **Other information of note:** intention-to-treat analysis noted in methods, but only completing participants were analyzed. Trial authors carried out an intention-to-treat analysis on the 18 participants who required additional analgesia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The drugs were supplied according to a restricted randomization method in blocks of 8 to ensure that equal numbers of patients were allocated to each group." **Comment:** block randomisation carried out therefore it can be assumed that this was adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "The analgesics were in the form of identical capsules and were stored in sealed, numbered containers. The random allocation sequence was concealed in an envelope and held centrally." **Comment:** adequate method of allocation concealment

Bradley 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The investigator, the clinicians, the subjects, and the statistician were all blinded to each subject's treatment group." **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The investigator, the clinicians, the subjects, and the statistician were all blinded to each subject's treatment group." **Comment:** adequate method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	28/187 dropouts = 15% attrition (85% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review reported appropriately
Other bias	Low risk	No other sources of bias detected

Bruno 2011

Methods	**Setting:** Dentistry School of Universidade Federal Fluminense, (Niterói, RJ, Brazil) **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** at least 18 years of age; presence of second molars and second bicuspids, since separating elastics had to be fixed on the first molars; no clinical signs of gingival inflammation **Exclusion criteria:** use of any medication that could interfere with results > 2 weeks before the procedure; any of the following conditions, screened through a questionnaire: cardiopathies, nephropathies, hepatopathies or GI disorders, diabetes, high cholesterol, blood vessel obstructions, allergy to anti-inflammatory drugs, intolerance to lactose, pregnancy **Orthodontic intervention:** separator placement **Participant sampling:** n = 87 recruited and randomized n = 38 dropouts or excluded from analysis (n = 18 missing or incomplete information; n = 10 discomfort due to elastic, sought treatment elsewhere; n = 6 used analgesic medication during the study; n = 2 lost their diaries and were unwilling to be resubmitted to the intervention) n = 51 data analyzed **Group A** (n = 17) 4 male:13 female, mean age 24.64 years **Group B** (n = 17) 4 male:13 female, mean age 22.64 years **Group C** (n = 17) 5 male:12 female, mean age 22.47 years
Interventions	**Comparison: NSAID vs placebo** **Lumiracoxib (400 mg) vs placebo vs no treatment**; provided pre-emptively to separator placement **Group A:** lumiracoxib 1 h before separator placement

Bruno 2011 *(Continued)*

	Group B: placebo 1 h before separator placement **Group C:** no intervention
Outcomes	Pain score (VAS) recorded at 2 h, 6 h and 24 hours and at 2 and 4 days after separator placement
Notes	**Conflict of interests/funding: quote:** "The authors have reported no conflicts of interest." **Adverse events/harm:** not reported **Data handling by review authors:** study reports Group A as placebo, Group B as lumiracoxib and Group C as control For the purposes of aligning with the protocol for this systematic review, the figures for Groups A and B have been inverted to reflect ibuprofen as an intervention and placebo and no treatment as its controls. **Other information of note:** we received data for means and standard deviations via correspondence with the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were randomly assigned into one of three groups by drawing lots. To ensure similarity in size of the groups, randomisation was stratified in blocks of ten (permuted-block randomisation)." **Comment:** block randomisation carried out, therefore it can be assumed that this was adequate.
Allocation concealment (selection bias)	High risk	**Quote:** "Patients were randomly assigned into one of three groups by drawing lots"; "As each volunteer attended the Department of Orthodontics, in Universidade Federal Fluminense (the University), he was allocated to the group following the last participant had entered. The search was not started with the sample enclosed." **Comment:** allocation concealment not achieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** "The placebo and lumiracoxib capsules were perfectly identical and neither the researchers nor the subjects knew the group of each subject. Patients of the non-medication group knew about the use of capsules by the other two groups." **Comment:** adequate method of blinding where appropriate. Not possible to blind participants and personnel to allocated control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The VAS was given to a statistician blinded to the study group." **Comment:** adequate method of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	36/87 dropouts = 41.4% attrition (58.6% completion)
Selective reporting (reporting bias)	Low risk	Raw data not presented in paper, only statistical analysis and significance. Further information regarding data was received via correspondence with the author.
Other bias	Low risk	No other source of bias detected

Eslamian 2014

Methods	**Setting:** Orthodontics Department of Shahid Beheshti University, School of Dentistry and a private clinic in Tehran **Design:** cross-over (3 arms) **Number of centres:** 2 **Study duration:** not reported
Participants	**Inclusion criteria:** no pain at the onset of study; in previous sessions complained of pain > 50 based on the VAS; 6 mm to 8 mm crowding; no use of analgesics during the study period; no history of renal or liver disease or any other contraindication for the use of understudy medications (Comment: we have assumed a typographical error was made in the paper and that the trial authors meant 'liver' disease when they wrote 'river' disease.) **Exclusion criteria:** did not sign the consent form; used analgesics and anti-inflammatory drugs during the study; did not complete the questionnaire; did not use or used benzocaine or ketoprofen chewing gums improperly **Orthodontic intervention:** mid-treatment adjustments **Participant sampling:** n = 30 recruited and randomized n = 4 dropouts/excluded from analysis n = 26 data analyzed **Group A** (n = 26) 12 male:14 female, mean age 18.07 $\pm$ 3.19 years **Group B** (n = 26) 12 male:14 female, mean age 18.07 $\pm$ 3.19 years **Group C** (n = 26) 12 male:14 female, mean age 18.07 $\pm$ 3.19 years
Interventions	**Comparisons: NSAID vs placebo, local anaesthetic vs placebo, and NSAID vs local anaesthetic** **Ketoprofen chewing gum vs benzocaine chewing gum vs placebo chewing gum** provided postoperatively following appliance adjustments **Group A:** ketoprofen chewing gum every 8 h for 3 days after treatment **Group B:** benzocaine chewing gum every 8 h for 3 days after treatment **Group C:** placebo chewing gum every 8 h for 3 days after treatment
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, 24 hours, 10 am and 6 pm on day 2, 10 am and 6 pm on day 3, and 7 days after appliance adjustment
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** study did not allocate intervention to specific group labels. For the purposes of this systematic review, Group A is the ketoprofen arm, Group B the benzocaine arm and Group C the control arm. **Other information of note:** data for means and standard deviations were received via correspondence with the author. Orthodontic intervention involved in the study was described as "fixed orthodontic treatment". This was clarified through correspondence with the author as involving retie of an 0.016" or 0.018" NiTi archwire. 4-week washout period allowed between interventions

Eslamian 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Thirty patients were randomly divided into three groups of 10"; "In the first session patients 1-10 receive ketoprofen, 11-20 receive benzocaine, 21-30 receive placebo gums. In the next visit 1-10 benzocaine, 11-20 placebo, 21-30 ketoprofen; and in the last visit 1-10 placebo, 11-20 ketoprofen, 21-30 benzocaine". **Comment:** inadequate information and methods regarding method of randomisation, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Low risk	**Quote:** "Thirty patients were randomly divided into three groups of 10"; "random allocation by a third person who was responsible for explaining to the patients". **Comment:** appeared to be adequate method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The placebo chewing gum was manufactured with the same shape and packaging as the experimental gums. Patients and those administering the gums among patients were blinded to the type of chewing gums". **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Questionnaires were analyzed by a statistician blinded to the group allocation of patients". **Comment:*a***dequate method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/30 dropouts = 13.3% attrition (86.7% completion). However the reason for drop out was unclear.
Selective reporting (reporting bias)	High risk	Unclear data presented in paper and received from correspondence with the author. We were unable to use this study in pooling for meta-analysis.
Other bias	Low risk	No other source of bias detected

Eslamian 2016a

Methods	**Setting:** Orthodontics Department of Shahid Beheshti University, School of Dentistry, Tehran, Iran **Design:** cross-over (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** undergoing orthodontic treatment, currently experiencing no oral pain, positive history of pain after orthodontic appliance activation **Exclusion criteria:** currently taking analgesics, or medication with contraindictaions related to drug use **Orthodontic intervention:** mid-treatment **Patient sampling:** n = 30 recruited and randomized

Eslamian 2016a *(Continued)*

	n = 10 dropouts/excluded from analysis (protocol violations or unwillingness to co-operate (7)) n = 20 data analyzed (7 male:13 female, mean age 19.5 years range 15 to 25 years)
Interventions	**Comparison: Local anaesthetic vs placebo** **Local anaesthetic vs placebo gel**; provided postoperatively following activation of loop/archwire placement **GroupA:** 5% benzocaine gel twice a day (at 10 am and 10 pm) for 3 days **Group B:** 5% ketaprofen gel twice a day (at 10 am and 10 pm) for 3 days **GroupC:** p[lacebo gel twice a day (at 10 am and 10 pm) for 3 days
Outcomes	Pain score (VAS graded 0-4) - recorded at 2 h, 6 h, 24 h after gel application. and 2, 3 and 7 days after loop placement
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** data were presented as mean and 95% confidence intervals. We were unable to calculate standard deviation and therefore the data from this trial did not contribute to the analyses. **Other information of note:** 4-week washout period allowed between interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "By the use of a random number table, each patient was prescribed one of the three gels for the next three appointments" **Comment:** adequate method of randomisation
Allocation concealment (selection bias)	Low risk	**Quote:** "The same nurse conducted the crossover under the supervision of the clinician, who was unaware of the content of the gel tubes." **Comment:** adequate method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The colour and odour of all gels were identical and the tubes were not labelled, to make them indistinguishable to the patients and clinician." **Comment:** adequate method of randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** described as double-blind, but inadequate information provided regarding how blinding of outcome assessment was carried out, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	High risk	10/30 dropouts = 33.3 attrition (66.7% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were reported appropriately. We were unable to extract data for inclusion in pooled analysis.
Other bias	Low risk	No other source of bias detected.

Eslamian 2016b

Methods	**Setting:** Orthodontics Departmentof Shahid Beheshti University, School of Dentistry, Tehran, Iran **Design:** cross-over (2 arms) **Number of centres:** 1 **Study duration:** 14 months (January 2011 up to March 2012)
Participants	**Inclusion criteria:** signed informed consent of the included subjects or their legally authorised representatives, no current chronic or acute pain in the oral cavity, positive history of pain after first orthodontic appliance activation, and subject was in the levelling and alignment phase of treatment **Exclusion criteria:** taking analgesics or antibiotics, history of severe kidney or liver disease, and history of allergic reaction to local anaesthetic drugs or a history of methemoglobinemia **Orthodontic intervention:** mid-treatment adjustments **Patient sampling:** n = 30 recruited and randomized n = 5 dropouts/excluded from analysis (n = 1 refusal to continue, n = 2 imprecision in obeying the study protocol, n = 2 use of other pain relieving drugs during the study (exclusion of these participants is a bias)) n = 25 data analyzed (8 male:17 female, mean age 19.5 years range 15 to 25 years) **Group A** (n = 13) data for age and gender not presented **Group B** (n = 12) data for age and gender not presented
Interventions	**Comparison: Local anaesthetic vs placebo** **Local anaesthetic vs placebo gel**; provided postoperatively following appliance adjustments **Group A:** 5% benzocaine gel twice a day (at 10 am and 10 pm) for 3 days **Group B:** placebo gel twice a day (at 10 am and 10 pm) for 3 days
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, 24 h and day 2 at 10 am and 6 pm, day 3 10 am and 6 pm and 7 days after appliance adjustment
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** The data presented for the analysis were based on Figure 1, which showed mean pain scores (mean + SEM). The SEM was used to calculate SD. **Other information of note:** 4-week washout period allowed between interventions. We clarified that the orthodontic intervention involved in the study involved retie of an 0.016" or 0.018" NiTi archwire through correspondence with the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Randomization and sequence generation were carried out with the aid of random number generator in SPSS software". **Comment:** adequate method of randomisation

Eslamian 2016b *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote:** "Allocation concealment was achieved with sequentially numbered letters in opaque envelopes containing gel tube numbers." **Comment:** adequate method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Adequate method of allocation concealment. The tubes were essentially the same, and neither the subjects nor the clinicians knew whether the tubes contained placebo or benzocaine." **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** inadequate information regarding method of blinding of outcome assessment, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	High risk	5/30 dropouts = 16.7% attrition (83.3% completion). Participants were excluded as they used other pain relieving drugs - this is a source of bias as these were probably the participants experiencing the greatest pain.
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were not reported appropriately. The crossover structure of the data was ignored in the trialists' presentation and analysis of the data.
Other bias	Low risk	No other source of bias detected.

Farzanegan 2012

Methods	**Setting:** Orthodontic clinic of Mashhad University of Medical Sciences in Iran **Design:** parallel (5 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** female orthodontic patients between 13 and 18 years of age, scheduled for fixed orthodontic treatment, with no systemic diseases and not receiving analgesic therapy; with moderate crowding (4 mm to 8 mm) according to Little's irregularity index (Little 1975) All participants needed extraction of the 4 first premolars for orthodontic reasons, and the extractions were scheduled to be finished at least 2 weeks before the placement of the orthodontic appliances. **Exclusion criteria:** none specified **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 50 recruited and randomized and analyzed **Group 1** (n = 10) female only, age data not reported **Group 2** (n = 10) female only, age data not reported **Group 3** (n = 10) female only, age data not reported **Group 4** (n = 10) female only, age data not reported **Group 5** (n = 10) female only, age data not reported
Interventions	**Comparison: NSAID vs placebo**

Farzanegan 2012 *(Continued)*

	Ibuprofen (400 mg) vs placebo vs chewing gum vs soft viscoelastic bite wafer vs hard viscoelastic bite wafer; provided after initial archwire placement **Group 1:** ibuprofen immediately after archwire placement and at 8-h intervals for a week if pain persisted **Group 2:** placebo immediately after archwire placement and at 8-h intervals for a week if pain persisted **Group 3:** gum chewed for 5 minutes immediately after archwire placement and at 8-h intervals for a week if pain persisted **Group 4:** soft bite wafer chewed or bitten down on for 5 minutes at 8-h intervals for a week if pain persisted **Group 5:** hard bite wafer chewed or bitten down on for 5 minutes at 8-h intervals for a week if pain persisted
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime, 24 h and 2, 3 and 7 days after placement of initial archwires Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together (not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported. “None had used any analgesics” **Data handling by review authors:** study reports Group 1 as placebo arm and Group 2 as ibuprofen arm. For the purposes of aligning with this systematic review's own protocol, the figures for Groups 1 and 2 have been inverted to reflect ibuprofen as an intervention and placebo as its control. Data for Groups 3, 4 and 5 have not been included for the purposes of this review. **Other information of note:** only pain during chewing data were reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The subjects were randomly assigned to 1 of 5 parallel groups in a 1:1:1:1:1 ratio according to their clinical entrance number and a random number table." **Comment:** block randomisation carried out, therefore it can be assumed that this was adequate.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "The subjects were randomly assigned to 1 of 5 parallel groups". **Comment:** inadequate information regarding method of allocation concealment, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The subjects in these 2 groups (ibuprofen & placebo) were blinded about the drug that they took." **Comment:** adequate method of blinding was carried out where appropriate for Group 1 and Group 2. Not possible to blind participants and personnel regarding allocation to Groups 3, 4 or 5.

Farzanegan 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information regarding method of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/50 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Gupta 2014

Methods	**Setting:** Department of Orthodontics, AECS Maaruti College of Dental Sciences and Research Centre, Bangalore, India **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** patients undergoing bonding and initial archwire placement using a 0.014"/0.016" NiTi wire in at least in 1 arch **Exclusion criteria:** taking any antibiotics or analgesics; allergy to NSAIDs; oral pathology; had a tooth extracted within 2 weeks before bonding **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 45 recruited and randomized (23 female:22 male; aged 15-22 years) n = 0 lost to follow-up n = 45 data analyzed **Group 1** (n = 15) 8 male:7 female, age data not reported **Group 2** (n = 15) 7 male:8 female, age data not reported **Group 3** (n = 15) 7 male:8 female, age data not reported
Interventions	**Comparisons: NSAID vs paracetamol, NSAID vs etoricoxib, and NSAID vs placebo** **Paracetamol (500 mg) vs etoricoxib (60 mg) vs placebo**; provided 1 h before initial archwire placement and postoperatively **Group 1:** paracetamol 1 h before and thrice daily for 3 days after archwire placement **Group 2:** etoricoxib 1 h before and once daily for 3 days after archwire placement **Group 3:** placebo 1 h before and thrice daily for 3 days after archwire placement
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime, 24 h and 2nd day at nighttime, 48 h after initial archwire placement and 3rd day at nighttime

Gupta 2014 *(Continued)*

Notes	**Conflict of interests/funding:** "M. Gupta, S. Kandula, S.M. Laxmikant, S.S. Vyavahare, B.H.R. Satheesha, and C.S. Ramachandra state that there are no conflicts of interest. All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies." **Adverse events/harm:** not reported. “None of them had resorted to using any kind of additional medication” **Data handling by review authors:** study reported Group 2 as placebo arm and Group 3 as etoricoxib arm. For the purposes of aligning with this systematic review's own protocol, the figures for Groups 2 and 3 have been inverted to reflect etoricoxib as an intervention and placebo as its control. **Other information of note:** time points for 1st day bedtime, 2nd and 3rd day night-times were not specified. 1st day bedtime has been assumed to be approximately 10 h, 2nd day night-time has been assumed to be approximately 31 h and 3rd day night-time as approximately 53 h.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were randomly assigned to three different groups and blinding was done using the SNOSE technique (sequentially numbered opaque sealed envelopes)" **Comment:** randomisation appears to be adequate.
Allocation concealment (selection bias)	Low risk	**Quote:** "Patients were randomly assigned to three different groups and blinding was done using the SNOSE technique (sequentially numbered opaque sealed envelopes)." **Comment:** allocation concealment appears to be adequate.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Patients were enrolled in this double-blind, prospective study". **Comment:** described as double-blind, but inadequate information regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Patients were enrolled in this double-blind, prospective study". **Comment:** described as double-blind, but inadequate information regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/45 dropout = 0% (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Kawamoto 2010

Methods	**Setting:** 2 private practices in Lee’s Summit, Missouri

Kawamoto 2010 *(Continued)*

	Design: parallel (3 arms) **Number of centres:** 2 **Study duration:** not reported
Participants	**Inclusion criteria:** started orthodontic treatment that required banding of posterior teeth and placement of 2 or more separators; able to swallow analgesic pills; English speaking; 9 to 17 years of age; minimum weight requirement of 88 pounds based on mg/kg paediatric dosage recommendations **Exclusion criteria:** existing orthodontic or space maintenance appliances; contraindication to the use of acetaminophen or ibuprofen; taking antibiotics or analgesics; cognitive impairment, or any systemic disease that in the assessment of the investigator might impact pain perception **Orthodontic intervention:** separator placement **Patient sampling:** n = 35 enrolled n = 9 dropouts/excluded from analysis (Group 1 = 4, Group 2 = 2, Group 3 = 3 all failed to return questionnaires) n = 26 data analyzed for: **Group 1** (n = 7) 1 male:6 female, mean age 12.7 ± 1.3 years **Group 2** (n = 10) 3 male:7 female, mean age 13.0 ± 1.6 years **Group 3** (n = 9) 5 male:4 female, mean age 12.6 ± 1.8 years
Interventions	**Comparisons: NSAID vs placebo, NSAID vs paracetamol, and paracetamol vs placebo** **Ibuprofen (400 mg) vs paracetamol (650 mg) vs placebo (640 mg avicel)**; provided pre-emptively and post-treatment for separator placement **Group 1:** ibuprofen 1 h before placement and 6 h after initial dose **Group 2:** paracetamol 1 h before placement and 6 h after initial dose **Group 3:** placebo 1 h before placement and 6 h after initial dose
Outcomes	Pain score (VAS) - recorded immediately before and after, 2 h, 6 h, bedtime, 24 h after separator placement Pain was recorded during the following activities: • chewing • teeth not touching (not an outcome of this review) • biting (not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** study reports Group 1 as placebo arm and Group 3 as ibuprofen arm. For the purposes of aligning with this systematic review's own protocol, the figures for Groups 1 and 3 have been inverted to reflect ibuprofen as an intervention and placebo as its control. **Other information of note:** only pain during chewing data were reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kawamoto 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Quote:** "Computer generated random patient coding and group allocation was utilized". **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "The random allocation assignments were concealed and inaccessible to the investigator." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The ibuprofen, acetaminophen, and placebo tablets were compounded by a licensed pharmacist (O'Brien Pharmacy, Kansas City, MO) according to specifications and were all provided in identical white opaque capsules. Medications and placebo tablets were packed and distributed in sealed, coded envelopes"; "Subjects, patients and investigator would be blinded to group allocation". **Comment:** adequate method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The random allocation assignments were concealed and inaccessible to the investigator"; "Subjects, patients and investigator would be blinded to group allocation". **Comment:** adequate method of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	9/35 dropouts = 25.7% attrition (74.3% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	High risk	Large gender variation at baseline, more females in all groups indicating sampling bias.

Kluemper 2002

Methods	**Setting:** Graduate Orthodontic Clinic at the University of Kentucky College of Dentistry and the full-time and part-time faculty practices **Design:** parallel (2 arms) **Number of centres:** unclear **Study duration:** not reported
Participants	**Inclusion criteria:** orthodontic treatment included full, fixed orthodontic appliances (braces); males and females; periodontal tissues were in good health; no systemic disease that would compromise normal healing (e.g. diabetes); no medications being taken at the time of the study **Exclusion criteria:** none specified **Orthodontic intervention:** initial bracket placement without archwire **Patient sampling:** n = 80 randomized (Group 1 n = 40; Group 2 n = 40) n = 10 dropouts/excluded from analysis (lost to follow-up: not returning questionnaire = 7; did not require pain relief = 3)

Kluemper 2002 *(Continued)*

	n = 70 data analyzed for: **Group 1** (n = 35) 18 male:17 female, mean age 23.8 ± 10.3 years **Group 2** (n = 35) 16 male:19 female, mean age 25.2 ± 8.6 years Age P = 0.5 Sex: P = 0.6
Interventions	**Comparison: local anaesthetic wax vs placebo** **Benzocaine wax vs placebo**; provided post-treatment for topical use, not applied until 24 h after treatment **Group 1:** orthodontic menthol wax, medicated with 20% benzocaine **Group 2:** unmedicated orthodontic wax (without menthol)
Outcomes	Pain score (VAS) - recorded at baseline, 1 h, 17 h, 29 h, 41 h, 53 h after baseline
Notes	**Conflict of interests/funding:** not reported. The benzocaine wax product received a patent by the United States Patent and Trademark Office (Patent No.6,074,674) **Adverse events/harm:** not reported **Data handling by review authors:** only intervention study data included in this review. Study did not allocate intervention to specific group labels. For the purposes of this systematic review, Group 1 has been allocated as the benzocaine arm and group 2 as the control arm. Although multiple time points measured, intervention not taken until 24 h after visit, therefore data from this study has not contributed to analyses in this systematic review. **Other information of note:** much of the detail in the paper related to the pilot (e.g. the inclusion criteria) prior to the RCT. Both are presented collectively in the paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The medicated and unmedicated waxes were randomized and were contained in numerically coded cases." **Comment:** inadequate information regarding method of randomisation, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Low risk	**Quote:** "The medicated and unmedicated waxes were randomized and were contained in numerically coded cases." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The patients received dental wax without knowing whether the anaesthetic was incorporated into the wax". **Comment:** described as double-blind, both identically prepared, however, "neither the benzocaine nor the menthol" was included in the placebo. Intervention and control possessed different tastes, but patients unlikely to recognise whether active drug or not, or to discuss with other participants.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Randomised double-blind prospective RCT".

Kluemper 2002 *(Continued)*

		Comment: described as double-blind, but inadequate information provided regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/80 dropouts = 12.5% attrition (87.5% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Kohli 2011

Methods	**Setting:** Department of Orthodontics & Dentofacial Orthopedics, Hitkarini Dental College & Hospital, Jabalpur, India **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** at least 13 years of age and not older than 20 years; beginning orthodontic treatment for the first time; reporting no contraindications or adverse reactions related to ibuprofen and piroxicam; not using any antibiotics; and meeting a minimum weight requirement of 88 pounds, as per Food and Drug Administration approved-over-the-counter paediatric dosage labelling guidelines; required to provide written informed consent for participation in the study. **Exclusion criteria:** none specified **Orthodontic intervention:** separator placement **Patient sampling:** n = 90 randomized (Group 1 n = 30; Group 2 n = 30; Group 3 n = 30) n = 0 dropouts/excluded from analysis n = 90 analyzed (45 male: 45 female) **Group 1** (n = 30) 15 male:15 female, mean age 14.7 ± 3.4 years **Group 2** (n = 30) 15 male:15 female, mean age 14.2 ± 2.8 years **Group 3** (n = 30) 15 male:15 female, mean age 15.1 ± 3.6 years
Interventions	**Comparisons: NSAID vs placebo vs NSAID** **Ibuprofen (400 mg) vs piroxicam (20 mg) vs placebo**; provided 1 h pre-emptively **Group 1:** ibuprofen 1 h before separator placement **Group 2:** placebo 1 h before separator placement **Group 3:** piroxicam 1 h before separator placement
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime, 24 h and 2, 3 and 7 days after separator placement Pain was recorded during the following activities: • chewing

Kohli 2011 *(Continued)*

- biting (not an outcome of this review)
- fitting front teeth together (not an outcome of this review)
- fitting posterior teeth together (not an outcome of this review)

Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported. “None of them had resorted to the usage of any kind of ‘rescue medication.’” **Data handling by review authors:** study reports Group 1 as placebo arm of trial, Group 2 as ibuprofen arm and Group 3 as piroxicam arm. For the purposes of aligning with this systematic review's own protocol, the figures for Groups 1 and 2 have been inverted to reflect ibuprofen as an intervention and piroxicam and placebo as its controls. Additional information received through correspondence with the author. **Other information of note:** only pain during chewing data were reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "30 patients were randomly assigned to the three experimental groups". **Comment:** inadequate information regarding method of randomisation, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "30 patients were randomly assigned to the three experimental groups". **Comment:** inadequate information regarding method of allocation concealment, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The investigational drug pharmacy at the institute dispensed the drugs so that the investigator would be blinded to the experimental group." **Comment:** described as double-blind, but inadequate information regarding how blinding of participants was carried out, therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The investigational drug pharmacy at the institute dispensed the drugs so that the investigator would be blinded to the experimental group." **Comment:** adequate method of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/90 dropouts =0% attrition (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Lauritano 2000

Methods	**Setting:** San Raffaele Hospital, Madrid

Lauritano 2000 *(Continued)*

	Design: parallel (2 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** male and female mobile patients; aged between 18-40 years; fitted with a brace; moderate or severe pain in the mouth region measured using the VAS; at least 1 of the 2 signs of inflammation (oedema or hyperaemia) of a moderate intensity, or severe on a point scale from 0 to 3; written consent provided by the patient **Exclusion criteria:** none specified **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 120 patients selected and randomized n = 0 dropouts/excluded from analysis n = 120 data analyzed for: **Group 1** (n = 60) gender and age data not reported **Group 2** (n = 60) gender and age data not reported
Interventions	**Comparison: NSAID vs NSAID** **Ketoprofen (160 mg) vs benzidamine chloride (22.5 mg)**; mouthwash provided postoperatively **Group 1:** ketoprofen 10 ml in 100 ml of water twice a day (after breakfast and the evening meal) for up to 7 days **Group 2:** benzidamine chloride 15 ml twice a day (after breakfast and the evening meal) for up to 7 days
Outcomes	**Primary outcome:** pain score (VAS) - recorded at baseline, on days 1, 2, 3, 4, 5, 6, and 7, 1 h after breakfast and 1 h after the evening meal **Secondary outcome:** the seriousness of the following signs – oedema and hyperaemia were measured on a graduated scale of 0-3 (3 being intense pain). The pain was measured by the person conducting the experiment, on examination of the oral cavity when the brace was initially fitted, on the second visit and on the third and final visit. Resolution of any signs of inflammation was deducted from the data produced regarding seriousness, following the same marking procedure (complete remission of inflammation, a good improvement, slight improvement, no effect) 0 = a complete remission.
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not discussed **Data handling by review authors:** although multiple time points were measured, data were only presented for 4 days. Therefore, data from this study have not been used for this systematic review. No information is provided relating to dropouts, so we have assumed that all participants returned questionnaires and contributed to the final analysis. **Other information of note:** this paper was translated from Italian, with additional correspondence from the author.
Risk of bias	

Lauritano 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomised study in the single caesium for parallel groups". **Comment:** inadequate information regarding method of randomisation, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomised study in the single caesium for parallel groups". **Comment:** inadequate information regarding method of allocation concealment, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The study was carried out in 120 patients submitted to orthodontic therapy by oral route, under single blind conditions." **Comment:** described as single-blind, but inadequate information regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "The study was carried out in 120 patients submitted to orthodontic therapy by oral route, under single blind conditions." **Comment:** described as single-blind, but inadequate information regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/120 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes at all time points recorded were not reported, only data for 4 days were available.
Other bias	High risk	There are no data presented in the paper concerning baseline characteristics of the groups.

Minor 2009

Methods	**Setting:** University of Florida orthodontic clinic **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** 37 months
Participants	**Inclusion criteria:** at least 13 and not older than 30 years of age; not pregnant; beginning orthodontic treatment for the first time; orthodontic treatment required the placement of at least 1 separator in each of the 4 quadrants; no contraindications or adverse reactions to ibuprofen or almonds; and written informed consent to participate. **Exclusion criteria:** none specified **Orthodontic intervention:** separator placement **Patient sampling:** n = 51 enrolled n = 0 dropouts/excluded from analysis

Minor 2009 *(Continued)*

	n = 51 data analyzed for: **Group A** (n = 16) 6 male:10 female, mean age 17.6 ± -5.0 years **Group B** (n = 17) 10 male:7 female, mean age 14.9 ± 2.7 years **Group C** (n = 18) 5 male:13 female, mean age 16.4 ± 3.6 years
Interventions	**Comparison: NSAID vs placebo** **Ibuprofen (400 mg) vs placebo**; provided pre- and post-treatment to separator placement, or post-treatment, or both **Group A:** ibuprofen 1 h before placement, 3 h after and 7 h after placement **Group B:** placebo 1 h before placement, ibuprofen 3 h and 7 h after placement **Group C:** placebo 1 h before placement, placebo 3 h and 7 h after placement
Outcomes	Pain score (VAS) - recorded at pre-treatment expectation of pain, 2 h, 6 h, 10 h,/bedtime, 17 h,/awakening, 24 h and 2, 3 and 7 days after separator placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together (not an outcome of this review) Masticatory efficiency test (masticatory performance index (not an outcome of this review) Expectation of pain (VAS) (not an outcome of this review) Affective states (State and Trait Anxiety Inventory (STAI))
Notes	**Conflict of interests/funding:** none reported **Adverse events/harm:** not discussed **Data handling by review authors:** only pain during chewing data required for this systematic review, however it was unclear from the published data what the VAS measurements presented - Table III labelled as 'chewing' but the Discussion stated that the data for chewing was not included. Mean VAS data for 24 h showed values of over 10 cm, despite a 10 cm VAS being used. Therefore, data for 24 h has been excluded for the purposes of this review. For the purposes of this review, data from Group B have not been used, data from Group A and C have been used for the comparison of NSAID versus placebo. **Other information of note:** pain during chewing data as presented in Table III is reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "They were randomly assigned to 1 of 3 groups stratified by sex." **Comment:** inadequate information regarding method of randomisation, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "They were randomly assigned to 1 of 3 groups stratified by sex."

Minor 2009 *(Continued)*

		Comment: inadequate information regarding method of allocation, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Placebo-controlled, double-blind, parallel arm, prospective study". **Comment:** described as double-blind, but inadequate information regarding how blinding of participants and personnel was ensured, therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Placebo-controlled, double-blind, parallel arm, prospective study". **Comment:** described as double-blind, but inadequate information regarding how blinding of outcome assessment was ensured, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/51 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	High risk	Study protocol not available. Individual VAS scores for biting, chewing, fitting front teeth, and fitting back teeth were not recorded. 10 cm VAS used, but measurements show values of > 10 cm at 24 h for all 3 groups.
Other bias	Low risk	No other sources of bias detected.

Najafi 2015

Methods	**Setting:** Orthodontic Clinic of Dental School at Shiraz University of Medical Sciences, Iran **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** patients needing separator placement to begin orthodontic treatment in the maxillary arch; aged 15 years or older; were informed and signed the written informed consent; not using antibiotics, analgesics, anti-inflammatory, anti-coagulative, diuretics, oral anti diabetics, lithium, cyclosporine, or methotrexate; no need for antibiotic prophylaxis; no chronic systemic disease or clotting disorders; not reporting contraindication for NSAIDs; not pregnant or nursing **Exclusion criteria:** none specified, but excluded participants who took additional analgesics **Orthodontic intervention:** separator placement **Patient sampling:** n = 349 assessed for eligibility (Group 1 = 107, Group 2 = 107, Group 3 = 107) n = 28 excluded (12 did not meet inclusion criteria, 16 decided not to participate) n = 321 enrolled and randomized n = 16 dropouts (Group 1 = 5, Group 2 = 7, Group 3 = 4 lost to follow-up) n = 64 excluded from analysis (Group 1 = 26, Group 2 = 24, Group 3 = 14 did not complete questionnaire correctly (n = 46)/took additional analgesics (n = 18)) n = 241 data analyzed for: **Group 1** (n = 76) 21 male:55 female, mean age 22.1 $\pm$ 3.2 years

Najafi 2015 *(Continued)*

	Group 2 (n = 76) 19 male:57 female, mean age 21.7 ± 3.5 years **Group 3** (n = 89) 21 male:68 female, mean age 21.2 ± 3.8 years
Interventions	**Comparisons: NSAID vs NSAID, and NSAID vs paracetamol** **Ibuprofen (400 mg) vs paracetamol (650 mg) vs meloxicam (7.5 mg)**; provided pre-emptively to separator placement **Group 1:** ibuprofen 1 h before separator placement **Group 2:** paracetamol 1 h before separator placement **Group 3:** meloxicam 1 h before separator placement
Outcomes	Pain score (VAS) - recorded mmediately, and at 2 h, 6 h, 24 h and 48 h after separator placement Pain was recorded during the following activities: • chewing • rest (not an outcome of this review) • fitting posterior teeth together(not an outcome of this review)
Notes	**Conflict of interests/funding:** this work was supported by the Vice-Chancellery of Shiraz University of Medical Science (2168). The authors declare that they have no competing interests. **Adverse events/harm:** not reported **Data handling by review authors:** study does not allocate intervention to specific group labels. For the purposes of this systematic review, Group 1 has been allocated as the ibuprofen arm, Group 2 as the paracetamol arm and group 3 as the meloxicam arm. Although referred to as acetaminophen in the study, this group has been referred to as paracetamol for the purposes of this review. **Other information of note:** only pain during chewing data were reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The block randomization method was used with block length 9, and number of repetition for each group n = 3, to allocate subjects in each group. This method was used separately for each sex group to provide groups with equal numbers of male and female." **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "The block randomization method was used with block length 9, and number of repetition for each group n = 3, to allocate subjects in each group. This method was used separately for each sex group to provide groups with equal numbers of male and female." **Comment:** inadequate information regarding method of allocation, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "In each group, all tablets were covered by identical gelatin cover, so the investigators, the patients, and the statistician were all blind to the treatment groups." **Comment:** blinding appears to be adequate

Najafi 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "In each group, all tablets were covered by identical gelatin cover, so the investigators, the patients, and the statistician were all blind to the treatment groups." **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	80/321 = 25% dropouts (75% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Ngan 1994

Methods	**Setting:** Ohio State University Orthodontic Clinic **Design:** parallel (arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** not specified **Exclusion criteria:** not specified **Orthodontic intervention:** separator placement, 2nd stage of initial archwire placement **Patient sampling:** n = ? selected n = ? excluded/refused to participate 84 patients randomized; 28 per group. 34 female:43 male. n = 7 dropouts/excluded from analysis; Group 1 = 5, Group 2 = 0, Group 3 = 2. n = 77 separators and 56 archwires data analyzed for: **Group A** separators (n = 23) 15 male:8 female, mean age 16.1 ± 5.5 years **Group A** archwire (n = 17) 11 male:6 female, mean age data not available **Group B** separators (n = 28) 16 male:12 female, mean age 15.4 ± 6.9 years **Group B** archwire (n = 17) 10 male:7 female, mean age data not available **Group C** separators (n = 26) 12 male:14 female, mean age 18.1 ± 7.3 years **Group C** archwire (n = 22) 11 male:11 female, mean age data not available
Interventions	**Comparisons: NSAID vs placebo, NSAID vs aspirin, and aspirin vs placebo** **Ibuprofen (400 mg) vs aspirin (650 mg) vs placebo(beta-lactose)**; provided immediately after separator and initial archwire placement **Group A:** ibuprofen immediately after placement

Ngan 1994 *(Continued)*

	Group B: aspirin immediately after placement **Group C:** placebo immediately after placement
Outcomes	Pain score VAS) - recorded at 2 h, 6 h, 24 h and 2, 3 and 7 days after separator or initial archwire placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together(not an outcome of this review)
Notes	**Conflict of interests/funding:** none reported **Adverse events/harm:** not discussed **Data handling by review authors:** VAS data were recorded for chewing, biting, fitting or putting front teeth together, and fitting on the back teeth. However data were combined for analysis in the study and these have been used for this review, as the individual data were not available. **Other information of note:** different initial archwires and appliances were used, "11 had upper and lower arch Begg fixed appliances fitted with 0.016-inch base arch wires. In the remaining 45 patients, 0.022-inch edgewise brackets were bonded to the upper and lower arches, and all brackets fully engaged with an initial 0.0175-inch Response archwire."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Randomly divided into three groups". **Comment:** inadequate information regarding how randomisation was ensured, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding method of allocation, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The capsules appeared identical and were coded by number with the code kept by the pharmaceutical company who encapsulated the placebo and medications. The code was not revealed until the study was completed." **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The capsules appeared identical and were coded by number with the code kept by the pharmaceutical company who encapsulated the placebo and medications. The code was not revealed until the study was completed." **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/84 = 8% dropouts (92% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this study were not reported appropriately. We were unable to extract data for use in pooled analysis.
Other bias	Low risk	No other sources of bias detected.

Nik 2016

Methods	**Setting:** Dental faculty of Tehran University of Medical Sciences **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** participants started orthodontic treatment that required separators; had no systemic or GI diseases, not taking analgesics or any other drugs; no contraindication to the use of either acetaminophen (paracetamol) or liquefied ibuprofen; weight above 40 kg; first molar was without decay, filling or periodontal problem (this criterion was checked through clinical observation, probing and panoramic radiographs) **Exclusion criteria:** none specified, however, later stated they would exclude people who had taken additional analgesics **Orthodontic intervention:** separator placement **Participant sampling:** n = 101 randomized n = 12 dropouts/excluded from analysis (did not take drugs correctly = 8; did not complete questionnaire = 3) n = 89 data analyzed for: **Group 1** (n = 29) 13 male:16 female, mean age 15.6 ± 4.17 years **Group 2** (n = 32) 14 male:18 female, mean age 15.8 ± 3.49 years **Group 3** (n = 28) 12 male:16 female, mean age 15.3 ±3.15 years
Interventions	**Comparisons: NSAID vs placebo, paracetamol vs placebo, and NSAID vs paracetamol** **Ibuprofen (400 mg) vs paracetamol (650 mg) vs placebo**; provided pre-emptively to separator placement **Group 1:** ibuprofen 1 h before separator placement and every 6 h until 24 h (5 doses) **Group 2:** paracetamol 1h before separator placement and every 6 h until 24 h (5 doses) **Group 3:** placebo 1h before separator placement and every 6 h until 24 h (5 doses)
Outcomes	Pain score (VAS) - recorded immediately, and at 2 h, 6 h, bedtime and 24 h after separator placement
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** study did not allocate intervention to specific group labels. For the purposes of this systematic review, Group 1 has been allocated as the ibuprofen arm, Group 2 as the paracetamol arm and Group 3 as the placebo arm. Although referred to as 'acetaminophen' in the study, we have referred to this group as paracetamol for the purposes of this review. Gender data presented as a percentage, calculated as values for the purposes of this review.

Nik 2016 *(Continued)*

	Other information of note: no baseline information provided about groups before drop out. Mean age for Group 2 differed throughout study. For the purposes of the review, the data from Table 1 have been used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "To divide the patients into three groups, block randomization method was used. Each block contained three coded pockets (acetaminophen, liquefied ibuprofen, and placebo) and consisted of one sex (male or female)." **Comment:** inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness
Allocation concealment (selection bias)	Low risk	**Quote:** "The random allocation and coding of drugs was performed by an operator outside the study and was concealed in an envelope." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "To ensure that the patients were blind to the experimental group, the analgesics and placebo were placed in identical capsules"; "In each group, the male to female ratio was equal, and the patient and the operator were blind of the kind of drug." **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The patients were asked to put each questionnaire in a pocket and seal it after marking the scale"; "randomized triple blinded clinical trial". **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	12/101 = 12% dropouts (88% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other sources of bias detected.

Ousehal 2009

Methods	**Setting:** orthodontic consultation and dental treatment unit, Ibn Rochd Hospital Center, Casablanca, Morocco **Design:** parallel (2 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** no drug treatment during the study; good oral hygiene; good general health; adults stratified by age group with presenting malocclusion requiring orthodontic treatment; consent provided **Exclusion criteria:** contra-indication to the use of paracetamol or ibuprofen; taking medication including short-term anti-inflammatory analgesics or long-term corticosteroids; dropouts; non-compliance **Orthodontic intervention:** initial archwire placement

Ousehal 2009 *(Continued)*

	Participant sampling: n = 56 randomized and analyzed: **Group A** (n = 27) **Group B** (n = 29) Overall: 17 male:39 female; age < 15 years = 21.4%: aged > 15 years = 78.6%
Interventions	**Comparison: NSAID vs paracetamol** **Ibuprofen (600 mg; 2 x 300 mg/day for 5 days) vs paracetamol (2 g; 4 x 500 mg/day for 7 days)** **Group A:** ibuprofen provided immediately post-treatment, daily oral dose thereafter **Group B:** paracetamol provided immediately post-treatment, daily oral dose thereafter
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, 24 h and 2, 3 and 7 days after placement of initial archwire
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** additional information received through correspondence with the author. **Other information of note:** original paper translated from French to English.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The randomisation was carried out by a computer algorithm; random block was performed by the software". **Comment:** computer-generated block randomisation carried out, therefore appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "The distribution of study subjects was determined by a biostatistician who gave us the list of participants to the study". **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** "Double-blind was impossible because the patient could read the tablet trade name". **Comment:** blinding of the drugs was not carried out, therefore it was assumed that the researcher supplying the intervention and the participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Drug distribution was done with a single-blind method, single investigators were unaware of the drug". **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/56 = 0% dropout (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.

Ousehal 2009 *(Continued)*

Other bias	Unclear risk	Baseline information on gender and age not given by group.

Paganelli 1993

Methods	**Setting:** Orthodontic Clinic, Dental School, University of Brescia, Italy **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** healthy; 12 to 16 years of age; oral membrane lesions from 2 mm-6 mm caused by wearing a fixed brace; available to participate in the study **Exclusion criteria:** already treated for orthodontic or systemic pain during the last month; syndromes or mental retardation; unavailable to participate to the study; not suffering from anxiety according to parents' rating; no history of dental treatment refusal **Orthodontic intervention:** within 1 month of having a fixed or removable appliance fitted **Participant sampling:** n = 60 selected, randomized and analyzed: (30 male:30 female; < 14 years n = 30; > 14 years n = 30) **Group 1** (n = 20) 10 male:10 female, mean age 14 ± 2 years **Group 2** (n = 20) 10 male:10 female, mean age 14 ± 2 years **Group 3** (n = 20) 10 male:10 female, mean age 14 ± 2 years
Interventions	**Comparison: NSAID vs placebo** **Flurbiprofen (10 ml 0.25% mouthwash 3 times daily for 7 days) vs placebo (10 ml mouthwash 2-minute rinse duration 3 times daily for 7 days) vs control** **Group 1:** flurbiprofen; provided postoperatively after separator placement **Group 2:** placebo; provided postoperatively after separator placement **Group 3:** control, no treatment
Outcomes	Pain score (VAS) - recorded at baseline, 3 and 7 days after separator placement
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** "2 cases of reduced taste sensation with Flurbiprofen which did not cause discontinuation"; "No local or systemic ADRs were reported". **Data handling by review authors:** additional information received through correspondence with the author. Although multiple time points measured, due to variations in the time points of interest to this review, data from this study have not been used for this systematic review. **Other information of note:** original paper translated from Italian to English. All participants had pre-existing ulceration and had started orthodontic treatment within the last month.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Paganelli 1993 *(Continued)*

Random sequence generation (selection bias)	Low risk	**Quote:** "Separated randomization lists furnished by the statistical department of our university, conceived with a variable block size of 3, 6 and 9, and stratified for lesion type (vestibular ulcers, lower labial fraenum lesions, keratinized mucosa lesions, aphthous ulcers, decubitus ulcers), age (more than 14 and less than 14 years) and gender (5x2x2=20 strata), in order to obtain homogeneous and comparable group." **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Low risk	**Quote:** "Allocation concealment was obtained identifying patients with a progressive numeration from 1 to 60, after a casual names draw, and groups with a letter from A to C, assigned by lot." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** "Single blinding: patients were not aware of the treatment received". **Comment:** adequate blinding of participants, however no blinding of personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The statistician who analyzed outcome data were not blind regarding study aims but he was blind regarding treatment assigned to every single patient." **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/50 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other sources of bias detected.

Patel 2011

Methods	**Setting:** University of Florida Orthodontic clinic **Design:** cross-over study(4 arms) **Number of centres:** 1 **Study duration:** 57 days approximately
Participants	**Inclusion criteria:** between 18 and 30 years; not pregnant; second premolars, first molars and second molars in contact allowing the placement of 2 separators in each quadrant; not taking pain medications; no contraindications to the drugs under study or almonds; no need for antibiotic prophylaxis before dental treatment; informed consent for participation in the study **Exclusion criteria:** none specified **Orthodontic intervention:** separator placement **Patient sampling:** n = 24 randomized n = 0 dropouts/excluded from analysis

Patel 2011 *(Continued)*

	n = 24 data analyzed for: **Group 1** (n = 24) 13 male:11 female, mean age 26.4± 2.5 years **Group 2** (n = 24) 13 male:11 female, mean age 26.4± 2.5 years **Group 3** (n = 24) 13 male:11 female, mean age 26.4± 2.5 years **Group 4** (n = 24) 13 male:11 female, mean age 26.4± 2.5 years
Interventions	**Comparisons Ibuprofen (400 mg) vs naproxen sodium (500 mg/250 mg) vs paracetamol (650 mg) vs placebo**; provided before and after separator placement **Group 1:** ibuprofen; provided 1 h pre-operatively, and 3 h and 7 h postoperatively **Group 2:** naproxen sodium (500 mg) 1 h pre-operatively, placebo 3 h postoperatively and naproxen sodium (250 mg) 7 h postoperatively **Group 3:** paracetamol; provided 1 h pre-operatively, and 3 h and 7 h postoperatively **Group 4:** placebo; provided 1 h pre-operatively, and 3 h and 7 h postoperatively
Outcomes	Pain score (VAS) - recorded at: 2 h, 6 h, bedtime, awakening, and 24 hof separator placement.
Notes	**Conflict of interests/funding:** not reported **Adverse events/harms:** the authors reported no commercial, proprietary, or financial interest in the products or companies described in this article. **Data handling by review authors:** outcomes calculated as summary scores from biting, chewing, fitting front teeth together and fitting back teeth together in the paper. Estimated means as reported in Figure. Additional information received from the author to clarify baseline groups and methodology, however no data for standard deviations was available. **Other information of note:** SES reported as 75% White; 13% Asian; 8% Other; 4% Hispanic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Balanced incomplete block design.Crossover trial, each subject received 3 out of 4 possible interventions (A,I,N,P) so 4 possible combinations: AIN, AIP, INP, APN. Within each block 6 possible orders: AIN, ANI, INA, IAN, NAI or NIA. Gives 24 possible drugs and orders and each person randomly assigned one of the combinations / orders. Due to incomplete block design, this leads to 18 observations for each drug." **Comment:** through correspondence with the author, randomisation appears to have been adequate
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "Investigational Drug Service at Shands hospital, Gainesville encapsulated and dispensed the tablets, researchers blinded". **Comment:** described as double blind, but inadequate information regarding how blinding was ensured, therefore unable to evaluate method of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "The study was double-blind."

Patel 2011 *(Continued)*

		Comment: described as double blind but inadequate information regarding how blinding was ensured, therefore unable to evaluate method of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/50 dropouts = 0% attrition
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were reported appropriately. We were unable to extract data for inclusion in pooled analysis.
Other bias	Low risk	No other sources of bias detected.

Pelisson 2008

Methods	**Setting:** Institution of IASP Education - Institute for Support in Dentistry, Londrina, Parana, Brazil **Design:** parallel RCT (6 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** aged between 18 and 28 years; classified as healthy during the clinical history; able to provide written consent; not under prophylactic antibiotic coverage; absence of systemic disease with the use of drugs; no antibiotics or analgesics for a minimum of 15 days prior to the study; no contraindication for the use of the proposed study drugs; no extraction of teeth at least 2 weeks prior to installation of fixed orthodontic appliance; Index of Orthodontics Need (IOTN) Dental Health Component score 3 or above **Exclusion criteria:** history of hypersensitivity to the study drug (normal or idiosyncratic reaction to the drug); evidence of organ dysfunction or clinically significant deviation from normal; history of any psychiatric illness that might compromise the ability to provide written consent; history of GI, liver disease, renal, cardiovascular, pulmonary, neurologic or haematologic, diabetes, or glaucoma; consumption of more than 20 cigarettes per day or difficulty in refraining from smoking during the study period; history of drug or alcohol abuse; pregnant or lactating; participated in any similar clinical study during 6 weeks preceding the study. Participants were also excluded if they suffered an adverse reaction or allergic reaction clearly related to the drugs; were diagnosed with a systemic disease unrelated to the drugs during the study, that would require concomitant therapy; or did not fulfil the requirements of the Protocol, including rules related to the use of drugs, alcohol or lack of co-operation during the study. **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 180 recruited and randomized n = 0 excluded n = 180 analyzed **Group 1** (n = 30) 15 male:15 female, age data not reported **Group 2** (n = 30) 15 male:15 female, age data not reported **Group 3** (n = 30) 15 male:15 female, age data not reported **Group 4** (n = 30) 15 male:15 female, age data not reported **Group 5** (n = 30) 15 male:15 female, age data not reported

Pelisson 2008 *(Continued)*

	Group 6 (n = 30) 15 male:15 female, age data not reported
Interventions	**Comparisons: NSAID vs control (lactose placebo), and NSAID vs NSAID** **Group 1:** diclofenac sodium 50 mg 1 h before placement **Group 2:** lumiracoxib 400 mg 1 h before placement **Group 3:** dexamethasone 4 mg 1 before placement **Group 4:** nimesulide 100 mg 1 h before placement **Group 5:** ibuprofen 400 mg 1 h before placement **Group 6:** placebo 1 h before placement
Outcomes	Pain score (VAS) - recorded at 2 h, 12 h, 24 h and 2, and 7 days after initial archwire placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting back teeth together (not an outcome of this review) • fitting front teeth together (not an outcome of this review)
Notes	**Conflict of interests/funding:** no source of funding reported **Adverse events/harm:** no harms reported **Data handling by review authors:** this paper was translated from Portugese. The data presented for the analysis are based on Figure 1 which shows mean pain scores (mean + SEM). The SEM was used to calculate SD, but we were unable to calculate SD for lumiracoxib at 24 h from Figure 1. Data from Group 2 and Group 6 have been inverted to reflect lumiracoxib as an intervention and placebo as its control. Data from Group 3 did not contribute to the analyses. **Other information of note:** "This study was conducted in accordance with the guidelines established by Resolution 196/96 of the National Council of Health Ministry of Health published on October 10, 1996 and the Code of Professional Ethics Dental, according to Resolution 179/93 CFO ... This study was approved by the Ethics Committee of the Faculty of Dentistry and Dental Research Center São Leopoldo Mandic under protocol 06/333".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomly assigned to 1 of 3 experimental groups"; "The randomization of which of the three experimental conditions the patients were assigned to was computer generated". **Comment:** described as randomized, but inadequate information regarding method or randomisation to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The drugs were divided into different numeric codes". **Comment:** inadequate information regarding method of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	**Quote:** "The study was double-blind."

Pelisson 2008 *(Continued)*

All outcomes		**Comment:** inadequate information regarding method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/180 dropouts = 0% attrition
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Unclear risk	No data presented regarding age of participants in groups which could have resulted in sampling bias.

Polat 2005a

Methods	**Setting:** unspecified location, Turkey **Design:** parallel (6 arms) **Number of centres:** not reported **Study duration:** not reported
Participants	**Inclusion criteria:** no prophylactic antibiotic cover required; no systemic diseases; no current use of antibiotics or analgesics; no contraindication to the use of NSAID; minimum weight requirement based on Food and Drug Administration-approved over the counter paediatric dosage labelling guidelines; no teeth extraction at least 2 weeks before bonding **Exclusion criteria:** patients with minor or extreme crowding and patients with open bite **Orthodontic intervention:** initial archwire placement. **Patient sampling:** n = 150 randomized n = 30 dropouts/excluded from analysis (n = 22 did not return questionnaires; n = 8 over 30 years of age) n = 120 data analyzed for: **Group 1** (n = 20) 10 male:10 female, mean age 15.0 ± 3.7 years **Group 2** (n = 20) 15 male:5 female, mean age 15.0 ± 2.8 years **Group 3** (n = 20) 13 male:7 female, mean age 15.0 ± 4.5 years **Group 4** (n = 20) 15 male: 5 female, mean age 16.0 ± 4.6 years **Group 5** (n = 20) 13 male:7 female, mean age 15.0 ± 2.9 years **Group 6** (n = 20) 10 male:10 female, mean age 16.0 ± 6.1 years
Interventions	**Comparisons: NSAID vs placebo, NSAID vs NSAID, NSAID vs paracetamol, NSAID vs aspirin, and NSAID vs placebo** **Aspirin (300 mg) vs ibuprofen (600 mg) vs flurbiprofen (100 mg) vs paracetamol (500 mg) vs naproxen sodium (550 mg) vs placebo (lactose)** pre-emptively and post-treatment following archwire placement **Group 1:** aspirin 1 h before, and 6 h after bonding appointment **Group 2:** ibuprofen 1 h before, and 6 h after bonding appointment

Polat 2005a *(Continued)*

	Group 3: flurbiprofen 1 h before, and 6 h after bonding appointment **Group 4:** paracetamol 1 h before, and 6 h after bonding appointment **Group 5:** naproxen sodium; provided 1 h pre-operatively **Group 6:** placebo; provided 1 h pre-operatively
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime, 24 h and 2, 3 and 7 days after initial archwire placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together (not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** no harms found. “None had taken additional medication”. **Data handling by review authors:** study reports Group 1 as placebo arm of trial and Group 6 as aspirin arm. For the purposes of aligning with this systematic review's own protocol, the figures for Groups 1 and 3 have been inverted to reflect aspirin as an intervention and placebo as a control. Although referred to as acetaminophen, this group has been referred to as paracetamol for the purposes of this review. **Other information of note:** only pain during chewing data were reflected in this systematic review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomly assigned to one of six experimental groups." **Comment:** inadequate information regarding how randomisation was carried out therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Patients were randomly assigned to one of six experimental groups." **Comment:** inadequate information regarding how allocation was carried out, therefore, unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "All tablets were identical in color, and the patient and research assistant were both blind". **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "All tablets were identical in color, and the patient and research assistant were both blind". **Comment:** inadequate information regarding assessment, unclear if assessor was blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/150 dropouts = 15% attrition (85% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.

Polat 2005a *(Continued)*

Other bias	Low risk	No other sources of bias detected.

Polat 2005b

Methods	**Setting:** unspecified location, Turkey **Design:** parallel (3 arms) **Number of centres:** not reported **Study duration:** not reported
Participants	**Inclusion criteria:** no prophylactic antibiotic cover required; no systemic diseases; no current use of antibiotics or analgesics; no contraindication to the use of NSAID; minimum weight requirement based on Food and Drug Administration-approved over the counter paediatric dosage labelling guidelines; no teeth extraction at least 2 weeks before bonding **Exclusion criteria:** no patient with a history of systemic disease **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 60 randomized n = 0 dropouts/excluded from analysis n = 60 data analyzed for: **Group 1** (n = 20) 14 male:6 female, mean age 15.0 ± 2.2 years **Group 2** (n = 20) 13 male:7 female, mean age 17.0 ± 7.0 years **Group 3** (n = 20) 10 male:10 female, mean age 16.0 ± 6.1 years
Interventions	**Comparisons: NSAID vs placebo, and NSAID vs NSAID** **Naproxen sodium (550 mg; 1 dose) vs ibuprofen (400 mg; 1 dose) vs placebo (lactose; 1 dose)**; pre-emptively before archwire placement **Group 1:** naproxen sodium; provided 1 h pre-operatively **Group 2:** ibuprofen; provided 1 h pre-operatively **Group 3:** placebo; provided 1 h pre-operatively
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime, 24 h and 2, 3 and 7 days after initial archwire placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together(not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** no harms found. “None of them had taken additional medication”. **Data handling by review authors:** study reported Group 1 as placebo arm of trial, Group 2 as ibuprofen arm and Group 3 as naproxen sodium arm. For the purposes of aligning with this systematic re-

Polat 2005b *(Continued)*

view's own protocol, the figures for Groups 1 and 3 have been inverted to reflect naproxen sodium as an intervention and placebo as its control.

Although referred to as acetaminophen, this group has been referred to as paracetamol for the purposes of this review.

Other information of note: only pain during chewing data are reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Twenty patients were randomly assigned to each of the three experimental groups." **Comment:** inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Twenty patients were randomly assigned to each of the three experimental groups." **Comment:** inadequate information regarding how allocation was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The patient and research assistant were blinded to each subject's experimental group". **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "The patient and research assistant were blinded to each subject's experimental group". **Comment:** inadequate information regarding assessment, unclear if assessor was blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/60 dropouts = 0% attrition (100% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other sources of bias detected.

Salmassian 2009

Methods	**Setting:** Orthodontic Graduate Clinic, University of Colorado School of Dentistry **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** scheduled to begin comprehensive orthodontic treatment (banding/bonding of at least 10 teeth in 1 arch and archwire placement in at least 1 arch); extractions, if required, performed at least 2 weeks before appliance and archwire placement; healthy with no significant medical findings; no prophylactic antibiotic coverage required; not taking antibiotics or analgesics; no contraindications to the use of acetaminophen or ibuprofen; no lactose intolerance; minimum age of 12 years and mini-

Salmassian 2009 *(Continued)*

	mum weight of 88 pounds (as required by the FDA for the use of over-the-counter paediatric dosage label guidelines); and maximum age of 18 years to exclude adults **Exclusion criteria:** none specified **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 66 enrolled n = 6 excluded from analysis (did not return in timely manner for follow-up appointments (n = 4), consent withdrawn after archwire placement (n = 2)) n = 60 data analyzed for: **Group 1** (n = 21) 9 male:12 female, age data not reported **Group 2** (n = 19) 12 male:7 female, age data not reported **Group 3** (n = 20) 10 male:10 female, age data not reported
Interventions	**Comparisons: NSAID vs placebo, NSAID vs paracetamol, and paracetamol vs placebo** **Paracetamol (600 mg) vs ibuprofen (400 mg) vs placebo (2 tablets)** **Group 1:** paracetamol; immediately after each VAS time point, starting 3 h pre-operatively **Group 2:** ibuprofen; immediately after each VAS time point, starting 3 h pre-operatively **Group 3:** placebo; immediately after each VAS time point, starting 3 h pre-operatively
Outcomes	Pain score (VAS) - recorded at 3 h, 7 h, 19 h, 24 h, 31 h and 48 h and 3, 4 and 7 days after initial archwire placement
Notes	**Conflict of interests/funding:** "The authors report no commercial, proprietary, or financial interest in the products or companies described in this article." **Adverse events/harm:** no harms found. “No patients took additional analgesics during the study period”. **Data handling by review authors:** although referred to as acetaminophen in the study report, this group has been referred to as paracetamol for the purposes of this review. **Other information of note:** no discrimination was made between various activities (eating, chewing, or biting) when VAS was recorded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Random group allocation and coding of patients were made by a coinvestigator (W.C.S)". **Comment:** inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Random group allocation and coding of patients were made by a coinvestigator (W.C.S)". **Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.

Salmassian 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The subjects and the main investigator (R.S) were blinded to the group allocation"; "The ibuprofen, acetaminophen, and placebo tablets ... were all identical in shape and colour". **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The subjects and the main investigator (R.S) were blinded to the group allocation"; "The ibuprofen, acetaminophen, and placebo tablets ... were all identical in shape and colour". **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/66 dropout = 9.1% attrition (90.9% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other sources of bias detected.

Steen-Law 2000

Methods	**Setting:** University of Iowa College of Dentistry's Department of Orthodontics **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** scheduled to begin comprehensive orthodontic treatment; required no prophylactic antibiotic coverage; no debilitating systemic diseases; not using antibiotics or analgesics; no contraindication to the use of ibuprofen; and maximum age of 16 years and a minimum weight of 88 pounds. This weight requirement was based on FDA-approved over-the-counter paediatric dosage labelling guidelines. **Exclusion criteria:** none specified **Orthodontic intervention:** separator placement **Patient sampling:** n = 115 selected n = 4 refused to participate n = 111 randomized n = 52 dropouts/lost to follow-up (did not receive separators at their next appointment = 28, did not take medications and return questionnaires = 3) n = 63 data analyzed (15 male:38 female) **Group A** (n = 22) 10 male:12 female, mean age 13.4 ± 1.7 years **Group B** (n = 19) 6 male:13 female, mean age 13.3 ± 1.4 years **Group C** (n = 22) 9 male:13 female, mean age 13.1 ± 1.8 years
Interventions	**Comparisons: NSAID vs placebo, and pre-emptive vs post-treatment**

Steen-Law 2000 *(Continued)*

	Ibuprofen (400 mg) pre-emptive vs ibuprofen (400 mg) post-treatment vs placebo (lactose); provided pre-emptively to separator placement, or post-treatment **Group A:** ibuprofen 1 h before separator placement, placebo immediately after appointment **Group B:** placebo 1 h before separator placement, ibuprofen immediately after appointment **Group C:** placebo 1 h before separator placement, placebo immediately after appointment
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, 24 h and 2, 3 and 7 days after separator placement Pain was recorded during the following activities: • chewing • biting (not an outcome of this review) • fitting front teeth together (not an outcome of this review) • fitting posterior teeth together(not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported. Rescue analgesia required in 10 participants: n = 4 (18%) Group A; n = 6 (32%) Group B **Data handling by review authors:** the data presented for the analysis are based on Figure 1, which shows mean pain scores (mean + SEM) for chewing. The SEM was used to calculate SD. Data from Group C did not contribute to the analyses, Groups A and B data were used for the comparison of pre-emptive versus postoperative analgesia. **Other information of note:** only pain during chewing data are reflected in this systematic review. No baseline information was provided regarding the initial groups at randomisation before loss to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Subjects were randomly assigned to 1 of 3 experimental conditions". **Comment:** inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Subjects were randomly assigned to 1 of 3 experimental conditions". **Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The ibuprofen and placebo tablets were alike in appearance. The placebo tablets were hardpressed and not readily dissolved, thus preventing a detectable difference in taste. The investigator, clinician, and patient were blinded to each subject's experimental group." **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The ibuprofen and placebo tablets were alike in appearance. The placebo tablets were hardpressed and not readily dissolved, thus preventing a detectable difference in taste. The investigator, clinician, and patient were blinded to each subject's experimental group." **Comment:** blinding appears to be adequate

Steen-Law 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	52/111 dropouts = 46.8% attrition (53.2% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other sources of bias detected.

Sudhakar 2014

Methods	**Setting:** Department of Orthodontics and Dentofacial Orthopaedics, Sathyabama University Dental College, India **Design:** parallel (4 arms) **Number of centres:** 1 **Study duration:** not reported
Participants	**Inclusion criteria:** age 14-21 years; no previous orthodontic treatment; not under any medication for systemic problems; no allergies to NSAIDs; no history of asthma, gastritis, bleeding disorders; no teeth extraction at least 2 weeks before or after separator placement; no missing teeth **Exclusion criteria:** none specified **Orthodontic intervention:** separator placement **Patient sampling:** n = 154 selected and randomized n = 16 dropouts/lost to follow-up (Group 1 = 4, Group 2 = 3, Group 3 = 2, Group 4 = 7; male = 11, female = 5) n = 138 data analyzed (66 male:72 female) **Group 1** (n = 34) 15 male (mean age 19.8 years):19 female (mean age 19.5 years) **Group 2** (n = 36) 18 male (mean age 19.5 years):18 female (mean age 18.9 years) **Group 3** (n = 34) 16 male (mean age 19.1 years):18 female (mean age 18.6 years) **Group 4** (n = 34) 17 male (mean age 18.9 years):17 female (mean age 18.0 years)
Interventions	**Comparisons: Paracetamol vs NSAID, paracetamol vs placebo, NSAID vs placebo, NSAID vs NSAID** **Paracetamol (650 mg) vs ibuprofen (400 mg) vs aspirin (300 mg) vs placebo**; provided pre-emptively and post-treatment following separator placement **Group 1:** paracetamol 1 h before separator placement, and 6 h after **Group 2:** ibuprofen 1 h before separator placement, and 6 h after **Group 3:** aspirin 1 h before separator placement, and 6 h after **Group 4:** placebo 1 h before separator placement, and 6 h after
Outcomes	Pain score (VAS) - recorded at 2 h, 6 h, bedtime on the day of the appointment, next day morning, 2 days, 3 days, and 7 days after separator placement Pain was recorded during the following activities:

Sudhakar 2014 *(Continued)*

- chewing food
- teeth not touching (not an outcome of this review)
- biting back teeth (not an outcome of this review)

Notes	**Conflict of interests/funding:** no conflict of interest declared. Funding not reported **Adverse events/harm:** none reported **Data handling by review authors:** data presented in the paper showed mean pain scores only. Data relating to chewing was presented in Figure 3. **Other information of note:** only pain during chewing data are reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomly divided in to four groups". **Comment:** inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "Patients and the research assistant were blind to experimental groups". **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Patients and the research assistant were blind to experimental groups". **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/154 dropouts = 10% attrition (90% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were reported not appropriately. We were unable to extract data for use in pooled analysis.
Other bias	Low risk	No other sources of bias detected.

Tuncer 2014

Methods	**Setting:** unspecified location, Turkey **Design:** parallel (3 arms) **Number of centres:** not reported **Study duration:** not reported
Participants	**Inclusion criteria:** no prophylactic antibiotic coverage required; no history of systemic diseases or allergies; not using antibiotics or analgesics; no contraindication to the use of NSAID; no teeth extraction at least 4 weeks before bonding; no history of orthodontic treatment; not being in the menstrual peri-

Tuncer 2014 *(Continued)*

	od for female patients; and minimal crowding of maximum 7 mm that could be treated without extractions **Exclusion criteria:** open bites; and participants who had additional doses of analgesic, although not stated as an exclusion criterion **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 60 selected n = 12 excluded/refused to participate (reasons not reported) n = 48 randomized n = 3 dropout/lost to follow-up (Group 1 = 2 additional dose consumption, Group 2 = 0, Group 3 = 1 lost to follow-up) n = 45 data analyzed (14 male:31 female) **Group 1** (n = 15) 17 male:8 female, mean age 114.66 ± 2.06 years **Group 2** (n = 15) 4 male:11 female, mean age 14.36 ± 1.91 years **Group 3** (n = 15) 3 male:12 female, mean age 14.5 ± 2.0 years
Interventions	**Comparisons: NSAID vs placebo, NSAID vs paracetamol, and paracetamol vs placebo** **Ibuprofen (400 mg) vs paracetamol (500 mg) vs placebo (lactose)**; provided pre-emptively and post-treatment following archwire placement **Group 1:** ibuprofen 1 h before archwire placement, and 6 h after **Group 2:** paracetamol 1 h before archwire placement, and 6 h after **Group 3:** placebo 1 h before archwire placement, and 6 h after
Outcomes	Pain score (VAS) - recorded at: pre-treatment, post-treatment and 1, 2, 3, 7 days after initial archwire placement Pain was recorded during the following activities: • chewing • fitting front teeth together (not an outcome of this review) • fitting back teeth together (not an outcome of this review) Prostaglandin E2 levels in the gingival crevicular fluid at the time points specified (not an outcome of this review)
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** median and IQR data presented in the paper - author contacted to obtain mean and standard deviation data however standard deviation data was not available. **Other information of note:** only pain during chewing data is reflected in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Forty-six patients were randomly allocated to one of three study groups in order".

Tuncer 2014 *(Continued)*

		Comment: inadequate information regarding how randomisation was carried out, therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Forty-six patients were randomly allocated to one of three study groups in order". **Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "The groups were named as A, B, and C and both the patient and the investigator (ZT), who was responsible from the clinical part of the study, did not have any knowledge about the type of analgesic that were given to each group. The tablets were identical in shape and colour and did not have any markings or labels that represented brand name. The tablets were put in small pill boxes with a sticker containing the name of the group. The pills were put in the boxes by the second investigator, and the first investigator who coordinated the clinical part of the study did not have any knowledge about the grouping." **Comment:** blinding appears to be adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "Prospective, randomized, double-blind, placebo-controlled study". **Comment:** inadequate information regarding blinding, unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/46 dropouts = 6% attrition (94% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were not reported appropriately. We were unable to use the data in pooled analysis.
Other bias	High risk	Large gender variation at baseline, more males in Group A, more females in Groups B and C, indicating possible selection bias

Wang 2012

Methods	**Setting:** West China Stomatology Hospital of Sichuan University **Design:** parallel (3 arms) **Number of centres:** 1 **Study duration:** 12 months
Participants	**Inclusion criteria:** aged over 10 years; able to comprehend and complete the study; consented to the research procedures and signed an informed consent form; minors with permission from a parent or legal guardian. **Exclusion criteria:** previous orthodontic treatment; recently experienced a toothache; diagnosed concurrently as having infectious diseases and/or systemic diseases; used analgesics within 3 days prior to orthodontic treatment or exhibited a contraindication to NSAIDs; displayed excessive anxiety as confirmed by the Trait-Anxiety Inventory (T-AI) score (males, ≥ 56; females, ≥ 57) and State-Anxiety Inventory (S-AI) score (males, ≥ 53; females, ≥ 55) (Shek 1993); pain threshold was < 3 seconds or > 60 seconds; or their endurance time was > 5 minutes according to the cold pressor test (CPT; Johnson 1997). **Orthodontic intervention:** initial archwire placement **Patient sampling:**

Wang 2012 *(Continued)*

	n = 502 assessed for eligibility n = 52 excluded (14 did not meet criteria, 33 declined to participate, 5 other reasons) n = 450 randomized n = 21 dropouts/lost to follow-up (7 did not wish to complete follow-up questionnaire (Group 1 = 3, Group 2 = 1, Group 3 = 3); 7 withdrew due to discomfort of orthodontic treatment (Group 1 = 2, Group 2 = 2, Group 3 = 3); 4 lost questionnaires (Group 1 = 1, Group 2 = 1, Group 3 = 2); 2 felt they had not received treatment (Group 1 = 1, Group 2 = 1; 1 unknown Group 3)) n = 429: **Group 1** (n = 143) 48 male:95 female, mean age 16.57 ± 5.0 years **Group 2** (n = 145) 37 male:108 female, mean age 17.68 ± 5.53 years **Group 3** (n = 141) 57 male:84 female, mean age 16.27 ± 5.02 years
Interventions	**Comparison: NSAID vs placebo** **Cognitive behavioural therapy (CBT) vs ibuprofen (300 mg) vs control (no treatment)** **Group 1:** CBT immediately after archwire placement, structured phone procedure at days 8, 9, 10, 14 and 30 **Group 2:** ibuprofen 6 h, 12 h and 24 h after initial archwire placement **Group 3:** placebo; routine diet and hygiene. Calls on days 8, 9,10, 14 and 30 after archwire placement
Outcomes	**Primary outcome:** pain score (VAS) - recorded at 1, 2, 3, 7, 14 and 30 days after initial archwire placement **Secondary outcome:** quality of life assessed by the SF-36 and SAS at baseline and at 30 days
Notes	**Conflict of interests/funding:** "This study was financially supported by the National Natural Science Foundation of China (30801304, 81071273, and 31170929) and the Science & Technology Department of Sichuan Province (2010SZ0116). The author(s) declare no potential conflicts of interest with respect to the authorship and/ or publication of this article." **Adverse events/harm:** not discussed **Data handling by review authors:** data presented for characteristics of groups at baseline were prior to drop out, no data available for age after drop out. Study did not allocate intervention to specific group labels. For the purposes of this systematic review, Group 1 has been allocated as the CBT arm, Group 2 as the ibuprofen arm and Group 3 as the placebo arm. Data from Group 1 did not contribute to the analyses, Groups 2 and 3 data were used for the comparison of pharmacological interventions only. We were unable to calculate standard deviation for Group 2 at 14 days or 30 days due to scale of graph. No further information available on correspondence with the author. **Other information of note:** additional published information available in the study's appendix.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Eligible patients were randomized into three groups via a computer generated sequence". **Comment:** randomisation appears to be adequate

Wang 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	**Quote:**"The randomization sequences were stored in opaque envelopes by two clinicians who were not involved in the enrolment, intervention implementation, or outcome assessments." **Comment:** allocation concealment appears to be adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the interventions, it was not possible to blind participants or personnel to the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "The outcome assessors and statisticians were blinded to the allocation." **Comment:** blinding appears to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/450 dropouts = 4.67% attrition (95.33% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	No other source of bias detected.

Young 2006

Methods	**Setting:** Baylor Orthodontic Department and Dallas private practices, USA **Design:** parallel (3 arms) **Number of centres:** unclear **Study duration:** not reported
Participants	**Inclusion criteria:** bracket placement to begin in the maxillary or mandibular arches (or both); 18 years of age or older; no antibiotic prophylaxis needed; no chronic systemic diseases or clotting disorders; not taking antibiotics or analgesics for any reason; not lactose intolerant; not pregnant or nursing; and no contraindications for the use of valdecoxib **Exclusion criteria:** existing brackets on any teeth **Orthodontic intervention:** initial archwire placement **Patient sampling:** n = 70 randomized n = 14 dropouts/excluded from analysis (did not return questionnaires n = 8; rescue medication used n = 1; survey not complete n = 2; surveys returned after the deadline n = 3); n = 56 data analyzed (aged 18 to 54 years, mean female age 36.4 $\pm$ 6.1 years, mean male age 34.9 $\pm$ 5.8 years): **Group 1** (n = 18) 8 male:10 female, mean age unreported **Group 2** (n = 21) 11 male:10 female, mean age unreported (n = 17) 8 male:9 female, mean age unreported
Interventions	**Comparison: NSAID pre-emptive vs post-treatment**

Young 2006 *(Continued)*

	Valdecoxib (40 mg) pre-emptive vs valdecoxib (40 mg) post-treatment; provided pre-emptively and post-treatment to initial archwire placement **Group 1:** placebo at least 30 minutes before initial archwire placement, 2 h after, and every 12 h starting the morning after bonding for 4 additional doses **Group 2:** placebo at least 30 minutes before initial archwire placement and 40 mg valdecoxib 2 h later, followed by 20 mg valdecoxib every 12 h for 4 additional doses **Group 3:** valdecoxib (40 mg) before initial archwire placement and placebo 2 h later, followed by 20 mg valdecoxib every 12 h for 4 additional doses
Outcomes	Pain score (VAS) - recorded at least 30 minutes before, 2 h, 6 h, 24 h and 2 days after initial archwire placement
Notes	**Conflict of interests/funding:** not reported **Adverse events/harm:** not reported **Data handling by review authors:** data from Group 1 have not contributed to the analyses. **Other information of note:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were randomly assigned to the placebo or active treatment groups using a random numbers table". **Comment:** randomisation appears to be adequate
Allocation concealment (selection bias)	Unclear risk	**Comment:** inadequate information regarding how allocation was carried out, therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** described as "double blind", however inadequate information provided regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** described as "double blind", however inadequate information provided regarding how blinding was carried out, therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/70 dropouts = 20% attrition (80% completion)
Selective reporting (reporting bias)	High risk	Data for outcomes of this review were not reported appropriately. We were unable to extract data to included in a pooled analysis.
Other bias	Unclear risk	Large age variation in overall sample, no data presented regarding age of participants in groups, therefore could have resulted in sampling bias.

Abbreviations
ADRs: Adverse drug reaction
GI: gastrointestinal
IASP: International Association for the Study of Pain
IQR: inter-quartile range(s)
NiTi: nickel-titanium

PGE2: prostaglandin E2
RCT: randomized controlled trial
SD: standard deviation
SEM: standard error of the mean
SES: Socio-economic status
VAS: visual analogue scale
VDS: verbal descriptive scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Melh 2017	Inappropriate study design
Cherubini 2003	Abstract: insufficient information for inclusion
Eslamian 2013	Inappropriate study design
Eslamian 2017a	Inappropriate study design
Ireland 2016	Possible confounding due to co-interventions and therefore not possible to attribute effect to specific analgesics; comparison group used positive control
Murdock 2010	Possible confounding due to co-interventions and therefore not possible to attribute effect to specific analgesics; comparison group used positive control
Ogata 1999	Abstract: insufficient information for inclusion
Parks 2001	Abstract: insufficient information for inclusion
Soheilifar 2016	Inappropriate study design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Eslamian 2017b

Methods	**Setting:** Orthodontic Department of Shahid Beheshti Univercity of Medical Science, Tehran, Iran **Design:** parallel RCT (3 arms) **Number of centres:** not reported in trial registration **Study duration:** not reported in trial registration
Participants	**Inclusion criteria:** orthodontic patients who reported pain in their previous meetings; no pain in the mouth (teeth and gums) at baseline; not using analgesics at baseline; no severe liver or kidney disease or any other contraindications for using the considered drugs; at levelling stage in orthodontic treatment **Exclusion criteria:** failure to complete the questionnaire at all recommended times; used other analgesics during the study **Orthodontic intervention:** mid-treatment **Patient sampling:** n = 115 recruited and randomized. No further information reported in trial registration.
Interventions	**Comparison: NSAID vs placebo**

Eslamian 2017b *(Continued)*

	Ketoprofen chewing gum vs placebo; ketoprofen gel vs placebo; provided postoperatively following appliance adjustments **Group A:** ketoprofen chewing gum 100 mg every 8 h for 3 days after treatment **Group B:** ketoprofen gel 160 mg per 100 ml every 8 h for 3 days after treatment **Group C:** placebo chewing gum every 8 h for 3 days after treatment
Outcomes	Pain score (5-score VAS) - recorded at 2 h, 6 h, 24 h and day 2 at 10 am and 6 pm, day 3 at 10 am and 6 pm and 7 days after appliance adjustment
Notes	**Conflict of interests/funding:** funding source: Vice Chancellor for Research Shahid Beheshti University of Medical Science **Adverse events/harm:** none reported in trial registration **Data handling by review authors:** nothing to report **Other information of note:** unable to retrieve any further information through contact with the authors.

Moradinejad 2014

Methods	**Setting:** Dental School, Ahvaz Jundishapur University of Medical Science, Iran **Design:** cross-over RCT (3 arms) **Number of centres:** 1 **Study duration:** not reported in trial registration
Participants	**Inclusion criteria:** no specific systemic disease; not using analgesics; no periodontal and endodontics problems **Exclusion criteria:** lack of any case inclusion criteria **Orthodontic intervention:** separator placement **Patient sampling:** n = 54 recruited. No further information reported in trial registration.
Interventions	**Comparisons: NSAID vs placebo, paracetamol vs placebo, and NSAID vs paracetamol**; **ibuprofen vs paracetamol vs placebo;** provided prior to separator placement. **Group A:** 650 mg acetaminophen oral tablet taken half an hour before separator placement **Group B:** 400 mg ibuprofen oral tablet taken half an hour before separator placement **Group C:** (control group) 500 mg starch oral tablet taken half an hour before separator placement
Outcomes	Pain score (VAS) - recorded at 2 h, at bed time and in the morning of days 2, 3, 4 and 5 after separator placement Pain was recorded during the following activities: • chewing • dental contact (not an outcome of this review) • rest with no contact (not an outcome of this review)

Moradinejad 2014 *(Continued)*

Notes	**Conflict of interests/funding:** none reported in trial registration **Adverse events/harm:** none reported in trial registration **Data handling by review authors:** nothing to report **Other information of note:** unable to retrieve any further information through contact with the authors.

Rooke 2012

Methods	**Setting:** Australia **Design:** parallel RCT (3 arms) **Number of centres:** not reported in trial registration **Study duration:** not reported in trial registration
Participants	**Inclusion criteria:** between the ages of 14 and 19 years old at commencement of treatment; agree, with consent of parent/guardian, to follow a strict analgesia protocol during the first 48 h of full fixed orthodontic therapy; agree, with consent of parent/guardian, to complete a 100 mm VAS at predetermined intervals within the first week of full fixed orthodontic therapy; begin full orthodontic fixed appliance therapy as per the following appliance protocols: 0.022-inch slot MBT Low Profile Victory Series brackets, 014 inch NiTi RMO Thermalloy plus archwires, Elastomeric modules; no dental extractions in the 2 weeks prior to fitting of fixed appliances; subject and parent/guardian consent to a randomly assigned analgesia protocol **Exclusion criteria:** requires prophylactic antibiotic coverage; systemic diseases; pregnanancy; contraindication to the use of NSAID **Orthodontic intervention:** initial archwire placement **Patient sampling:** it is anticipated at least 185 subjects will be recruited.
Interventions	**Comparisons: NSAID vs placebo, paracetamol vs placebo, and NSAID vs paracetamol** **Ibuprofen vs paracetamol vs placebo;** provided prior to placement of initial archwires **Group A:** 400 mg ibuprofen 1 h prior to ligating the orthodontic arch wire to the braces using elastomeric modules and continuing every 4 h for first 48 h after band-up **Group B:** 500 mg acetaminophen 1 h prior to ligating the orthodontic arch wire to the braces using elastomeric modules and continuing every 4 h for first 48 h after band-up **Group C:** (control group)placebo 1 h prior to ligating the orthodontic arch wire to the braces using elastomeric modules and continuing every 4 h for first 48 h after band-up
Outcomes	Pain score (5-score VAS) - recorded at 2 h, 6 h, night of fitting braces, 24 hs, 2, 3 and 7 days after archwire placement
Notes	**Conflict of interests/funding:** none reported in trial registration **Adverse events/harm:** none reported in trial registration **Data handling by review authors:** nothing to report **Other information of note:** Unable to retrieve any further information through contact with the authors.

Abbreviations
h: hour(s)
MBT: McLaughlin, Bennet and Trevisi
NiTi: nickel-titanium
NSAID: non-steroidal anti-inflammatory
RCT: randomized controlled trial
RMO: Rocky Mountain Orthodontics
VAS: visual analogue scale
vs: versus

Characteristics of ongoing studies *[ordered by study ID]*

Mohammed 2016

Trial name or title	Effectiveness of a preemptive ibuprofen on the control of pain before orthodontic separator placement in children and adolescents: a single center randomized controlled trial
Methods	**Setting:** Orthodontic Department of Shahid Beheshti University of Medical Science, Tehran, Iran **Design:** parallel RCT (3 arms) **Number of centres:** not reported in trial registration **Study duration:** not reported in trial registration
Participants	**Inclusion criteria:** orthodontic patients 15 to 25 years old without pain in the mouth at the start of the study; no renal disease or severe hepatic disease, or any other contraindications to the studied drug **Exclusion criteria:** failure to complete the questionnaire at all recommended times; use of other analgesics during the study **Orthodontic intervention:** mid-treatment **Participant sampling:** n = 115 recruited and randomized. No further information reported in trial registration.
Interventions	**Comparison: NSAID vs placebo** **Ketoprofen chewing gum vs placebo; ketoprofen gel vs placebo**; provided postoperatively following appliance adjustments **Group A:** ketoprofen chewing gum 100 mg every 8 h for 3 days after treatment **Group B:** ketoprofen gel 160 mg per 100 ml every 8 h for 3 days after treatment **Group C:** placebo chewing gum every 8 h for 3 days after treatment
Outcomes	Pain score (5-score VAS) - recorded at 2 h, 6 h, 24 h and day 2 at 10 am and 6 pm, day 3 at 10 am and 6 pm and 7 days after appliance adjustment
Starting date	11 August 2016
Contact information	Dr Hisham Mohammed, 63 Al-fatth, Nasr City, Cairo, Egypt, 11727
Notes	**Conflict of interests/funding:** funding source: Vice Chancellor for Research Shahid Beheshti University of Medical Science **Adverse events/harm:** none reported in trial registration **Data handling by review authors:** nothing to report

Mohammed 2016 *(Continued)*

Other information of note: unable to retrieve any further information through contact with the authors

Abbreviations
h: hour(s)
RCT: randomized controlled trial
VAS: visual analogue scale
vs: versus

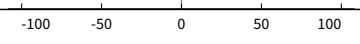
DATA AND ANALYSES

Comparison 1. Analgesic versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 2 hours	10	685	Mean Difference (IV, Random, 95% CI)	-11.66 [-16.15, -7.17]
1.1 Paracetamol versus control	4	107	Mean Difference (IV, Random, 95% CI)	-11.90 [-18.36, -5.44]
1.2 NSAID versus control	10	578	Mean Difference (IV, Random, 95% CI)	-11.72 [-16.93, -6.51]
2 6 hours	9	535	Mean Difference (IV, Random, 95% CI)	-24.27 [-31.44, -17.11]
2.1 Paracetamol versus control	4	107	Mean Difference (IV, Random, 95% CI)	-19.34 [-24.80, -13.88]
2.2 NSAID versus control	9	428	Mean Difference (IV, Random, 95% CI)	-25.69 [-34.47, -16.92]
3 24 hours	12	1012	Mean Difference (IV, Random, 95% CI)	-21.19 [-28.31, -14.06]
3.1 Paracetamol versus control	6	161	Mean Difference (IV, Random, 95% CI)	-22.09 [-35.99, -8.18]
3.2 NSAID versus control	12	851	Mean Difference (IV, Random, 95% CI)	-21.05 [-29.44, -12.65]
4 Other pain outcome data			Other data	No numeric data

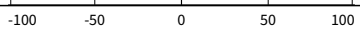
Analysis 1.1. Comparison 1 Analgesic versus control, Outcome 1 2 hours.

Study or subgroup	Analgesic N	Analgesic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Paracetamol versus control							
Gupta 2014	15	32 (14)	8	44 (8)		6.38%	-12[-21,-3]
Kawamoto 2010	10	27.1 (33.9)	4	34.3 (33.3)		1.16%	-7.2[-46.01,31.61]
Nik 2016	32	8.8 (14.7)	14	20.6 (16.3)		6.04%	-11.8[-21.74,-1.86]
Polat 2005a	20	22.8 (26.5)	4	38.1 (32.8)		1.44%	-15.3[-49.48,18.88]
Subtotal ***	**77**		**30**			**15.02%**	**-11.9[-18.36,-5.44]**
Heterogeneity: Tau²=0; Chi²=0.1, df=3(P=0.99); I²=0%							
Test for overall effect: Z=3.61(P=0)							
1.1.2 NSAID versus control							
Bruno 2011	9	6 (10)	17	10 (16.6)		5.93%	-4[-14.24,6.24]
Bruno 2011	8	6 (10)	17	12.4 (13)		6.28%	-6.4[-15.68,2.88]
Farzanegan 2012	10	51 (22)	10	48 (30.6)		2.59%	3[-20.36,26.36]
Gupta 2014	15	12 (9)	7	44 (8)		6.93%	-32[-39.47,-24.53]
Kawamoto 2010	7	26.7 (18.6)	5	34.3 (33.3)		1.58%	-7.6[-39.88,24.68]
Kohli 2011	30	11.3 (26.6)	15	41 (30.9)		3.54%	-29.7[-48.01,-11.39]
Kohli 2011	30	31.8 (29.9)	15	41 (30.9)		3.4%	-9.2[-28.15,9.75]
Minor 2009	16	36 (12)	18	48 (10)		6.93%	-12[-19.48,-4.52]
Nik 2016	29	6.3 (8.8)	14	20.6 (16.3)		6.34%	-14.3[-23.42,-5.18]
Pelisson 2008	30	22.8 (8)	7	25.5 (6.7)		7.53%	-2.7[-8.43,3.03]
Pelisson 2008	30	8.7 (4)	8	25.5 (6.7)		7.8%	-16.8[-21.66,-11.94]
Pelisson 2008	30	22.8 (8)	8	25.5 (6.7)		7.61%	-2.7[-8.15,2.75]
Pelisson 2008	30	23.6 (9.4)	7	25.5 (6.7)		7.44%	-1.9[-7.9,4.1]
Polat 2005a	20	37 (27.5)	4	38.1 (32.8)		1.43%	-1.1[-35.43,33.23]
Polat 2005a	20	17.1 (22.1)	4	38.1 (32.8)		1.48%	-21[-54.57,12.57]
Polat 2005a	20	11.9 (20.9)	4	38.1 (32.8)		1.49%	-26.2[-59.62,7.22]
Polat 2005a	20	25.3 (32)	4	38.1 (32.8)		1.38%	-12.8[-47.87,22.27]
Polat 2005b	20	14.3 (26.6)	10	39.2 (31.8)		2.66%	-24.9[-47.8,-2]
Polat 2005b	20	21.8 (26.8)	10	39.2 (31.8)		2.65%	-17.4[-40.34,5.54]
Subtotal ***	**394**		**184**			**84.98%**	**-11.72[-16.93,-6.51]**
Heterogeneity: Tau²=74.36; Chi²=73.16, df=18(P<0.0001); I²=75.4%							
Test for overall effect: Z=4.41(P<0.0001)							
Total ***	**471**		**214**			**100%**	**-11.66[-16.15,-7.17]**
Heterogeneity: Tau²=61.28; Chi²=73.47, df=22(P<0.0001); I²=70.05%							
Test for overall effect: Z=5.09(P<0.0001)							
Test for subgroup differences: Chi²=0, df=1 (P=0.97), I²=0%							

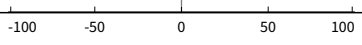


Analysis 1.2. Comparison 1 Analgesic versus control, Outcome 2 6 hours.

Study or subgroup	Analgesic N	Analgesic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Paracetamol versus control							
Gupta 2014	15	31 (8)	8	51 (7)		8.7%	-20[-26.32,-13.68]
Kawamoto 2010	10	49.1 (35.7)	4	50.2 (40.4)		1.97%	-1.1[-46.45,44.25]
Nik 2016	32	11.8 (13.1)	14	28.8 (20.8)		7.45%	-17[-28.8,-5.2]
Polat 2005a	20	21.3 (29.4)	4	51.9 (33.1)		2.9%	-30.6[-65.5,4.3]

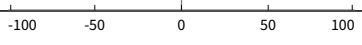


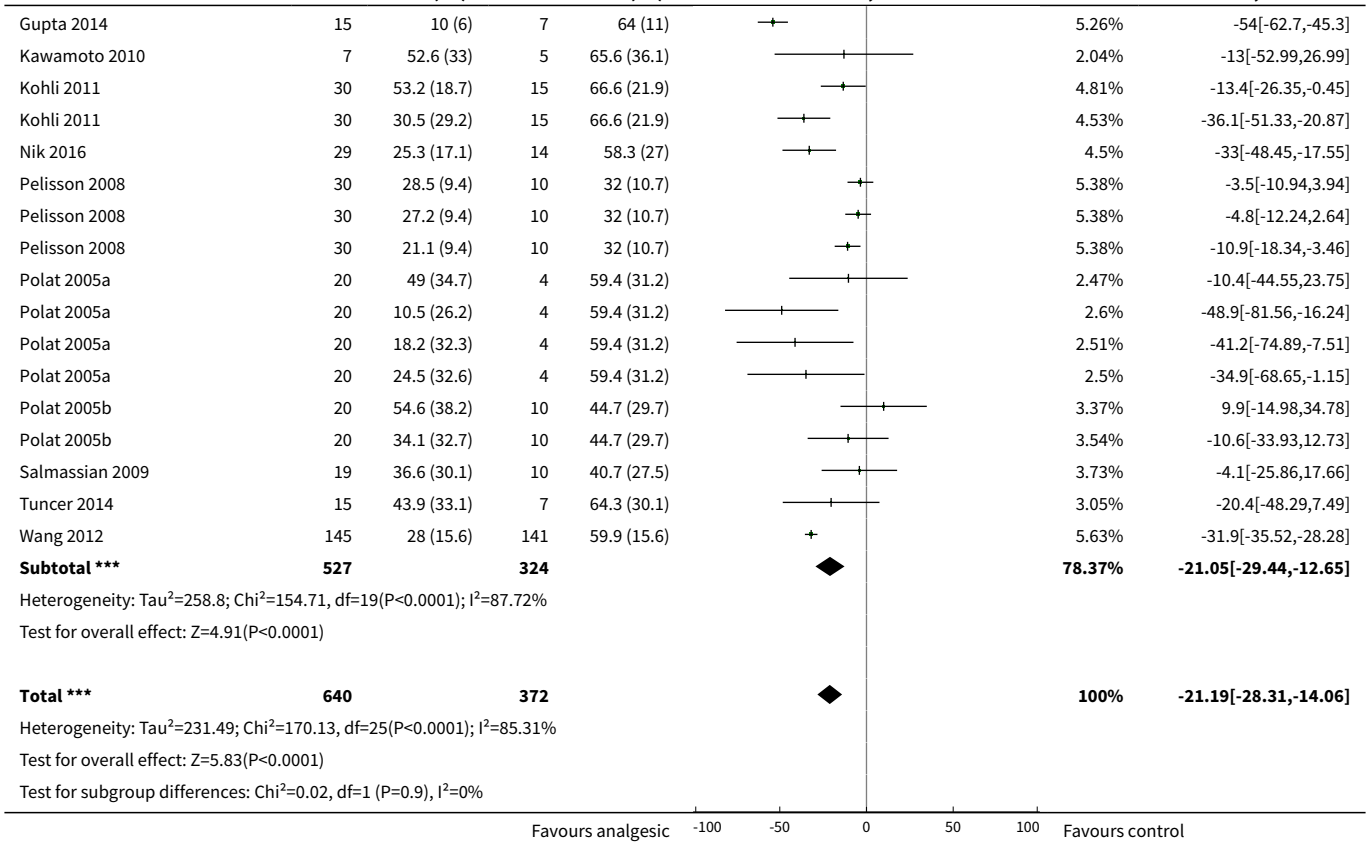
Study or subgroup	Analgesic N	Analgesic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**77**		**30**			**21.03%**	**-19.34[-24.8,-13.88]**
Heterogeneity: Tau²=0; Chi²=1.21, df=3(P=0.75); I²=0%							
Test for overall effect: Z=6.94(P<0.0001)							
1.2.2 NSAID versus control							
Bruno 2011	8	12.9 (14)	17	22.4 (23.1)		6.71%	-9.5[-24.15,5.15]
Bruno 2011	9	12.9 (14)	17	18.2 (17.8)		7.28%	-5.3[-17.76,7.16]
Farzanegan 2012	10	41.8 (24.7)	10	64.5 (25.8)		4.94%	-22.7[-44.84,-0.56]
Gupta 2014	15	10 (9)	7	51 (7)		8.59%	-41[-47.9,-34.1]
Kawamoto 2010	7	37.3 (26.7)	5	50.2 (40.4)		2.34%	-12.9[-53.46,27.66]
Kohli 2011	30	46.9 (31.4)	15	57.8 (29.6)		5.7%	-10.9[-29.63,7.83]
Kohli 2011	30	17.3 (21.7)	15	57.8 (29.6)		6.15%	-40.5[-57.37,-23.63]
Minor 2009	16	41 (13)	18	85 (13)		8.19%	-44[-52.75,-35.25]
Nik 2016	29	10.5 (10.1)	14	28.8 (20.8)		7.53%	-18.3[-29.8,-6.8]
Polat 2005a	20	12.3 (29.8)	4	51.9 (33.1)		2.9%	-39.6[-74.57,-4.63]
Polat 2005a	20	29.9 (24)	4	51.9 (33.1)		3%	-22[-56.1,12.1]
Polat 2005a	20	12.6 (20.8)	4	51.9 (33.1)		3.05%	-39.3[-72.99,-5.61]
Polat 2005a	20	27.3 (31.8)	4	51.9 (33.1)		2.86%	-24.6[-59.9,10.7]
Polat 2005b	20	34.9 (30.4)	10	51.8 (30.7)		4.71%	-16.9[-40.13,6.33]
Polat 2005b	20	16.2 (24)	10	51.8 (30.7)		5.02%	-35.6[-57.34,-13.86]
Subtotal ***	**274**		**154**			**78.97%**	**-25.69[-34.47,-16.92]**
Heterogeneity: Tau²=184.66; Chi²=55.1, df=14(P<0.0001); I²=74.59%							
Test for overall effect: Z=5.74(P<0.0001)							
Total ***	**351**		**184**			**100%**	**-24.27[-31.44,-17.11]**
Heterogeneity: Tau²=143.29; Chi²=66.7, df=18(P<0.0001); I²=73.01%							
Test for overall effect: Z=6.64(P<0.0001)							
Test for subgroup differences: Chi²=1.45, df=1 (P=0.23), I²=31.03%							



Analysis 1.3. Comparison 1 Analgesic versus control, Outcome 3 24 hours.

Study or subgroup	Analgesic N	Analgesic Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 Paracetamol versus control							
Gupta 2014	15	32 (8)	8	64 (11)		5.27%	-32[-40.63,-23.37]
Kawamoto 2010	10	64 (30.9)	4	65.6 (36.1)		2.03%	-1.6[-41.83,38.63]
Nik 2016	32	22.8 (18.7)	14	58.3 (27)		4.49%	-35.5[-51.06,-19.94]
Polat 2005a	20	13.1 (24.7)	4	59.4 (31.2)		2.62%	-46.3[-78.74,-13.86]
Salmassian 2009	21	35.9 (27.7)	10	40.7 (27.5)		3.85%	-4.8[-25.56,15.96]
Tuncer 2014	15	64.6 (26.2)	8	64.3 (30.1)		3.39%	0.3[-24.42,25.02]
Subtotal ***	**113**		**48**			**21.63%**	**-22.09[-35.99,-8.18]**
Heterogeneity: Tau²=173.09; Chi²=14.4, df=5(P=0.01); I²=65.27%							
Test for overall effect: Z=3.11(P=0)							
1.3.2 NSAID versus control							
Bruno 2011	8	26.5 (23.4)	17	48.2 (24.3)		3.95%	-21.7[-41.61,-1.79]
Bruno 2011	9	26.5 (23.4)	17	40 (26.5)		3.96%	-13.5[-33.31,6.31]
Farzanegan 2012	10	44.5 (20.7)	10	74.7 (27.3)		3.79%	-30.2[-51.43,-8.97]





Analysis 1.4. Comparison 1 Analgesic versus control, Outcome 4 Other pain outcome data.

Study	Other pain outcome data
Abtahi 2006	Data from the trial is incomplete and inappropriately presented and cannot be used for pooled analysis. *"Ibuprofen and Tramadol groups have experienced less pain than Placebo group and the difference between two medication groups was insignificant. In placebo group pain was higher in chewing than biting."*
Arantes 2009	*"Pain intensity in these groups (tenoxicam before and after orthodontic activation) was lower than in the placebo group. The difference in pain intensity between the active and the control was greatest at the assessment made 12 h after activation."*
Bayani 2016	*"ANOVA demonstrated significant between-group differences in pain perceived at chewing, biting, fitting front teeth and fitting back teeth at all time points (p<0.001). The results of the Tukey test revealed that at almost all intervals, pain intensity in the placebo group was comparable to that of the LLRL group (p>0.05), and both groups experienced significantly greater pain than subjects in the bite wafer, ibuprofen and LLIL."* We can infer that participants in the ibuprofen group experienced less pain than those in the placebo group.
Eslamian 2014	Data from cross-over trial inappropriately presented (and from authors) cannot be used for pooled analysis. *"The mean pain score recorded in benzocaine group was lower than that in the ketoprofen and placebo groups but a significant difference was only observed between benzocaine and the ketoprofen groups during the first two hours using Friedman and Wilcoxon tests (P=0.042). Compared to the control group, both ketoprofen and benzocaine chewing gums significantly decreased pain at all time points except for day 7."* Ketoprofen and benzocaine gums were both significantly effective for orthodontic pain reduction.
Eslamian 2016a	Data from cross-over trial inappropriately presented and cannot be used for pooled analysis.

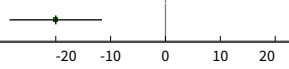
Study	Other pain outcome data
	"The recorded pain scores were subjected to non-parametric analysis"; "The highest pain was recorded at 2 and 6 hours. Pain scores were significantly different between the three groups (Kruskal–Wallis test, p < 0.01). The overall mean (SD) pain scores for the benzocaine 5%, ketoprofen, and control (placebo) groups were 0.89 (0.41), 0.68 (0.34), and 1.15 (0.81), respectively. The pain scores were significantly different between the ketoprofen and control groups (mean difference = 0.47, p = 0.005)." A significant pain reduction was observed following the use of ketoprofen when tested against a control gel (placebo).
Eslamian 2016b	Data from cross-over trial inappropriately presented and cannot be used for pooled analysis. *"The overall mean value of pain intensity for benzocaine and placebo gels was 0.89 and 1.15, respectively. The Mann–Whitney U-test indicated that there was no significant difference between overall pain in both groups (mean difference = 0.258 p < 0.21)."* Benzocaine gel caused a decrease in pain perception at 2 h compared with placebo gel. Peak pain intensity was at 2 h for placebo gel and at 6 h for benzocaine gel, followed by a decline in pain perception from that point to day 7 for both gels. The P-values comparing pain intensity between the groups at each time point were all non-significant. Probably no differences found.
Ngan 1994	*"A repeated measures analysis of variance and post hoc studentized range statistics showed that the placebo group had significantly more discomfort than either the ibuprofen or the aspirin group at all the time intervals tested."*
Patel 2011	Although there was a sophisticated analysis undertaken we can only use the fixed-effect estimates for pain summary score (over 2, 6, bedtime, awaking 24 hours) presented in Table 1 in the paper. These estimates indicated that ibuprofen reduced pain when compared with a placebo with an effect size of -7.89 (95% CI -13.18 to -2.60; P = 0.003), on 0 to 100 mm VAS. There was some evidence of a difference for naproxen sodium (effect size -5.04, 95% CI -9.94 to -0.14; P = 0.04) when compared with placebo, but not for acetaminophen (effect size 3.67, 95% CI -8.57 to 1.23; P = 0.14).
Sudhakar 2014	*"Overall results showed Group 3 (Aspirin 300 mg) patients experienced very less pain in terms of mild discomfort, closely followed by Group 2 (Ibuprofen 400 mg). Group 1 (Paracetamol 650 mg) patients experienced mild to moderate pain on bed time and next day morning, after which gradually reduced to no pain from 3rd day morning. However, Group 4 (Placebo) patients had a bitter experience of moderate to severe pain at `all-time` intervals."*
Young 2006	Unable to draw conclusions due to poor reporting of data.

Comparison 2. NSAID versus paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 2 hours	7	664	Mean Difference (IV, Random, 95% CI)	-2.92 [-8.48, 2.65]
2 6 hours	7	664	Mean Difference (IV, Random, 95% CI)	-5.17 [-11.71, 1.37]
3 24 hours	9	734	Mean Difference (IV, Random, 95% CI)	-0.51 [-8.93, 7.92]
4 Qualitative pain			Other data	No numeric data

Analysis 2.1. Comparison 2 NSAID versus paracetamol, Outcome 1 2 hours.

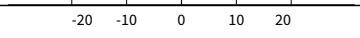
Study or subgroup	NSAID N	NSAID Mean(SD)	Paracetamol N	Paracetamol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bradley 2007	77	18.6 (18.3)	82	25.9 (21.9)		15.3%	-7.3[-13.56,-1.04]
Gupta 2014	15	12 (9)	15	32 (14)		13.22%	-20[-28.42,-11.58]



Study or subgroup	NSAID N	NSAID Mean(SD)	Paracetamol N	Paracetamol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kawamoto 2010	7	26.7 (18.6)	10	27.1 (33.9)		3.9%	-0.4[-25.53,24.73]
Najafi 2015	76	13.7 (21.5)	38	13.6 (15.6)		14.66%	0.1[-6.83,7.03]
Najafi 2015	89	15 (18.6)	38	13.6 (15.6)		15.27%	1.4[-4.89,7.69]
Nik 2016	29	6.3 (8.8)	32	8.8 (14.7)		15.53%	-2.5[-8.52,3.52]
Ousehal 2009	27	47.2 (31)	29	32.4 (31.4)		7.19%	14.8[-1.55,31.15]
Polat 2005a	20	11.9 (20.9)	5	22.8 (26.5)		3.94%	-10.9[-35.87,14.07]
Polat 2005a	20	37 (27.5)	5	22.8 (26.5)		3.65%	14.2[-11.97,40.37]
Polat 2005a	20	17.1 (22.1)	5	22.8 (26.5)		3.89%	-5.7[-30.87,19.47]
Polat 2005a	20	25.3 (32)	5	22.8 (26.5)		3.44%	2.5[-24.63,29.63]
Total * **	**400**		**264**			**100%**	**-2.92[-8.48,2.65]**

Heterogeneity: Tau²=42.51; Chi²=26.81, df=10(P=0); I²=62.71%

Test for overall effect: Z=1.03(P=0.3)

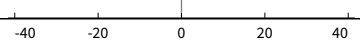


Analysis 2.2. Comparison 2 NSAID versus paracetamol, Outcome 2 6 hours.

Study or subgroup	NSAID N	NSAID Mean(SD)	Paracetamol N	Paracetamol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bradley 2007	77	25.2 (21.2)	82	35.9 (22.8)		14.36%	-10.7[-17.54,-3.86]
Gupta 2014	15	10 (9)	15	31 (8)		14.84%	-21[-27.09,-14.91]
Kawamoto 2010	7	37.3 (26.7)	10	49.1 (35.7)		3.78%	-11.8[-41.48,17.88]
Najafi 2015	76	18.9 (24.2)	38	19.6 (18.4)		13.58%	-0.7[-8.69,7.29]
Najafi 2015	89	20.1 (21.4)	38	19.6 (18.4)		14.02%	0.5[-6.85,7.85]
Nik 2016	29	10.5 (10.1)	32	11.8 (13.1)		14.99%	-1.3[-7.14,4.54]
Ousehal 2009	27	41.7 (28.3)	29	38.2 (34.6)		8.17%	3.5[-13.01,20.01]
Polat 2005a	20	29.9 (24)	5	21.3 (29.4)		4.17%	8.6[-19.23,36.43]
Polat 2005a	20	12.3 (29.8)	5	21.3 (29.4)		3.94%	-9[-37.89,19.89]
Polat 2005a	20	12.6 (20.8)	5	21.3 (29.4)		4.29%	-8.7[-36.03,18.63]
Polat 2005a	20	27.3 (31.8)	5	21.3 (29.4)		3.86%	6[-23.3,35.3]
Total * **	**400**		**264**			**100%**	**-5.17[-11.71,1.37]**

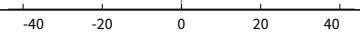
Heterogeneity: Tau²=65.45; Chi²=35.1, df=10(P=0); I²=71.51%

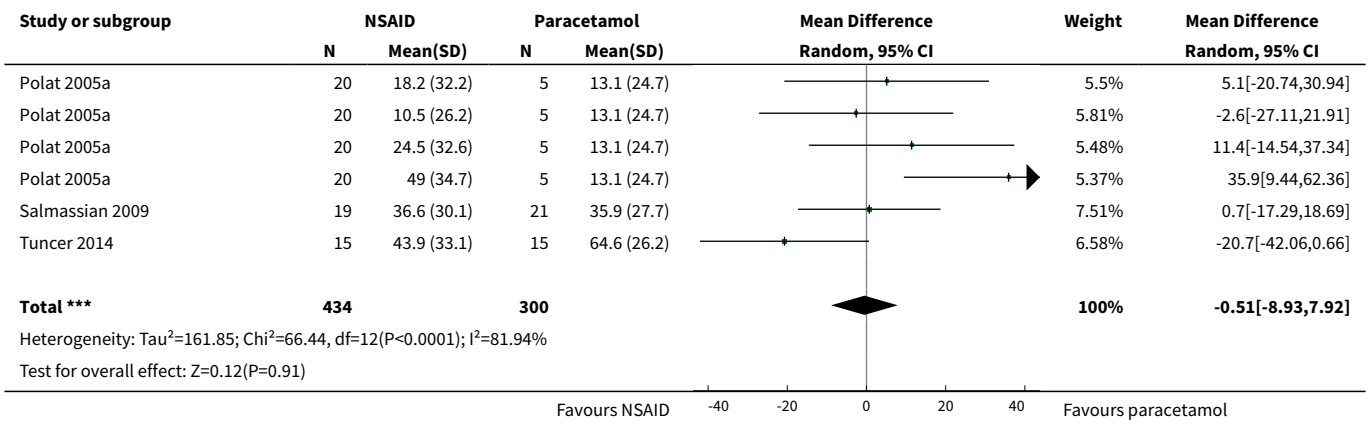
Test for overall effect: Z=1.55(P=0.12)



Analysis 2.3. Comparison 2 NSAID versus paracetamol, Outcome 3 24 hours.

Study or subgroup	NSAID N	NSAID Mean(SD)	Paracetamol N	Paracetamol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bradley 2007	77	34.6 (14.7)	82	34.4 (23.8)		10.77%	0.2[-5.91,6.31]
Gupta 2014	15	10 (6)	15	32 (8)		10.97%	-22[-27.06,-16.94]
Kawamoto 2010	7	52.6 (33)	10	64 (30.9)		4.48%	-11.4[-42.45,19.65]
Najafi 2015	76	36.6 (32.4)	38	30.8 (29.7)		9.29%	5.8[-6.13,17.73]
Najafi 2015	89	30.5 (28.1)	38	30.8 (29.7)		9.53%	-0.3[-11.4,10.8]
Nik 2016	29	25.3 (17.1)	32	22.8 (18.7)		10.11%	2.5[-6.48,11.48]
Ousehal 2009	27	34.1 (27.7)	29	31.1 (26.7)		8.6%	3[-11.27,17.27]





Study or subgroup	NSAID N	NSAID Mean(SD)	Paracetamol N	Paracetamol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Polat 2005a	20	18.2 (32.2)	5	13.1 (24.7)		5.5%	5.1[-20.74,30.94]
Polat 2005a	20	10.5 (26.2)	5	13.1 (24.7)		5.81%	-2.6[-27.11,21.91]
Polat 2005a	20	24.5 (32.6)	5	13.1 (24.7)		5.48%	11.4[-14.54,37.34]
Polat 2005a	20	49 (34.7)	5	13.1 (24.7)		5.37%	35.9[9.44,62.36]
Salmassian 2009	19	36.6 (30.1)	21	35.9 (27.7)		7.51%	0.7[-17.29,18.69]
Tuncer 2014	15	43.9 (33.1)	15	64.6 (26.2)		6.58%	-20.7[-42.06,0.66]
Total ***	**434**		**300**			**100%**	**-0.51[-8.93,7.92]**
Heterogeneity: Tau²=161.85; Chi²=66.44, df=12(P<0.0001); I²=81.94%							
Test for overall effect: Z=0.12(P=0.91)							

Favours NSAID -40 -20 0 20 40 Favours paracetamol

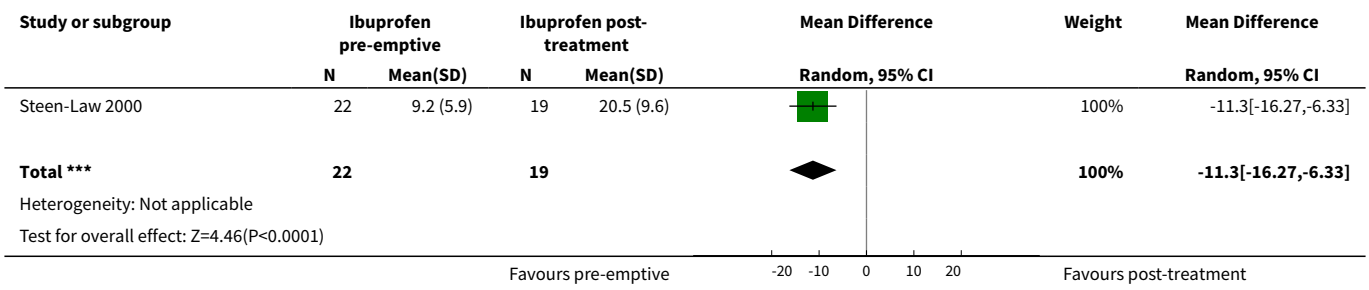
Analysis 2.4. Comparison 2 NSAID versus paracetamol, Outcome 4 Qualitative pain.

Study	Qualitative pain
Sudhakar 2014	*"Overall results showed Group 3 (Aspirin 300 mg) patients experienced very less pain in terms of mild discomfort, closely followed by Group 2 (Ibuprofen 400 mg). Group 1 (Paracetamol 650 mg) patients experienced mild to moderate pain on bed time and next day morning, after which gradually reduced to no pain from 3rd day morning. However, Group 4 (Placebo) patients had a bitter experience of moderate to severe pain at* `all-time` *intervals"*

Comparison 3. Ibuprofen pre-emptive versus post-treatment

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 2 hours	1	41	Mean Difference (IV, Random, 95% CI)	-11.3 [-16.27, -6.33]
2 6 hours	2	69	Mean Difference (IV, Random, 95% CI)	-8.43 [-30.37, 13.50]
3 24 hours	2	69	Mean Difference (IV, Random, 95% CI)	-9.74 [-47.88, 28.40]

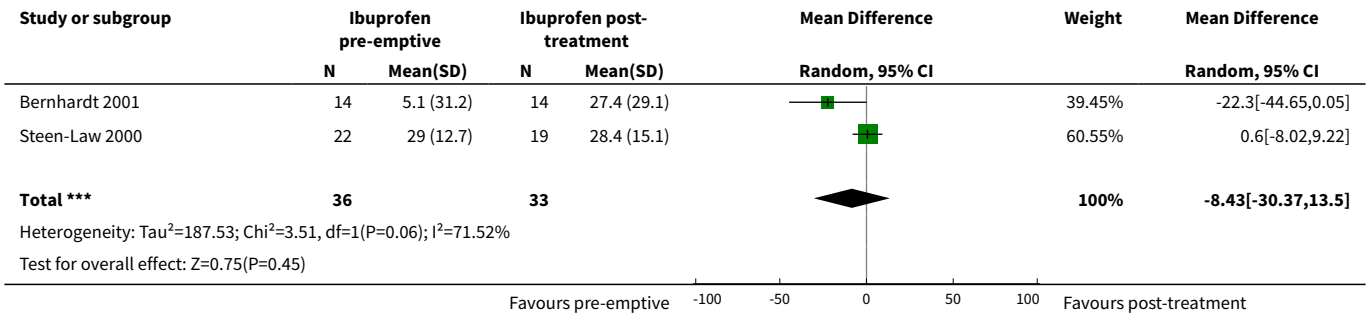
Analysis 3.1. Comparison 3 Ibuprofen pre-emptive versus post-treatment, Outcome 1 2 hours.



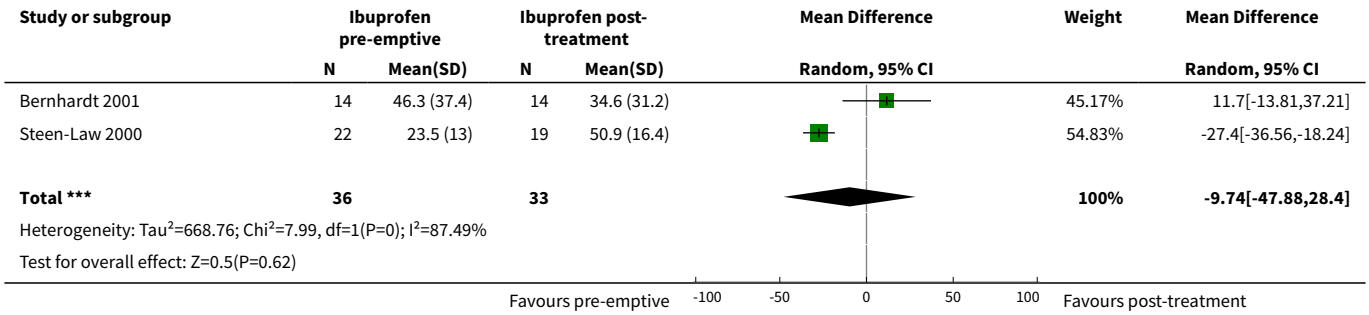
Study or subgroup	Ibuprofen pre-emptive N	Ibuprofen pre-emptive Mean(SD)	Ibuprofen post-treatment N	Ibuprofen post-treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Steen-Law 2000	22	9.2 (5.9)	19	20.5 (9.6)		100%	-11.3[-16.27,-6.33]
Total ***	**22**		**19**			**100%**	**-11.3[-16.27,-6.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.46(P<0.0001)							

Favours pre-emptive -20 -10 0 10 20 Favours post-treatment

Analysis 3.2. Comparison 3 Ibuprofen pre-emptive versus post-treatment, Outcome 2 6 hours.



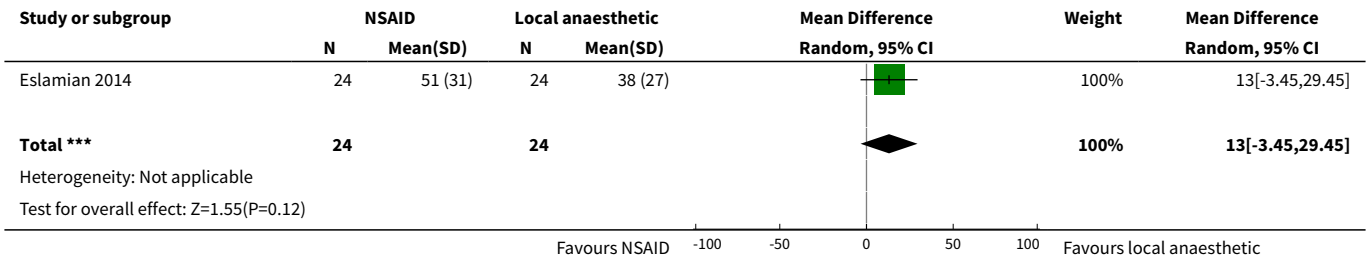
Analysis 3.3. Comparison 3 Ibuprofen pre-emptive versus post-treatment, Outcome 3 24 hours.



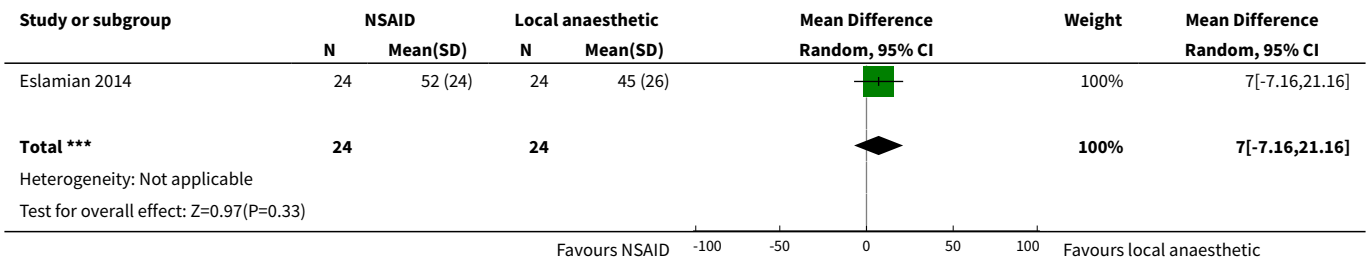
Comparison 4. NSAID versus local anaesthetic

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 2 hours	1	48	Mean Difference (IV, Random, 95% CI)	13.0 [-3.45, 29.45]
2 6 hours	1	48	Mean Difference (IV, Random, 95% CI)	7.0 [-7.16, 21.16]
3 24 hours	1	48	Mean Difference (IV, Random, 95% CI)	7.0 [-5.19, 19.19]

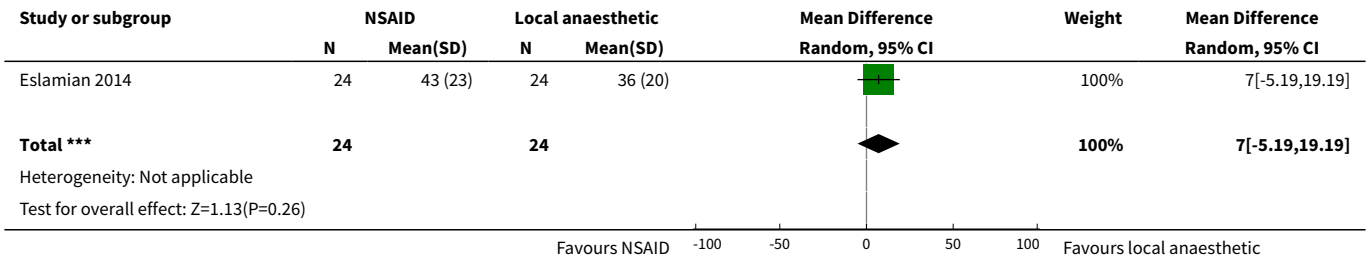
Analysis 4.1. Comparison 4 NSAID versus local anaesthetic, Outcome 1 2 hours.



Analysis 4.2. Comparison 4 NSAID versus local anaesthetic, Outcome 2 6 hours.



Analysis 4.3. Comparison 4 NSAID versus local anaesthetic, Outcome 3 24 hours.



ADDITIONAL TABLES

Table 1. Paracetamol versus control (no treatment or placebo) - separators

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Paracetamol	Pain VAS	2 (79)	MD -11.51 (-19.15 to -3.86)	0.003	0.77	0%
6 hours						
Paracetamol	Pain VAS	2 (79)	MD -16.00 (-24.65 to -7.34)	0.0003	0.38	0%
24 hours						
Paracetamol	Pain VAS	2 (79)	MD -21.51 (-54.10 to 11.09)	0.2	0.04	76%

Abbreviations
CI: confidence interval
MD: mean difference
RR: risk ratio
SMD: standardised mean difference

Table 2. Paracetamol versus control (no treatment or placebo) - bonding

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Paracetamol	Pain VAS	2 (70)	MD -14.04 (-21.51 to -6.58)	0.0002	0.88	0%
6 hours						
Paracetamol	Pain VAS	2 (70)	MD -21.03 (-27.19 to -14.87)	< 0.00001	0.30	6%
24 hours						
Paracetamol	Pain VAS	4 (141)	MD -21.55 (-40.42 to -2.68)	0.03	0.0001	85%

Abbreviations
CI: confidence interval
MD: mean difference
RR: risk ratio
SMD: standardised mean difference

Table 3. NSAID versus control (no treatment or placebo) - separators

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Ibuprofen	Pain VAS	4 (152)	MD -12.80 (-17.59 to -8.01)	< 0.00001	0.91	0%
Lumiracoxib		1 (51)	MD -5.32 (-112.20 to 1.56)	0.13	0.73	0%
Piroxicam		1 (45)	MD -29.70 (-48.01 to -11.39)	0.001	N/A	N/A
Subtotal		**5 (248)**	**-11.10 (-15.78** to**-6.42)**	**< 0.00001**	**0.25**	**23%**
6 hours						
Ibuprofen	Pain VAS	4 (150)	MD -23.41 (-41.43 to -5.39)	0.01	0.0001	86%
Lumiracoxib		1 (51)	MD -7.06 (-16.55 to 2.43)	0.14	0.67	0%
Piroxicam		1 (45)	MD -40.50 (-57.37 to -23.63)	< 0.00001	N/A	N/A
Subtotal		**5 (248)**	**MD -8.80 (-13.47 to -4.12)**	**0.0002**	**0.97**	**0%**
24 hours						
Ibuprofen		3 (118)	MD -21.85 (-37.33 to -6.37)	0.006	0.07	62%
Lumiracoxib		1 (51)	MD -17.58 (-31.62 to -3.54)	0.01	0.57	0%

Table 3. NSAID versus control (no treatment or placebo) - separators *(Continued)*

Piroxicam	1 (45)	MD -36.10 (-51.33 to -20.87)	< 0.00001	N/A	N/A
Subtotal	**4 (214)**	**MD -23.66 (-32.81 to-14.51)**	**< 0.00001**	**0.12**	**42%**

Abbreviations
CI: confidence interval
MD: mean difference
N/A: not applicable
RR: risk ratio
SMD: standardised mean difference

Table 4. NSAID versus control (no treatment or placebo) - initial archwire

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Aspirin	Pain VAS	1 (25)	MD -26.20 (-56.37 to 3.97)	0.09	N/A	N/A
Etoricoxib		1 (30)	MD -32.00 (-38.09 to -25.91)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD -21.00 (-51.34 to 9.34)	0.17	N/A	N/A
Ibuprofen		3 (75)	MD -6.02 (-20.52 to 8.47)	0.42	0.45	0%
Naproxen sodium		2 (55)	MD -20.80 (-39.42 to -2.18)	0.03	0.55	0%
Subtotal		**4 (210)**	**MD -19.23 (-29.90 to-8.56)**	**0.0004**	**0.07**	**47%**
6 hours						
Aspirin	Pain VAS	1 (25)	MD -39.30 (-69.71 to -8.89)	0.01	N/A	N/A
Etoricoxib		1 (30)	MD -41.00 (-46.77 to -35.23)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD -22.00 (-52.86 to 8.86)	0.16	N/A	N/A
Ibuprofen		3 (75)	MD -20.87 (-35.21 to -6.52)	0.004	0.91	0%
Naproxen sodium		2 (55)	MD -36.87 (-54.82 to -18.92)	< 0.0001	0.84	0%
Subtotal		**4 (210)**	**MD -35.42 (-42.15 to-28.68)**	**< 0.00001**	**0.35**	**10%**
24 hours						
Aspirin	Pain VAS	1 (25)	MD -41.20 (-71.99 to -10.41)	0.09	N/A	N/A
Etoricoxib		1 (30)	MD -54.00 (-60.34 to -47.66)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD -10.40 (-41.69 to 20.89)	0.51	N/A	N/A
Ibuprofen		6 (420)	MD -19.71 (-33.60 to -5.82)	0.005	0.004	71%

Table 4. NSAID versus control (no treatment or placebo) - initial archwire *(Continued)*

Naproxen sodium	2 (55)	MD -28.61 (-66.08 to 8.86)	0.13	0.05	75%
Subtotal	**7 (555)**	**MD -26.26 (-37.81 to-14.71)**	**< 0.0001**	**< 0.00001**	**85%**

Abbreviations
CI: confidence interval
MD: mean difference
N/A: not applicable
RR: risk ratio
SMD: standardised mean difference

Table 5. NSAID versus control (no treatment or placebo) - mid-treatment

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Ketoprofen (chewing gum)	Pain VAS	1 (48)	MD -22.00 (-36.14 to -7.86)	0.002	N/A	N/A
6 hours						
Ketoprofen (chewing gum)	Pain VAS	1 (48)	MD -40.50 (-57.37 to -23.63)	< 0.00001	N/A	N/A
24 hours						
Ketoprofen (chewing gum)	Pain VAS	1 (48)	MD -40.50 (-57.37 to -23.63)	< 0.00001	N/A	N/A

Abbreviations
CI: confidence interval
MD: mean difference
N/A: not applicable
RR: risk ratio
SMD: standardised mean difference

Table 6. NSAID versus paracetamol - separators

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Ibuprofen	Pain VAS	4 (351)	MD -3.36 (-7.00 to 0.28)	0.07	0.46	0%
Meloxicam		1 (127)	MD 1.40 (-4.89 to 7.69)	0.66	N/A	N/A
Subtotal		**4 (478)**	**MD -2.16 (-5.44 to1.12)**	**0.20**	**0.37**	**6%**
6 hours						

Table 6. NSAID versus paracetamol - separators *(Continued)*

Ibuprofen	Pain VAS	4 (351)	MD -4.53 (-10.23 to 1.18)	0.12	0.14	44%
Meloxicam		1 (127)	MD 0.50 (-6.85 to 7.85)	0.89	N/A	N/A
Subtotal		**4 (478)**	**MD -3.35 (-8.05 to1.35)**	**0.16**	**0.15**	**40%**
24 hours						
Ibuprofen	Pain VAS	4 (351)	MD 1.38 (-3.22 to 5.98)	0.56	0.71	0%
Meloxicam		1 (127)	MD -0.30 (-11.40 to 10.80)	0.96	N/A	N/A
Subtotal		**4 (478)**	**MD 1.14 (-3.11 to5.39)**	**0.60**	**0.83**	**0%**

Abbreviations
CI: confidence interval
MD: mean difference
N/A: not applicable
RR: risk ratio
SMD: standardised mean difference

Table 7. NSAID versus paracetamol - initial archwire

Experimental intervention	Outcome	Number of studies (number of participants)	Effect measure RR, MD, SMD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Aspirin	Pain VAS	1 (25)	MD -10.90 (-35.87 to 14.07)	0.39	N/A	N/A
Etoricoxib		1 (30)	MD -20.00 (-28.42 to -11.58)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD -5.70 (-20.82 to 9.42)	0.46	N/A	N/A
Ibuprofen		2 (81)	MD 14.63 (0.77 to 28.50)	0.04	0.97	0%
Naproxen sodium		1 (25)	MD 2.50 (-24.63 to 29.63)	0.86	N/A	N/A
Subtotal		**3 (201)**	**MD -2.230 (-16.06 to11.61)**	**0.75**	**0.002**	**73%**
6 hours						
Aspirin	Pain VAS	1 (25)	MD -8.70 (-36.03 to 18.63)	0.53	N/A	N/A
Etoricoxib		1 (30)	MD -21.00 (-27.09 to -14.91)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD 8.60 (-19.23 to 36.43)	0.54	N/A	N/A
Ibuprofen		2 (81)	MD 4.10 (-10.28 to 18.48)	0.58	0.88	0%
Naproxen sodium		1 (25)	MD -9.00 (-37.89 to 19.89)	0.54	N/A	N/A
Subtotal		**3 (201)**	**MD -5.66 [-18.97 to7.64]**	**0.40**	**0.02**	**63%**

Table 7. NSAID versus paracetamol - initial archwire *(Continued)*

24 hours						
Aspirin	Pain VAS	1 (25)	MD 5.10 (-20.77 to 30.97)	0.70	N/A	N/A
Etoricoxib		1 (30)	MD -22.00 (-27.06 to -16.94)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	MD 35.90 (9.44 to 62.36)	0.008	N/A	N/A
Ibuprofen		4 (151)	MD -1.36 (-13.04 to 10.33)	0.82	0.21	33%
Naproxen sodium		1 (25)	MD -2.60 (-27.11 to 21.91)	0.84	N/A	N/A
Subtotal		**5 (256)**	**MD -0.37 (-14.41 to13.67)**	**0.96**	**< 0.00001**	**82%**

Abbreviations
CI: confidence interval
MD: mean difference
N/A: not applicable
RR: risk ratio
SMD: standardised mean difference

APPENDICES

Appendix 1. Cochrane Oral Health Trials Register search strategy

1 (orthodontic*:ti,ab) AND (INREGISTER)
2 ((pain* or discomfort or headache* or migraine* or neuralgi* or earache* or ear-ache* or "ear ache*" or toothache* or tooth-ache* or "tooth ache*" or odontalgi*):ti,ab) AND (INREGISTER)
3 (analgesi*:ti,ab) AND (INREGISTER)
4 (((local or topical*) and (anaesthe* or anesthe*)):ti,ab) AND (INREGISTER)
5 (("anti inflammatory agent*" or "antiinflammatory agent*" or "anti-inflammatory agent*" or "aspirin like agent*" or "aspirin-like agent*" or NSAID*):ti,ab) AND (INREGISTER)
6 ((opioid* or aspirin* or paracetamol* or acetaminophen* or medication* or drug*):ti,ab) AND (INREGISTER)
7 (#3 or #4 or #5 or #6) AND (INREGISTER)
8 (#1 and #2 and #7) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Clinical Trials (CENTRAL) search strategy

#1 MeSH descriptor Orthodontics explode all trees
#2 orthodontic* in All Text
#3 (#1 or #2)
#4 MeSH descriptor Pain this term only
#5 MeSH descriptor Facial pain this term only
#6 MeSH descriptor Headache this term only
#7 MeSH descriptor Neuralgia this term only
#8 MeSH descriptor Earache this term only
#9 MeSH descriptor Toothache this term only
#10 MeSH descriptor Pain measurement this term only
#11 (pain* in All Text or discomfort in All Text or headache* in All Text or migraine* in All Text or neuralgi* in All Text or earache* in All Text or ear-ache* in All Text or "ear ache*" in All Text or toothache* in All Text or tooth-ache* in All Text or "tooth ache*" in All Text or odontalgi* in All Text)
#12 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
#13 MeSH descriptor Analgesics explode all trees
#14 analgesi* in All Text
#15 MeSH descriptor Anesthetics, Local this term only
#16 ((local in All Text or topical in All Text) and (anaesthe* in All Text or analgesi* in All Text or anesthe* in All Text))
#17 MeSH descriptor Anti-inflammatory agents, non-steroidal explode all trees

#18 ("anti inflammatory agent*" in All Text or "antiinflammatory agent*" in All Text or "anti-inflammatory agent*" in All Text or "nonsteroidal analgesi*" in All Text or "non steroidal analgesi*" in All Text or "non-steroidal analgesi*" in All Text or "aspirin like agent*" in All Text or "aspirin-like agent*" in All Text or NSAID* in All Text)
#19 (opioid* in All Text or aspirin* in All Text or paracetamol* in All Text or acetaminophen* in All Text or medication* in All Text or drug* in All Text)
#20 (#13 or #14 or #15 or #16 or #17 or #18 or #19)
#21 (#3 and #12 and #20)

Appendix 3. MEDLINE Ovid search strategy

1. exp Orthodontics/
2. orthodontic.mp.
3. 1 or 2
4. Pain/
5. Facial pain/
6. Headache/
7. Neuralgia/
8. Earache/
9. Toothache/
10. Pain measurement/
11. (pain$ or discomfort or headache$ or migraine$ or neuralgi$ or earache$ or ear-ache$ or "ear ache$" or toothache$ or tooth-ache$ or "tooth ache$" or odontalgi$).mp.
12. or/4-11
13. exp Analgesics/
14. analgesi$.mp.
15. Anesthetics, Local/
16. ((local or topical) and (anaesthe$ or analgesi$ or anesthe$)).mp.
17. exp Anti-inflammatory agents, non-steroidal/
18. ("anti inflammatory agent$" or "antiinflammatory agent$" or "anti-inflammatory agent$" or "nonsteroidal analges$" or "non steroidal analges$" or "non-steroidal analges$" or "aspirin like agent$" or "aspirin-like agent$" or NSAID$).mp.
19. (opioid$ or aspirin$ or paracetamol$ or acetaminophen$ or medication$ or drug$).mp.
20. or/13-19
21. 3 and 12 and 20

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 [updated March 2011](Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. exp Orthodontics/
2. orthodontic.mp.
3. 1 or 2
4. Pain/
5. Face pain/
6. Headache/
7. Neuralgia/
8. Otalgia/

9. Tooth pain/
10. Pain assessment/
11. (pain$ or discomfort or headache$ or migraine$ or neuralgi$ or earache$ or ear-ache$ or "ear ache$" or toothache$ or tooth-ache$ or "tooth ache$" or odontalgi$).mp.
12. or/4-11
13. exp Analgesic agent/
14. analgesi$.mp.
15. Local anesthetic agent/
16. ((local or topical) and (anaesthe$ or analgesi$ or anesthe$)).mp.
17. exp Nonsteroid antiinflammatory agent/
18. ("anti inflammatory agent$" or "antiinflammatory agent$" or "anti-inflammatory agent$" or "nonsteroidal analges$" or "non steroidal analges$" or "non-steroidal analges$" or "aspirin like agent$" or "aspirin-like agent$" or NSAID$).mp.
19. (opioid$ or aspirin$ or paracetamol$ or acetaminophen$ or medication$ or drug$).mp.
20. or/13-19
21. 3 and 12 and 20

The above subject search was linked to Cochrane Oral Health's filter for identifying RCTs in Embase Ovid:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

Appendix 5. CINAHL EBSCO search strategy

S1 (MH "Orthodontics+")
S2 orthodontic*
S3 S1 or S2
S4 MH "Pain"
S5 MH "Facial Pain"
S6 MH "Headache"
S7 MH "Neuralgia"
S8 MH "Earache"
S9 MH "Toothache"
S10 MH "Pain Measurement"
S11 (pain* or discomfort or headache* or migraine* or neuralg* or earache* or ear-ache* or "ear ache*" or toothache* or tooth-ache* or "tooth ache*" or odontalgi*)
S12 S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S13 MH "Analgesics+"
S14 analgesi*
S15 (MH "Anesthetics, Local+")
S16 ((local or topical) and (anaesthe* or analgesi* or anesthe*))
S17 (MH "Antiinflammatory Agents, Non-Steroidal+")
S18 ("anti inflammatory agent*" or "antiinflammatory agent*" or "anti-inflammatory agent*" or "nonsteroidal analgesi*" or "non steroidal analgesi*" or "non-steroidal analgesi*" or "aspirin like agent*" or "aspirin-like agent*" or NSAID*)
S19 (opioid* or aspirin* or paracetamol* or acetaminophen* or medication* or drug*)
S20 S13 or S14 or S15 or S16 or S17 or S18 or S19
S21 S3 and S12 and S20

Appendix 6. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

orthodontic and pain

Appendix 7. World Health Organization International Clinical Trials Registry Platform search strategy

orthodontic and pain

WHAT'S NEW

Date	Event	Description
20 December 2017	Amended	Minor copy edit to reference

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 11, 2017

Date	Event	Description
18 September 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Jayne Harrison (JH) conceived the review. James Cooper (JC) and JH wrote the protocol. The review was co-ordinated by Aoife Monk (AM). AM, with the assistance of Anne Littlewood (Information Specialist, Cochrane Oral Health), developed the search strategy and undertook the electronic searches. AM undertook the handsearching. AM, Annabel Teague (AT) and JH screened the search results and retrieved papers, appraised the risk of bias in the papers, extracted data from them and assessed the quality of the evidence overall. Helen Worthington checked the data extraction, undertook the data analysis and assisted with the interpretation of the data. AM and JH wrote the review.

DECLARATIONS OF INTEREST

The review authors declare that there is no financial conflict of interest and that they do not have any associations with industry regarding the subject of this review.

Aoife B Monk: none known
Jayne E Harrison: administrative support for this review was funded by an NHS Research & Development grant. The time I spent on the review was largely outside contractual hours, but meetings were attended within the working day, for which I was given study leave.
Helen V Worthington: none known. I am one of two Co-ordinating Editors of Cochrane Oral Health.
Annabel Teague: none known

SOURCES OF SUPPORT

Internal sources

- The Royal Liverpool and Broadgreen Hospitals NHS Trust, UK.
- The University of Manchester, Manchester Academic Health Sciences Centre (MAHSC) and UKNIHR Manchester Biomedical Research Centre, UK.

External sources

- Cochrane Oral Health Global Alliance, Other.

  The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (oralhealth.cochrane.org/partnerships-alliances). Contributors over the past year have been the American Association of Public Health Dentistry, USA; the British Association for the Study of Community Dentistry, UK; the British Society of Paediatric Dentistry, UK; the

Canadian Dental Hygienists Association, Canada; the Centre for Dental Education and Research at All India Institute of Medical Sciences, India; the National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; and NHS Education for Scotland, UK; Swiss Society of Endodontology, Switzerland.

- National Institute for Health Research (NIHR), UK.

This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We altered objectives to include timing of analgesia taken during orthodontic treatment.
- We removed quasi-randomized controlled clinical trials from the inclusion criteria.
- We adjusted exclusion criteria to include participants who had received orthodontic treatment involving the use of temporary anchorage devices.
- We removed duration of pain from primary outcomes.
- We removed handsearching from the methodology.
- We rewrote parts of the review for clarity.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; Analgesics [*therapeutic use]; Analgesics, Non-Narcotic [therapeutic use]; Anesthetics, Local [therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Orthodontics, Corrective [*adverse effects]; Pain Measurement; Pain, Procedural [*drug therapy] [etiology] [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Humans