Pharmacological interventions for pain relief during orthodontic treatment

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Chapter 1: Abstract

Pharmacological interventions for pain relief during orthodontic treatment.
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Background: Pain is a common and unwanted side effect of orthodontic treatment, caused by a reduction in blood flow during tooth movement using orthodontic appliances. Pain has been shown to be the most common reason for patients wanting to discontinue treatment. Pharmacological methods of pain relief have been investigated in the literature showing promising results, although there remains some uncertainty among orthodontists as to which painkillers are most suitable and whether pre-emptive analgesia is beneficial and therefore present as a simple intervention to prevent this unwanted side effect of treatment. Therefore a Cochrane review is warranted to assess and summarise the international evidence.[1]
Objectives: To determine the most effective drug intervention for pain relief during orthodontic treatment.[1]
Search methods: We searched the following databases up to August 2016: Cochrane Oral Health Group Trials Register, Cochrane Pain, Palliative and Supportive Care Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via Ovid, EMBASE via Ovid and CINAHL via EBSCO. We searched the US National Institutes of Health Trials Registry, and the WHO Clinical Trials Registry Platform for ongoing trials. No restrictions were placed on language or date of publication when searching databases.[1]
Selection criteria: We included randomized controlled trials (RCTs) relating to pain control during orthodontic treatment measured on a visual analogue scale (VAS), numerical rating scale (NRS) or any categorical scale.
Data collection and analysis: Two reviewers independently extracted information regarding methods, participants, interventions, outcomes, harms and results, independently and in duplicate. The Cochrane risk of bias tool was used to assess the methodological quality of the studies.[1]
Main results: 22 RCTs were identified which included 2110 participants. A meta-analysis was carried out on twelve papers that compared analgesics versus control, nine that compared NSAIDs versus paracetamol and two comparing pre-emptive versus post-treatment ibuprofen for pain control following orthodontic treatment. Analgesics were found to effectively reduce pain at 2, 6 and 24 hours following orthodontic treatment (mean difference -24.48, 95% CI -30.54 to -18.43, P=<0.00001). No difference was found between the efficacy of NSAIDs and paracetamol, except low quality evidence that paracetamol is more effective at reducing pain associated with initial archwire placement at 2 hours (MD 14.63, 95% CI 0.77 to 28.50, P=0.04). Pre-emptive ibuprofen gives better pain relief at 2 hours (MD -11.33, 95% CI -16.09 to -6.58, P=<0.00001) however the effect reduces over time. No difference was found between the use of topical NSAIDs and local anaesthetic. However overall quality of evidence was poor and levels of heterogeneity were variable (I^2 results varied from 0% to 87%).
Authors' conclusions: Analgesics are effective at reducing pain following orthodontic treatment. There is no difference between the efficacy of systemic NSAIDs and paracetamol, or topical NSAID and local anaesthetic. Pre-emptive ibuprofen gives better pain relief at 2 hours however the effect reduces over time. More high quality research is needed to investigate the effect of NSAID and paracetamol and the effect of pre-emptive and post-treatment administration of analgesics for orthodontic pain.

Chapter 2: Introduction

Orthodontic treatment plays a vital role in the correction of malocclusions for both children and adults. However, orthodontic movement of teeth is often associated with discomfort or pain, of varying intensity and duration which can be a major concern for patients, guardians, and clinicians.[2] The effect that this has on patients' decision making regarding treatment can differ; from having little or no effect to resulting in patients discontinuing or even not commencing treatment.[3] Management of the pain associated with orthodontic treatment is therefore fundamental to the successful management of orthodontic patients.[4,5] Pharmacological and non-pharmacological managements of acute dental pain have been discussed in the literature since the late nineteenth and early twentieth centuries.[6] Advances in our knowledge and understanding of both the cause of orthodontic pain and the pharmacology of analgesic drugs, has led to improvements in the management of pain pre-, peri- and post-operatively over the past four decades.[7] Orthodontic treatment, in its various forms and with appropriate pain management, has therefore assumed an important role in the modern day management of malocclusions in order to provide functional and aesthetic changes to patients who may have otherwise refused treatment for fear of the associated pain.

Chapter 2: Literature Review

2.1: The Role of Orthodontics

Orthodontics is the branch of dentistry concerned with the growth and development of the face and jaws and the treatment of irregularities of the teeth.[8] It also involves the treatment of the teeth and jaws when they are irregular in their alignment, morphology and/or function. Orthodontics is typically carried out to improve the functioning and appearance of the teeth. This may involve moving teeth by applying a force via fixed appliances (braces where the components are attached to the teeth for the duration of the treatment); removable appliances (braces which, although normally worn full-time during treatment, can be removed from the mouth for cleaning during treatment); and/or functional appliances (braces that aim to move the teeth and modify the direction of growth of the jaws to induce an orthopaedic change. These functional appliances can either be removable from the mouth or fixed to the teeth during treatment).[8]

Orthodontic treatment may also involve the extraction of teeth in order to provide space to allow the teeth to be aligned, surgery to expose unerupted or impacted teeth in an attempt to guide them into alignment, and occasionally jaw surgery to correct the underlying position of the jaws.[9,10,11]

Most patients undergoing orthodontic treatment are children or adolescents although an increasing number of adults are seeking treatment.[12]

Treatment typically begins with the construction and placement of the orthodontic appliance; whether fixed, removable or functional; usually over two thirty to forty-five minute visits. Routine adjustments are then carried out every four to six weeks over the course of treatment, which normally lasts approximately twelve to twenty-four months. Following treatment, the removal of fixed appliances takes approximately thirty to forty-five minutes and retainers are then provided to maintain the teeth in their newly aligned position.[9]

2.2: Pain associated with orthodontics

2.2.1: Definition of pain

Pain is a complex experience and therefore difficult to define. The International Association for the Study of Pain (IASP) defines pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[13]

Pain can also be subcategorised depending on its characteristics and/or the stimulus that has elicited the emotional experience. Examples include allodynia, where pain occurs as a result of a stimulus which would normally not provoke pain, hyperalgesia, where pain is increased to beyond the normal threshold from a stimulus which normally provokes pain, and hypoalgesia, which is a diminished response from a normally painful stimulus.

In addition, pain may be categorised by duration. Acute pain is a biological process, provoked by a normal stimulus and is self-limiting. Chronic pain, however, serves no biological process and outlasts the normal times of healing.[14] The appropriate pain management regime can differ significantly for acute and chronic pain; as too can the management of pain of varying characteristics. It is therefore important to understand the physiology of pain and identify the nature of the pain being experienced so as to treat the patient appropriately. Conversely, experiences which resemble pain but are not unpleasant; pricking for example; should not be called pain. They may be categorised as discomfort.

It is also important to note that pain is described as always being subjective. Each individual learns the application of the word pain through previous experiences related to injury and therefore large individual variations are seen.[15] For example, patients may report pain in the absence of any tissue damage or likely pathophysiological cause. There is usually no way to distinguish their experience from that of one caused by tissue damage due to the subjective nature of pain experience and therefore its reporting. If a patient regards their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. It is, therefore, important to remember that pain is a highly personal experience, with the degree of pain and suffering reported not always related to the amount of tissue injury.[16]

2.2.2: Factors which influence pain perception

A number of factors have been identified throughout the literature which are thought to influence a patient's perception of pain. However, evidence is varying and often contradictory. These factors include age, gender, race, individual pain threshold, expectations, treatment received, the magnitude of the force applied, time since the force was applied, present emotional state and stress, cultural differences, and previous pain experiences.[13,14,15] A summary of a selection of evidence which has been presented to demonstrate the effect of some of these factors on a patient perception of pain is shown in Table 1.

Firestone et al.[16] investigated fifty adolescent orthodontic patients who had undergone recent placement of initial archwires. Patients were given questionnaires pre-treatment to assess their expectations regarding pain and how they expect it will influence their daily lives. When compared with reported levels of pain following bond-up and placement of initial aligning archwires, a positive correlation was identified between the level of anticipated pain and the level of experienced pain. Conversely, a study in 2012 by Kafle and Rajbhandari,[17] of 45 orthodontic patients undergoing treatment, found a significant difference between the anticipated pain before orthodontic treatment and the pain experienced following treatment. They also found that perception of pain between males and females was significantly different however, anticipated pain among males and females did not differ. When comparing the same procedure, female patients had experienced more pain than male patients.

Brown and Moerenhout[18] carried out a longitudinal study to assess age-related changes in psychological measurement of pain in patients undergoing orthodontic treatment. They found a significant difference in reported pain experienced during banding and archwire adjustments in an adolescent group (aged fourteen to seventeen years), compared to a pre-adolescent group (aged eleven to thirteen years) and an adult group (aged eighteen and above), with the adolescent group reporting significantly more pain than the pre-adolescent and adult groups. As a result, the authors hypothesise that adolescents may be more vulnerable to undesirable psychological effects of orthodontic treatment.

Jones and Chan,[19] when comparing different aligning archwires, noted similar associations between age and pain experienced. However, contrary to the finding of

previous researchers, they did not find a relationship between pain experienced and gender, social class or crowding.

It would therefore appear, from the evidence, that pain response is highly variable and consistently subjective.

Table 1. A summary of literature exploring factors that influence patients' perception of pain following orthodontic treatment.

Study	Participants	Method	Comparison	Outcomes	Results
	•		•	•	•
Firestone, Scheurer, Burgin. 1999.[16]	• N = 50 consecutively treated patients. • 28 females, 22 males. • Age range 8.9-39.3 years. Mean = 15.5 years.	Pre-treatment oral and written VAS questionnaire.	A second questionnaire was completed 1 week after initial archwire placement.	• Patient expectations of pain as a result of orthodontic treatment. • Anticipated effects of pain on lives. • True experienced pain and effect of pain on lives.	• No difference between anticipated and reported pain. • Patients significantly underestimated the changes they would have to make to diet as a result of pain. • Patients who anticipated greater pain, experienced greater pain and disruption to their daily lives.
Kafle and Rajbhandari. 2012.[17]	• N = 45 patients.	Pre-treatment VAS scale for anticipated pain.	Post-treatment VAS scale for pain experienced following orthodontic procedure.	• Anticipated pain before treatment. • Intensity of pain experienced following orthodontic treatment.	• Significant difference between anticipated pain and actual pain experienced during orthodontic treatment. • For the same procedure, females experienced significantly more pain than males.
Brown and Moerenhout. 1991.[18]	• N = 76. • Aged 11 years and above.	Longitudinal series of 4 pain questionnaires.	• T1: 1 day after separation. • T2: 1 day after banding. • T3: 1 day after adjustment 3-4weeks in treatment. • T4:1 day after adjustment 3-4 months in treatment.	• Pain intensity and duration in relation to treatment stage. • Pain intensity and duration in relation to patient age.	• Significant differences in the response profiles of the adolescent age group (14 to 17 years) compared to the preadolescent (11 to 13 years) and adult groups (18 years and older).
Jones and Chan. 1992.[19]	• N = 43 patients.	Pre and post-treatment pain questionnaires and VAS.	• Randomisation to: – Superelastic archwire. – Multistrand stainless steel archwire.	• Nature, prevalence, duration and intensity of pain experienced. • Analgesic consumption.	• No difference in prevalence, intensity, and duration of pain after insertion of archwire. • Pain more severe than post-extraction. • Pain peaked the morning after arch wire placement, typically lasting 5-6 days.
Ngan, Kess, Wilson. 1989.[20]	• Control = 29 patients (19 female, 10male). • Intervention = 65 patients (42 female, 23 male). • Age range 10.5-38 years.	Discomfort index and visual analogue scale (VAS) questionnaires.	• Placement of separators for 7 days. • Removal of separators, placement of Begg appliances and initial arch wires.	• Pain intensity. • Pain duration.	• Significant increase in discomfort after insertion of separators/arch wires at 4 hours and 24 hours, but not at 7 days. • No significant difference in pain for patients over 16 years of age compared with those 16 years and under.

2.2.3: Neural pathways of pain

In order to appreciate the effect of analgesics on orthodontic pain, it is important to understand the biology and neural pathways behind the production of pain sensation.

The neural pathway for pain consists of four processes; these are transduction, transmission, modulation and perception.[21] Transduction is where noxious stimuli cause electrical stimulation in specific free nerve endings called nociceptors. These are the peripheral receptors in the face and mouth which respond to noxious, pain-causing orofacial stimuli.[22] The noxious input is then transmitted, via the neural system, to the CNS for processing. The neural system, which processes the noxious input, consists of three parts; the peripheral sensory nerve primary afferent neuron carries the nociceptive input via the dorsal root, to the dorsal horn in the spinal cord. All cell bodies of primary neurons are located in the dorsal root ganglion; followed by the second order neuron, which can involve more than one neuron and carries the input across the spinal cord, and via the anterolateral spinothalamic pathway, to the thalamus; the final part of the system involves neural interactions between the thalamus, cortex and limbic system. This is where modulation occurs, as the cortex and brainstem can control the pain-transmitting neurons. This is known as the gate control theory, where the signal can be blocked, transmitted, or modified to enhance or reduce the arriving input at different central regions.[23]

Finally, perception is achieved when nociceptive input reaches the cortex and a complex interaction of neurons between the higher centres of the brain occurs and pain behaviours begin.[24]

2.2.4: The Trigeminal System

Orofacial sensory input enters the spinal cord via the fifth cranial nerve, the trigeminal nerve.[25] The trigeminal nerve is made up of three sensory branches: the ophthalmic division (V_1), the maxillary division (V_2) and the mandibular division (V_3); as illustrated in Figure 1.

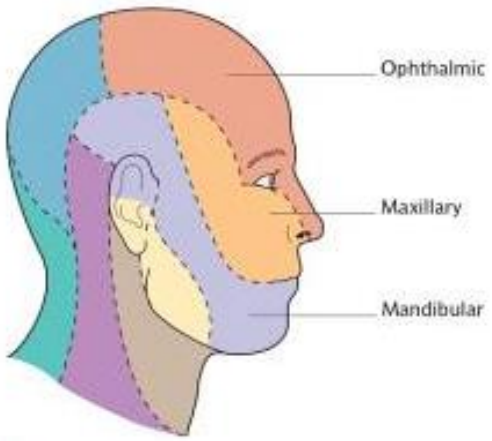


Figure 1. Sensory fields of the trigeminal nerve branches[26]

The trigeminal spinal pathway also receives and transmits input from the glossopharyngeal (ninth cranial nerve) and the vagus nerve (tenth cranial nerve).[27] Furthermore, the trigeminal system transmits motor impulses, from the muscles of mastication for example. Transmission cells exist in three types in the trigeminal system.[22] However, it the small-diameter polymodal nociceptive fibres which are responsible for transmission of orthodontic pain. They are each responsible for an area known as a receptive field. They are activated by high-intensity orofacial stimulus applied to their localised receptive field.[28] Two types of nociceptors have been identified. The first is the C-fibre, which is the most common fibre found in the dental pulp. It is sensitive to mechanical, chemical and heat stimuli[29] and conveys a burning or dull aching pain sensation. They have a receptive field of 10cm, a diameter of 0.5-1µm and are unmyelinated, making them slower at conducting impulses. The second type of nociceptor is the A-delta (A-δ) fibre, which elicits a pricking, sharp pain and is sensitive to mechanical and heat stimuli.[29] A-δ-fibres are myelinated, and therefore they have faster signal transduction.

2.2.5: Biology of orthodontic pain

The pressure-tension theory is the classic theory behind our understanding of orthodontic tooth movement. The theory suggests that, when force is applied to a tooth, areas of pressure and tension are generated within the periodontal ligament (PDL). Early histological studies, carried out at tissue level by Standstedt[30,31,32] in the early 20th century, demonstrate the chemical signalling and cellular changes that occur on the pressure and tension sides when force was applied to maxillary incisors in dogs. In areas of tension, bone is deposited with both light and heavy forces.

Whilst in areas of pressure/compression, light forces result in resorption of bone directly by multinucleate osteoclasts in the Howship's lacunae. However, when forces are heavy and exceed capillary blood pressure, the PDL is compressed and cell death occurs resulting in the development of a localised cell-free area, termed "hyalinisation". This is due to its glass-like appearance under light microscopy similar to that of hyaline cartilage.[33] Resorption in these areas is termed "undermining resorption" and occurs at a delayed rate due to delayed migration of osteoclasts from adjacent tissues. This results in slower tooth movement and more pain for the patient.[33] Continuous forces, as light as 30g, can cause hyalinisation; particularly when tipping teeth, because forces are more concentrated compared to evenly and uniformly distributed force exerted during bodily movement.[32]

When pressure is delivered to a tooth by orthodontic appliances, ischemia, inflammation, and oedema will occur immediately in the area of compression of the periodontal ligament.[34] The tooth will be displaced within the periodontal ligament space, loading the alveolar bone. The mechanical strain produced alters blood flow within the periodontal ligament, stimulating the synthesis and release of algogens such as histamine, prostaglandin PGE2, and leukotrienes, thus activating an inflammatory reaction.[31] This will result in pain for the patient, usually commencing about two hours after application of orthodontic force, reaching a peak level at 24 hours, and lasting approximately five days.[16] In addition to the mechanically-induced inflammatory response, pain is transmitted directly from periodontal nerve ending. Nerve endings in the periodontal ligament consist of low-threshold mechano-receptors and nociceptors. Pain is initiated via compression and stretch of the low-threshold mechano-receptors, whilst nociceptors are activated by tissue injury or heavy forces.[35]

2.2.6: Sources of orthodontic pain

It is generally understood by patients that pain and discomfort are common clinical symptoms, especially in the period immediately following fixed appliance placement.[36]

Literature shows that the pain experience during treatment begins with initial discomfort when orthodontic force is applied, but this disappears immediately. The second response appears much later, with peak intensity on day one and lasts a few days.[19] However, the source of this pain varies and therefore the ultimate discomfort

experienced by the patient will depend on the appliances, auxiliaries and order of treatment used by their clinician. A summary of a selection of evidence exploring common sources of orthodontic pain is shown in Table 2.

Different forms of orthodontic appliances or auxiliaries will have a varying effect on the intensity of pain experienced. Literature has shown that patients wearing fixed or functional appliances have a significantly higher level of pain than those who are undergoing treatment with removal upper and/or lower appliances.[37]

Pain experienced during the placement of separators has been shown in the literature to be of particular significance. A study by Bergius et al. in 2002[38] investigated fifty-five adolescent patients who had bilateral molar elastic separators placed. The vast majority (87%) of patients reported pain the first evening. The highest intensity of pain was reached the day after placement of separators whilst at day 7, 42% of the patients still reported pain. Although pain experience varied substantially, their findings reflect those of other researchers.[39]

Pain, during the initial alignment stage of treatment, can be expected. In the literature, the severity of this pain has been compared to that of premolar extractions when they have been carried out to aide correction of the malocclusion. This has shown that patients who underwent both premolar extractions and orthodontic tooth movement experienced more pain 24 hours after initial arch wire placement than they did 24 hours after tooth extraction.[19]

In addition to the pain experience at the beginning of treatment; with both separation and placement of initial aligning archwires, patients may also experience pain for 1 to 2 days following each adjustment appointment. This can be experienced acutely or continuously in between adjustment visits.

Table 2. A summary of literature exploring sources of orthodontic pain.

Study	Participants	Method	Outcomes	Results
Sergl, Klages, Zentner. 1998.[37]	• N = 84 patients undergoing orthodontic treatment. • 45 female: 39 male. • Mean age: 12.8 years.	• Questionnaires and rating scale at 1, 2, 6 weeks and 3, 6months after appliance insertion. • Patients had either: – 1 removable plate (25) – 2 removable plates (31) – Functional appliances (14) – Fixed appliances (14)	• Pain experience. • Patient attitude towards treatment. • Compliance at 1, 2, 6 weeks and 3, 6months.	• Adaptation to pain occurred in the first 3-5 days after appliance placement. • Severity of pain wearing functional or fixed appliances was significantly higher than by those treated with upper and/or lower removable plates. • Patients who had higher perception of the severity of their malocclusion seemed to adapt faster and have less pain.
Bergius, Berggren, Kiliaridis. 2002.[38]	• N =55 patients. • 12-18 years old. • Treatment due to crowding.	• Bilateral molar separators. • Telephone interviews for 7 days.	• Pain intensity on a VAS scale. • Pain medication required.	• 87% reported pain in the first evening. • Highest intensity of pain one day after separator placement. • 42% still had pain at day 7. • Analgesics taken by 27% within 2 days. • No patients took analgesics after 2 days. • Females had higher pain ratings at day 3-7.
Mangnall, Dietrich, Scholey. 2013.[39]	• N = 90 patients. • 45 control: 45 intervention).	• Multicentre RCT. • Control: No intervention during debond. • Intervention: Soft acrylic wafer in situ during debond.	• Pain experience during treatment. • Expectations of pain during debond. • Pain experienced during debond.	• Biting on an acrylic wafer significantly reduced pain during debond of posterior teeth. • 39% found debond of lower anteriors most painful. • Expected pain was significantly greater than pain experienced. • Greater pain during treatment correlated with increased expectations and increased pain experienced at debond.
Stewart, Kerr, Taylor. 1997.[40]	• N = 52 Caucasian patients. • 35 female: 17 male. • Consecutively enrolled. • 31 fixed, 21 removable.	• Questionnaires at 7, 14 and 90 days after appliance insertion. • Treatment with either: – two-arch fixed appliances – upper removable appliance	• Pain following insertion of appliances. • Convenience of appliance. • Self-comfort of appliance.	• Fixed appliances are more painful for the first 7 days. • Removable appliances cause more disturbance to speech and swallowing. Even after 3 months, influence on speech remains. • Fixed appliances no more socially embarrassing than removable.
Fleming, DiBiase, Sarri, Lee. 2009.[41]	• N = 66 patients. • Aged 11-21 years. • Equally distributed amongst control/intervention groups.	• Multi-centre randomised controlled trial. • Questionnaire with VAS at 4 hours, 24 hours, 3 days and 1 week after initial visit. • Randomised to either: – SmartClip self-ligating bracket system. – Conventional bracket system.	• Pain experience during initial alignment. • Pain experience during insertion and removal of rectangular archwires.	• Pain experience at 4 hours, 24 hours, 3 days, and 7 days following appliance placement is independent of bracket type. • Insertion and removal of rectangular archwires may result in an enhanced pain experience with the SmartClip™ passive self-ligating appliance.

2.3: The impact of orthodontic pain for patients

The literature suggests that up to 95% of orthodontic patients report pain at some stage during their treatment.[38,41,42,43] However, the effect that this pain will have on a patient's ongoing treatment varies between individuals. 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.[44]
For patients who opt to continue with treatment, the true extent and impact of orthodontic pain can often differ from a patient's own expectations. It has been shown that patients significantly under-estimate the changes they need to make in their diet, in response to pain, after archwire insertion. The influence of pain on diet was marked. In addition, it was found that patients who anticipated a greater effect of pain on their leisure activities, reported higher levels of pain and more disruption to their daily lives as a result.[16] Therefore, it is important to ensure that patients are sufficiently informed of all aspects regarding the impact that orthodontic pain may have on their day-to-day lives.

2.4: Pharmacological Interventions

Pain relief in dentistry has been well studied in the literature but the management of pain associated with orthodontic treatment is less well known.[45] As clinicians, we are often asked whether it will be necessary for patients to take pain killers during orthodontic treatment and if so, which is likely to be the most effective? Some studies have shown that pre-treatment doses of non-steroidal anti-inflammatory drugs (NSAIDs) may help to reduce the amount of pain experienced immediately after treatment.[34] However, there is some uncertainty among orthodontists as to which painkillers are most suitable and whether pre-emptive analgesia is beneficial.

2.4.1: Opioid

Opioids, 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, as earlier discussed, and therefore prevent transmission to the brain.[46] However, the specific mechanism of action differs slightly when considering tramadol. In addition to the mechanism

described above, 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.[47] 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 experienced with other, traditional opioids; however, under experimental situations this has not been the case.[47]

2.4.2: NSAIDs

Non-steroidal anti-inflammatory drugs are the most popular method of pain control during orthodontic treatment.[2,48] These include drugs like ibuprofen and aspirin. These drugs function by inhibition of the activity of the enzyme cyclooxygenase (COX), which modulates the transformation of prostaglandins from arachidonic acid in the cellular plasma membrane.[49] As prostaglandins are responsible for pain; by inhibiting COX, prostaglandin production is suppressed and pain is therefore reduced. However, as has been discussed earlier, prostaglandins including PGE1 and PGE2 are important mediators of bone resorption and suppression of their activity using NSAIDs has been suggested to affect the rate of orthodontic tooth movement.[50] Kehoe et al.[51] found a significant difference in the rate of tooth movement achieved with elastic separators in guinea pigs when comparing treatment with misoprostol or ibuprofen to a control group. However, the significance of this on a clinical level is negligible, with a 1mm average difference between intervention and control groups; and the doses used experimentally differ from those routinely used in practice.

2.4.3: 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.[52] 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 over cell membranes.[53] 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.

2.4.4: Local Anaesthetic

Local anaesthetic, in the form of a topical gels, have been suggested as safer alternatives to systemic analgesics as a method of pain management before or during orthodontic procedures.[52] The mode of action of the gel is by localised delivery of the anaesthetic into the gingival crevice. Because of this, their use has been suggested during local orthodontic procedures such as band placement, archwire ligation or bracket removal.[54]

2.4.5: Non-pharmacological Management

In response to increasing concerns regarding the possible side effects related to regular use of analgesics and a rise in drug related allergies, alternative, non-pharmacological management techniques have been developed.[33] Interventions include the use of bite wafers and chewing gum,[55] low level laser therapy to the periodontal tissues (LLLT), vibratory or transcutaneous electrical nerve stimulation (TENS),[56,57] topical application of ice or cryotherapy, acupuncture or acupressure, and psychological intervention, for example, structured telephone call to the patients during treatment.[33]

We will be investigating the relief of pain, using pharmacological interventions, arising during and after the placement of orthodontic appliances. This may include one or more of the following orthodontic interventions: separators, fixed braces, removable braces, headgear and during routine treatment to adjust appliances. We will not include pain relief using non-pharmacological interventions, as this is the topic of another Cochrane systematic review[33] or following tooth extraction, placement of temporary anchorage devices (TADs) or surgical procedures associated with orthodontic treatment.

Chapter 3: Aims, Objectives and Null Hypothesis

3.1: Aims

The aims of this review were to determine:

1. The effectiveness of pharmacological interventions for pain relief during orthodontic treatment;
2. Whether there is a difference in the analgesic effect provided by different types, doses and timing of analgesia taken during orthodontic treatment.

3.2: Objectives

The objectives of this review were to search and analyse the literature systematically surrounding the effectiveness of drug interventions for orthodontic pain to establish the most effective drug regime for the prevention and/or management of pain during orthodontic treatment and to test the null hypothesis.

3.3: Null hypothesis

The null hypothesis of this review is that there is no difference in the analgesic effect provided by different types, forms and doses of pain management drugs taken during orthodontic treatment, which was tested against the alternate hypothesis of a difference.

Chapter 4: Methods

4.1: Criteria for considering studies for this review

4.1.1: Types of studies

All randomised controlled clinical trials (RCTs) of orthodontic treatments where a pharmacological intervention for pain relief was compared concurrently to a placebo or no intervention or another pharmacological intervention.

If a randomised controlled trial compared pharmacological and non-pharmacological interventions to a placebo or no intervention, the study was included but only the data for a pharmacological intervention were used.

4.1.2: Types of participants

4.1.2.1: Inclusion Criteria

Trials were eligible for inclusion in the review if they recruited patients who had received pharmacological pain relief following any type of orthodontic treatment.

All age groups were considered.

4.1.2.2: Exclusion Criteria

Trials were excluded from the review if they recruited patients who had received pain relief following surgical interventions, placement of temporary anchorage devices (TADs) and/or dental extractions in combination with orthodontic treatment.

4.1.3: Types of interventions

4.1.3.1: Active interventions

The following active interventions to alleviate pain were assessed:

- Opioid analgesics
- Any NSAID
- Paracetamol
- Local anaesthetic

Any intervention taken by any route, dose, form or combination, at any time during treatment was evaluated.

Studies, in which the interventions were given at any time following treatment or up to 2 hours before treatment, were evaluated.

4.1.3.1: Controls

Interventions were included if they were compared to each other, a placebo, or the same intervention but at a different dose, intensity or time interval.

4.1.4: Types of outcome measures

4.1.4.1: Primary Outcomes

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

4.1.4.2: Secondary Outcomes

Harms were recorded and reported in descriptive terms.

- Rescue analgesia (alternative pain relief taken/prescribed, including dose and time, following last treatment).
- Adverse effects (harms) of pain treatment e.g. total gastro-intestinal side effects.
- Quality of life and/or patient satisfaction.
- Time off school/work.
- Withdrawal from the study for any reason.
- Failure to complete orthodontic treatment due to the pain experienced.
- Response to treatment (defined as a reduction in pain by at least 50%).

4.1.4.3: Comparisons

1. Any analgesic, at any dose, taken at any time versus placebo at any dose taken at any time. If there was evidence of effectiveness, further analysis of the class and type of drug was undertaken.
2. Opioid of any type, at any dose taken at any time versus placebo at any dose taken at any time.
    a. Subgroup analysis of type of opioid at any dose taken at any time versus placebo at any dose taken at any time.
3. NSAID of any type, at any dose taken at any time versus placebo at any dose taken at any time.
    a. Subgroup analysis of type of NSAID at any dose taken at any time versus placebo at any dose taken at any time.
4. Paracetamol at any dose taken at any time versus placebo at any dose taken at any time.

   a. Subgroup analysis of type of paracetamol at any dose taken at any time versus placebo at any dose taken at any time.
5. Local anaesthesia at any dose taken at any time versus placebo at any dose taken at any time.
   a. Subgroup analysis of type of local anaesthesia at any dose taken at any time versus placebo at any dose taken at any time.
6. If there was effectiveness in any of the classes or subgroups, further analysis was undertaken to determine the effectiveness and harms at different doses of opioid/ NSAID/ paracetamol/ local anaesthetic versus placebo.
7. Head to head comparisons of the best doses for each class and/or type of analgesic would have been undertaken if sufficient data had been available.
8. Head to head comparisons of the best timing for each class and/or type of analgesic would have been undertaken if sufficient data had been available.
9. Head to head comparisons of the best in each class and/or type of analgesic.

4.2: Search methods for identification of studies

4.2.1: Electronic searching

For the identification of studies included or considered for this review, a detailed search strategy was developed for each database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free text terms based on the search strategy for MEDLINE (Appendix 3). For the MEDLINE search, the subject search was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.a. of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011).[57]

4.2.2: Databases searched

The following databases were searched:

- Cochrane Oral Health Group's Trials Register (to current date)
- Cochrane Pain, Palliative and Supportive Care Group's Trials Register
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* at current issue)

- MEDLINE (from 1966 to present)
- EMBASE (from 1980 to present)
- CINAHL (from 1982 to present).

The date of the last search was 19th August 2016.

4.2.3: Searching other resources

A check was made to identify journals which had already been handsearched as part of the Cochrane Journal Handsearching Programme. The handsearching of the following journals would have then been updated to the most current issue if appropriate:

- American Journal of Orthodontics and Dentofacial Orthopedics;
- The Angle Orthodontist;
- European Journal of Orthodontics;
- Journal of Orthodontics;
- Australian Orthodontic Journal;
- Seminars in Orthodontics;
- Orthodontics and Craniofacial Research;
- Journal of Orofacial Orthopaedics.

If it appeared, from searching the Cochrane Pain, Palliative and Supportive Care Group Trials Register, that relevant studies were being identified in non-orthodontic journals, these were also handsearched as necessary.

The bibliographies of the clinical trials identified were checked for references to trials published outside the handsearched journals.

Personal references were checked.

Additionally, other resources such as The British Library EThOS service (http://ethos.bl.uk) were searched for relevant theses and ClinicalTrials.gov was searched for otherwise unpublished and ongoing studies.

Conference proceeding of the European Orthodontic Congress, International Association of Dental Research, British Orthodontic Conference and American Association of Orthodontists were also searched to identify presented trials.

4.2.4: Language

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

4.2.5: Unpublished studies

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

Trials databases were also searched to identify registered, ongoing trials.

4.3: Data collection and analysis

4.3.1: Management of records produced by the searches

All references were downloaded into EndNote reference management software and merged to produce a single database to facilitate retrieval of relevant articles. Non-electronic references, that could not be downloaded, were entered into the database manually after which duplicates were removed.

4.3.2: 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 as being potentially relevant. This was carried out independently and in duplicate.

For studies with insufficient information in the title and abstract to make a clear decision to exclude, or studies where there was disagreement between the review authors about eligibility, a full report was obtained. These full reports 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.

Disagreements were resolved by discussion between AM and JH. We consulted a third review author if we could not resolve disagreements. A record of all decisions made about the potentially eligible studies was kept. Full reports were also obtained for those studies that were ultimately included in this review.

The review authors were not blinded to trial author(s), institution or site of publication.

4.3.3: Data extraction and management

Data extraction was carried out independently and in duplicate by two review authors (AM and JH or AT) using a pre-designed and piloted data collection form and saved electronically. We contacted study authors for clarification on missing data where necessary and feasible. We resolved any disagreements through discussion, consulting a third reviewer to achieve a consensus where necessary. We recorded

the following key data for each included study in the Characteristics of Included Studies table:

- Trial design, source of participants, method of recruitment, recruitment period and study duration.
- Inclusion/exclusion criteria, age and gender and ethnicity of participants, and number selected, excluded, randomised and analysed.
- Detailed description of the invention and comparison including time, dose and route. Information relating to compliance was also noted 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/conflicts of interest.

The primary outcome was the relief of pain. Adverse events / harms (e.g. total gastro-intestinal side effects) were recorded and the results reported in descriptive terms.

All outcome data were extracted. They were then grouped into the timepoints which we felt were the most clinically relevant: 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, then consideration was given to examining those as well.

4.3.4: Assessment of risk of bias in included studies

The Cochrane risk of bias tool was used to assess the methodological quality of the studies. This was undertaken independently and in duplicate by the two review authors (AM and JH) as a part of the data extraction process. This was carried out using the Cochrane domain-based, two-part tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Inteventions.[58] Seven specific domains were investigated: random sequence generation; allocation concealment; blinding of participants and personnel, blinding of outcome assessment; incomplete outcome data; selective outcome reporting and ‘other sources of bias’. These are discussed in more detail below.

Each domain was assigned a judgement of high, low or unclear as an indication of its risk of bias according to the following criteria:

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at 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 unclear risk of bias.

Sequence generation, allocation concealment and selective outcome reporting were assessed for the study as a whole. Blinding and incomplete outcome data were assessed on the level of the study and for each outcome as appropriate.

4.3.4.1: Method of sequence generation

Adequate sequence generation

- Referring to the use of a random component including random number table; using a computer random number generator, repeated coin tossing, dealing previously shuffled cards or envelopes, throwing dice, drawing of lots or minimization*.
- Restricted or stratified randomisation can also be included.

*Minimization may be implemented without a random element as a means of making small groups closely similar with respect to several characteristics. This is considered to be equivalent to being random.

Inadequate sequence generation

- Quasi-randomisation, where the sequence has been generated by odd or even date of birth, some rule based on date (or day) of admission, hospital or clinic record number, or allocation based on judgement of the clinician.

4.3.4.2: Method of allocation concealment

Adequate concealment schemes

- Central allocation (including telephone, web-based and pharmacy-controlled randomization).
- Sequentially numbered drug containers of identical appearance or opaque, sealed envelopes.

Inadequate concealment schemes

- Using an open random allocation schedule (e.g. a list of random numbers).

- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered), alternation or rotation, date of birth, case record number and any other explicitly unconcealed procedure.

Unclear concealment schemes

- Insufficient information to permit judgement of 'Yes' or 'No'.
- This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

4.3.4.3: Blinding of participants, personnel and outcome assessors

Adequate blinding

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Inadequate blinding

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

- Insufficient information to permit judgement of 'Yes' or 'No'; or the study did not address this outcome.

4.3.4.4: Incomplete outcome data

Adequately addressed

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- Missing data have been imputed using appropriate methods.

Inadequately addressed

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
- Potentially inappropriate application of simple imputation.

Unclear

- Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided);
- The study did not address this outcome.

4.3.4.5: Selective outcome reporting

Adequate outcome reporting

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Inadequate outcome reporting

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

- Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.

4.3.4.6: Other potential threats to validity

Adequate

- The study appears to be free of other sources of bias.

Inadequate

The study:

- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- Had extreme baseline imbalance; or

- Has been claimed to have been fraudulent; or
- Had some other problem.

Unclear

- Insufficient information to assess whether an important risk of bias exists; or
- Insufficient rationale or evidence that an identified problem will introduce bias.

4.3.5: Measure of treatment effect

For continuous outcomes (e.g. pain measured on a visual analogue scale) 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). Where different scales were used we would have considered expressing the treatment effect as standardised mean difference (SMD) with 95% CI.

4.3.6: Unit of analysis issues

The participant was the unit of analysis.

4.3.7: 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.[58] We did not use any other statistical methods or perform any further imputation to account for missing data.

4.3.8: 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-square (chi^2) test, where a P value < 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 is as follows[58]:

- 0% to 40%: might not be important;

- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

4.3.9: Assessment of reporting bias

If at least 10 studies were included in a meta-analysis, we planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry, as described in Section 10.4 of the Cochrane Handbook for Systematic Reviews of Interventions.[58] If asymmetry was identified, we would examine 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 containing less than 10 studies.

4.3.10: 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 not suitable for inclusion in a meta-analysis, including data analysed by treatment intervention.

4.3.11: Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to type of pharmacological intervention given and different interventions. We stated in the protocol that we would also use dose, timing and class as categories for subgroup analyses. However, these categories were very closely related, and there were insufficient numbers of studies with these differing populations and so it did not make sense to do so.

4.3.12: Sensitivity analysis

As all studies except one 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 the studies 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 comparing the effect

estimates from both random-effects and fixed-effect models. If these were different we would have reported on both analyses as part of the results section, and we would have considered possible interpretation.

4.3.13: Cross-over trials

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

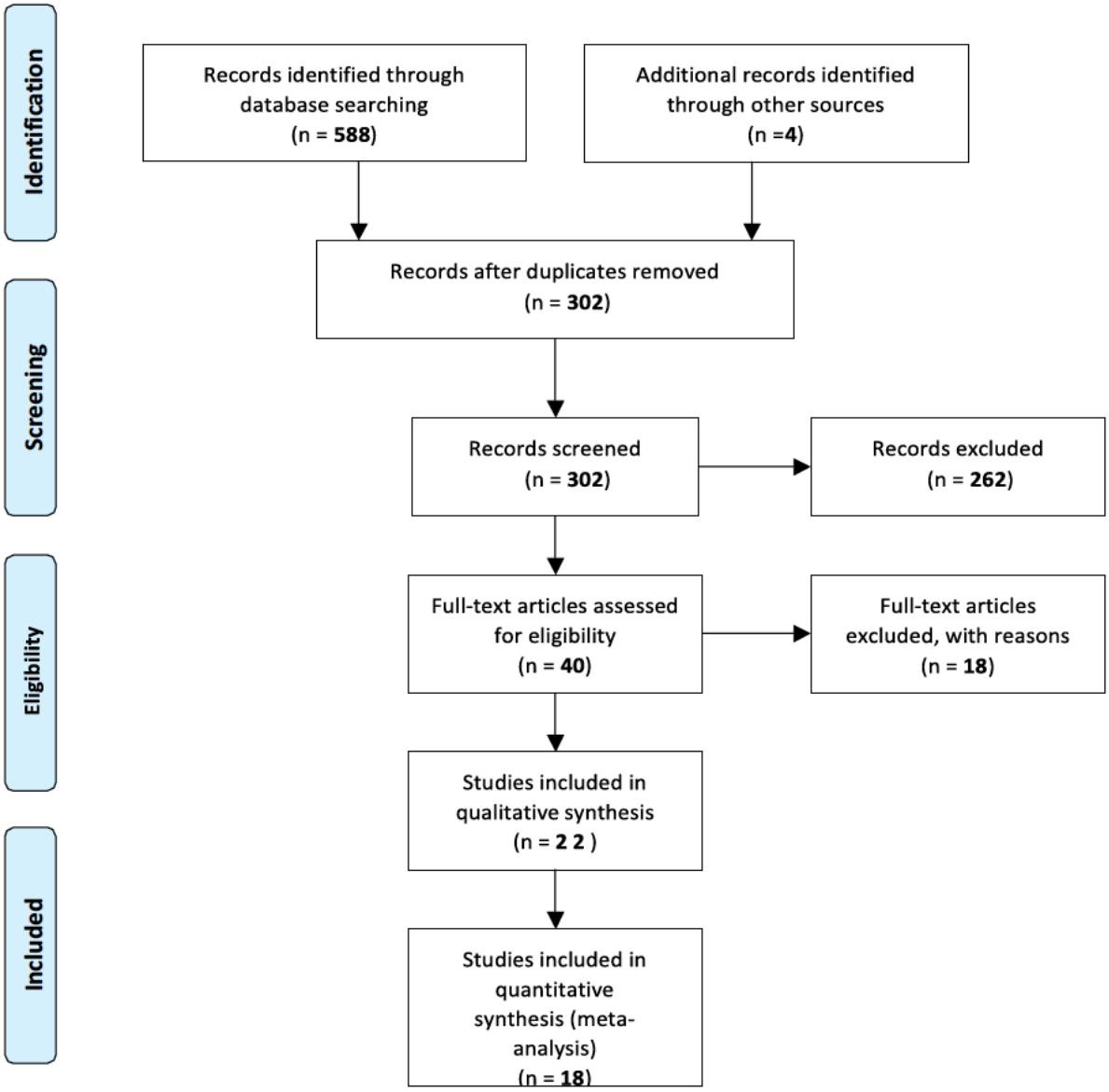
Chapter 5: Results

5.1: Description of studies

5.1.1: Results of the search

The electronic database search identified 588 references to studies and 4 additional articles were identified from additional sources (authors of this review). 290 of the studies were duplicates, leaving 302 studies. 262 were discarded by screening the titles and abstracts. Of the remaining 40 articles, we obtained full-text articles where possible, and excluded 5 of the studies at this stage. The remaining 35 studies appeared to meet our inclusion criteria and we were finally able to include 22 of the studies. Of the remaining 13 studies, 6 are awaiting assessment due to insufficient information in the abstract or trial registry record, to allow inclusion in the review and 7 presented insufficient data for inclusion in the analyses, having made attempts to contact authors to obtain the data. This process is presented as a flow chart in Figure 2.

Figure 2. Study flow diagram.



5.1.2: Included studies

Twenty-two studies, involving a total of 2,110 participants (n =1,800) were included in this review.

5.1.3: Characteristics of the trial designs and settings

Design

Twenty-one studies were of parallel design, with the remaining one study using a cross-over design (Eslamian 2014[59]). Five studies had two arms (Bradley 2007[60]; Kluemper 2002[61]; Lauritano 2000[62]; Ousehal 2009[63]; Yassaei 2012[64]); fifteen studies had three arms however, four of these studies had one arm excluded from this review because it involved data relating to non-pharmacological interventions (Wang 2012[65]) or non-comparable data (Bernhardt 2001[66]; Minor 2009[67]; Steen-Law 2000[34]). One study had five arms, with three of those arms being excluded from this review because they involved data relating to non-pharmacological interventions (Farzanegan 2012[68]). One study had 6 arms (Polat March 2005[48]).

Setting

Six studies were conducted in the USA (Bernhardt 2001[66]; Kawamoto 2010[69]; Kluemper 2002[61]; Minor 2009[68]; Salmassian 2009[70]; Steen Law 2000[34]), five in Iran (Eslamian 2014[59]; Farzanegan 2012[68]; Najafi 2015[71]; Nik 2016[72]; Yassaei 2012[64]), three in Turkey (Polat March 2005[48]; Polat September 2005[73]; Tunçer 2014[74]), two in India (Gupta 2014[75]; Kohli 2011[76]) and one in each of Brazil (Bradley 2007[60]), China (Wang 2012[65]), Italy (Paganelli 1993[78]), Morocco (Ousehal 2009[63]), Spain (Lauritano 2000[62]) and the UK (Bradley 2007[60]).

There were fifteen single centre studies, two with two centres (Eslamian 2014[59]; Kawamoto 2010[69]), one with three centres (Bradley 2007[60]) and four studies in which it was unclear as to how many centres were involved (Kluemper 2002[61]; Polat March 2005[48]; Polat September 2005[73]; Tunçer 2014[74]).

Funding

Three studies reported their funding source (Bradley 2007[60]; Najafi 2015[71]; Wang 2012[65]), all of which were in the form of independent funding from government, charities or universities. The remaining nineteen studies did not report any funding source.

Conflict of interest

Five studies declared that there were no conflicts of interest (Bruno 2011[77]; Gupta 2014[75]; Najafi 2015[71]; Salmassian 2009[70]; Wang 2012[65]), whilst the other seventeen did not mention conflicts of interest.

5.1.4: Characteristics of the participants

There were 2,110 participants randomized to interventions (including only the intervention groups relevant to this review), of which 1,800 were included in the studies' analyses. Ages ranged from 9 to 34 years. In general, there were comparable numbers of males and females in the studies however, two studies recruited only female participants (Farzanegan 2012[68]; Yassaei 2012[64]) and two studies reported large gender variations between groups at baseline (Najafi 2015[71]; Tunçer 2014[74]).

5.1.5: Orthodontic interventions

In ten studies, participants had placement of an initial aligning archwire (Farzanegan 2012[68]; Gupta 2014[75]; Lauritano 2000[62]; Najafi 2015[71]; Ousehal 2009[63]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Tunçer 2014[74]; Wang 2012[65]). In nine of the studies, participants had separators placed (Bernhardt 2001[66]; Bradley 2007[60]; Bruno 2011[77]; Kawamoto 2010[69]; Kohli 2011[76]; Minor 2009[67]; Nik 2016[72]; Steen Law 2000[34]). Two studies included participants who were in the middle of treatment (Eslamian 2014[59]; Paganelli 1993[78]) and one study included patients who had brackets placed only, without placement of an archwire (Kluemper 2002[61]).

5.1.6: Characteristics of the interventions and comparisons

Paracetamol

Six studies compared paracetamol with a control group (Gupta 2014[75]; Kawamoto 2010[69]; Nik 2016[72]; Polat March 2005[48]; Salmassian 2009[70]); all of which had a control group who received a placebo intervention. One study compared paracetamol with calcium (Yassaei 2012[64]).

NSAIDs

Fourteen studies compared NSAIDs with a control group (Bruno 2011[77]; Eslamian 2014[59]; Farzanegan 2012[68]; Gupta 2014[75]; Kawamoto 2010[69]; Kohli 2011[76]; Minor 2009[67]; Nik 2016[72]; Paganelli 1993[78]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Tunçer 2014[74]; Wang 2012[65]). Two of these studies compared

NSAIDs with both a placebo group and a group with no intervention (Bruno 2011[77]; Paganelli 1993[78]). Nine studies compared NSAIDs with paracetamol (Bradley 2007[60]; Gupta 2014[75]; Kawamoto 2010[69]; Najafi 2015[71]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Tunçer 2014[74]). Five studies compared the different classes of NSAIDs with one another (Kohli 2011[76]; Lauritano 2000[62]; Najafi 2015[71]; Polat March 2005[48]; Polat September 2005[73]). Two studies compared ibuprofen taken pre-emptively with ibuprofen taken post-operatively (Bernhardt 2001[66]; Steen Law 2000[34]).

Local anaesthetic

Two studies compared benzocaine local anaesthetic with a control. One of these studies had the benzocaine intervention in chewing gum form (Eslamian 2014[59]) and one had the benzocaine intervention in wax form for the management of orthodontic related ulceration (Kluemper 2002[61]). One group compared NSAIDs with local anesthetic (Eslamian 2014[59]).

Duration

The duration of treatment varied between studies, from one dose one hour before treatment to seven days of treatment. However, one study had a duration of treatment lasting 30 days (Yassaei 2012[64]).

5.1.7: Characteristics of the outcomes

5.1.7.1: Primary outcome

For the primary outcome of pain, we were interested in either the pain relief or pain intensity, and also different levels of severity. All included studies measured pain intensity using a 10cm visual analogue scale (VAS), reported in either centimetres or millimetres. For the purposes of this review, VAS data, in relation to the primary outcome, were analysed in millimetres. Therefore, in studies that recorded results in centrimetres, the data were converted into millimetres. Most studies recorded this value based on an overall summary of the participant's pain experience however, some studies reported pain intensity for additional specified activities.

Seven studies recorded pain intensity during chewing, biting, fitting front teeth together and fitting posterior teeth together (Bernhardt 2001[66]; Farzanegan 2012[68]; Kohli 2011[76]; Minor 2009[67]; Polat March 2005[48]; Polat September 2005[73]; Steen-Law 2000[34]). One study recorded pain intensity during chewing, biting and teeth not

touching (Kawamoto 2010[69]); one study recorded pain intensity during chewing, rest and fitting posterior teeth together (Najafi 2015[71]) and one study recorded pain intensity during chewing, fitting front teeth together and fitting back teeth together (Tunçer 2014[74]). For the purposes of this review, data for chewing only were included in the analysis for these studies.

A total of twenty-three time points were recorded across all twenty-two included studies. These ranged from one hour pre-treatment to 30 days post-treatment. We decided to include data from 2 hours, 6 hours and 24 hours for our analysis as we thought these were the most important time points from a clinical perspective, in addition to being some of the most commonly reported time points across all 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 thought that analysing data beyond this point would provide little valuable information. As a result, data from Kluemper 2002[61]; Paganelli 1993[78] and Yassaei 2012[64] 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 had to be excluded following attempts to contact the authors because data relating to the primary outcome were presented unclearly, without standard deviations or in median and interquartile format (Abtahi 2006[79]; Arantes 2009[80]; Bird 2007[81]; Ngan 1994[82]; Patel 2010[83]; Sudhakar 2014[84]; Young 2005[85]). Data presented in standard error format were converted appropriately to present standard deviation.

5.1.7.2: Secondary outcomes

Rescue analgesia

Use of rescue analgesia was reported in six studies (Bernhardt 2001[66]; Bradley 2007[60]; Bruno 2011[77]; Najafi 2015[71]; Steen-Law 2000[34]; Tunçer 2014[74]). However, data relating to class and dose were not reported in any study, and timing was reported in only one study (Bradley 2007[60]), despite all studies stating that patients were asked to record this information on the VAS questionnaires.

Adverse events

Adverse events were only reported by Bradley 2007[60]. All other studies did not mention adverse events. We therefore decided to report this outcome in narrative form.

Quality of life and/or patient 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 Self-Rating Anxiety Scale (SAS) at baseline and at 30 days (Wang 2012[65]). One study reported anxiety and depression status measured using the Hospital Anxiety and Depression Scale (HADS) (Yassaei 2012[64]). One study reported affective states assessed with the State and Trait Anxiety Inventory (STAI) and the Positive Affect Negative Affect Schedule (PANAS) (Minor 2009[67]).

Time off school/work

No studies reported this outcome.

Withdrawal from the study

Twelve studies reported withdrawal of participants for a variety of reasons. In some studies, is it was unclear if this withdrawal was a decision taken by the participant or the researchers. For the purposes of this review, in these cases all participants have been considered as withdrawal from the study.

Failure to complete orthodontic treatment due to the pain experienced

No studies reported this outcome.

Response to treatment

Response to treatment was defined as a reduction in pain by at least 50%. This was not reported in any study.

5.1.8: Excluded Studies

We excluded eighteen studies (See Appendix 2: Characteristics of excluded 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[86]; Murdock 2010[87]).
- Not a randomized controlled trial (RCT): systematic reviews (Angelopoulou 2012[88]; Ashley 2016[89]; Xiaoting 2010[90]).

- Inadequate data presented to allow inclusion in analyses (Abtahi 2006[79]; Arantes 2009[80]; Bird 2007[81]; Ngan 1994[82]; Patel 2010[83]; Sudhakar 2014[84]; Young 2006[85]).
- Insufficient information in the abstract or trial registration record to allow inclusion (Cherubini 2003[91]; Eslamian 2016[92]; Moradinejad 2014[93]; Ogata 1999[94]; Parks 2001[95]; Rooke 2012[96]).

5.2: Risk of bias in included studies

5.2.1: Allocation

5.2.1.1: Random sequence generation

Ten studies described an adequate method of random sequence generation (Bernhardt 2001[66]; Bradley 2007[60]; Bruno 2011[77]; Farzanegan 2012[68]; Gupta 2014[75]; Kawamoto 2010[69]; Najafi 2015[71]; Oueshal 2009[63]; Paganelli 1993[78]; Wang 2012[65]), including both information published in the papers and further information received via correspondence with the authors. These ten papers were therefore assessed as being at low risk of bias for this domain. The remaining twelve studies simply stated that participants were randomized, however either did not describe their methods, or the method remained unclear, so they were assessed as being at unclear risk of bias for this domain.

5.2.1.2: Allocation concealment

Eleven studies described an adequate method of allocation concealment (Bernhardt 2001[66]; Bradley 2007[60]; Eslamian 2014[59]; Gupta 2014[75]; Kawamoto 2010[69]; Kluemper 2002[61]; Najafi 2015[71]; Nik 2016[72]; Oueshal 2009[63]; Paganelli 1993[78]; Wang 2012[65]), including both information published in the papers and further information received via correspondence with the authors. These eleven papers were therefore assessed as being at low risk of bias for this domain. Ten of the remaining studies did not mention any methods used to conceal the random sequence, and we assessed them as being at unclear risk of bias. One study, through correspondence of the author, stated that the allocation was not concealed as so was assessed as being a high risk of bias for this domain (Bruno 2011[77]). Overall, eight studies were at low risk of selection bias, meaning that we assessed both of the above domains as being at low risk of bias (Bernhardt 2001[66]; Bradley

2007[60]; Gupta 2014[75]; Kawamoto 2010[69]; Najafi 2015[71]; Ousehal 2009[63]; Paganelli 1993[78]; Wang 2012[65]).

5.2.2: Blinding

5.2.2.1: Blinding of participants and personnel (performance bias)

Fourteen studies described adequate methods of blinding of participants and personnel and were therefore assessed as being a low risk of bias for this domain (Bernhardt 2001[66]; Bradley 2007[60]; Eslamian 2014[59]; Farzanegan 2012[68]; Kawamoto 2010[69]; Kluemper 2002[61]; Kohli 2011[76]; Najafi 2015[71]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Steen-Law 2000[34]; Tunçer 2014[74]). It was not possible to blind participants to the type of intervention allocated in four studies (Bruno 2011[77]; Oueshal 2009[63]; Paganelli 1993[78]; Wang 2012[65]). These four papers were therefore assessed as being at high risk of bias for this domain. The remaining four studies only stated that blinding was achieved however, they did not describe their methods and so they were assessed as being at an unclear risk of bias for this domain (Gupta 2014[75]; Lauritano 2000[62]; Minor 2009[67]; Yassaei 2012[64]).

5.2.2.2: Blinding of outcome assessment (detection bias)

Fourteen studies described an adequate method of blinding of outcome assessment (Bernhardt 2001[66]; Bradley 2007[60]; Bruno 2011[77]; Eslamian 2014[59]; Kawamoto 2010[69]; Kohli 2011[76]; Najafi 2015[71]; Nik 2016[72]; Oueshal 2009[63]; Paganelli 1993[78]; Salmassian 2009[70]; Steen-Law 2000[34]; Wang 2012[65]; Yassaei 2012[64]). These fourteen papers were therefore assessed at being at low risk of bias for this domain. Eight studies only stated that blinding was achieved however, they did not describe their methods and so there were assessed as being at unclear risk of bias for this domain (Farzanegan 2012[68]; Gupta 2014[75]; Kluemper 2002[61]; Lauritano 2000[62]; Minor 2009[67]; Polat March 2005[48]; Polat September 2005[73]; Tunçer 2014[74]).

5.2.3: Incomplete outcome data

Five studies were at high risk of attrition bias (Bernhardt 2001[66]; Bruno 2011[77]; Kawamoto 2010[69]; Najafi 2015[71]; Steen-Law 2000[34]) due to high numbers of attrition across the studies. The remaining seventeen studies had negligible or no attrition and were therefore assessed as being at low risk of attrition bias.

5.2.4: Selective reporting

Two studies were at high risk of selective reporting bias. One of these studies did not report outcomes for all time points investigated (Lauritano 2000[62]). The other did not report on the outcome of bite efficiency as measured with a modified mastication performance index (Minor 2009[67]). One study was unclear about the time points at which outcomes were measured and therefore was assessed as unknown risk for selective reporting (Yassaei 2012[64]). The remaining nineteen studies appropriately reported on all outcomes and were therefore assessed as being at low risk for this domain.

5.2.5: Other potential sources of bias

Six studies were assessed as high risk of other sources of bias a result of gender bias in sampling. Two of these papers recruited only female participants (Farzanegan 2012[68]; Yassaei 2012[64]); whilst the other four had large variations in the groups at baseline (Najafi 2015[71]; Ousehal 2009[63]; Tunçer 2014[74]; Wang 2012[65]). The remaining sixteen studies were not considered to have any other potential sources of bias and were therefore assessed as being at low risk of bias for this domain.

5.2.6: Overall risk of bias

Only one study was assessed as being at low overall risk of bias (Bradley 2007[60]). Eight studies were assessed as being at unknown overall risk of bias (Eslamian 2014[59]; Gupta 2014[75]; Kluemper 2002[61]; Kohli 2011[76]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Steen-Law 2000[34]). The remaining thirteen studies were assessed as being at high overall risk of bias (Figure 3 and Figure 4).

Figure 3: Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

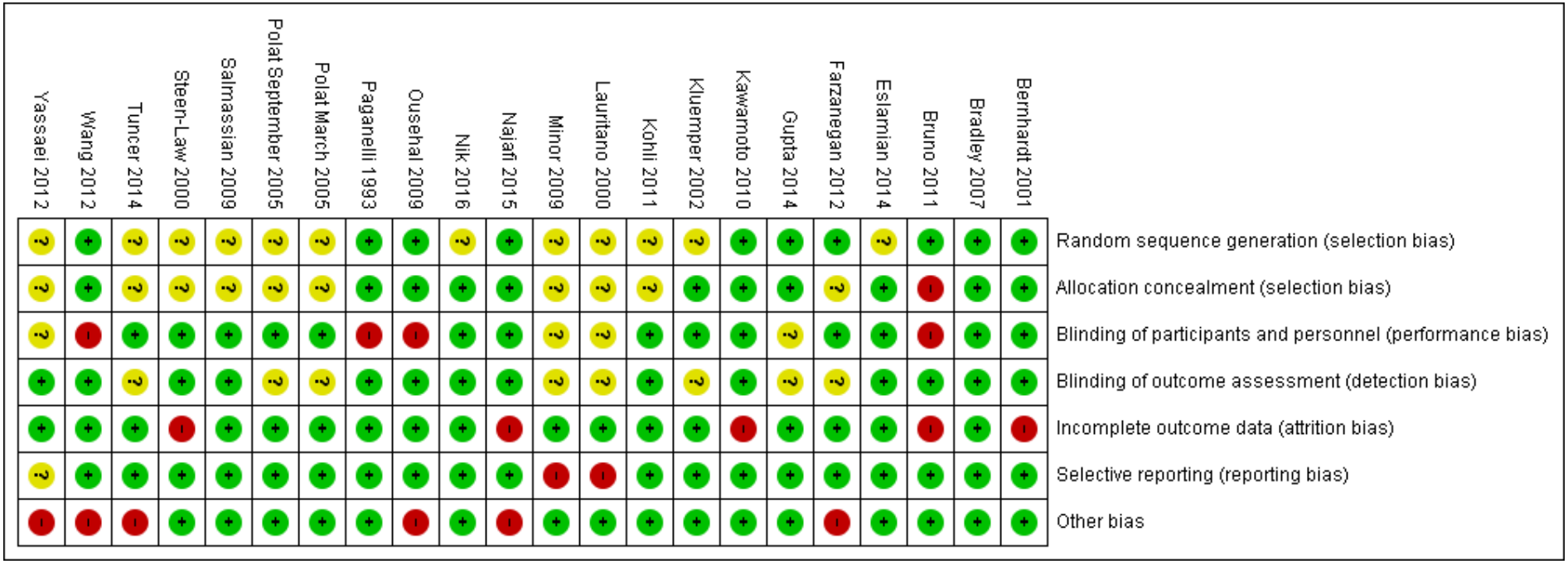
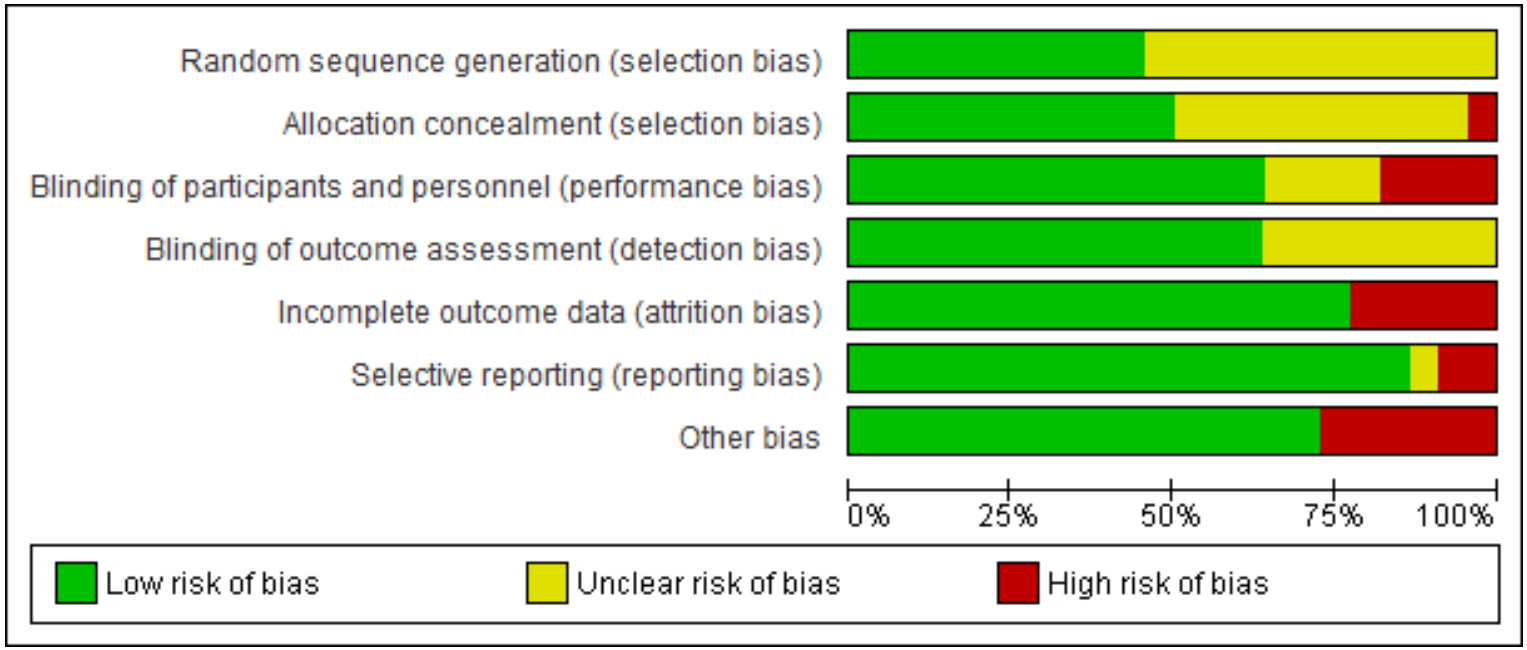


Figure 4: Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.



5.3: Effects of interventions

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

Pain

At 2 hours and 6 hours, ten studies were combined in a meta-analysis. Four of these studies (Bruno 2011[77]; Farzanegan 2012[68]; Kawamoto 2010[69]; Minor 2009[67]), were all at high risk of bias; whilst the remaining six studies (Eslamian 2014[59]; Gupta 2014[75]; Kohli 2011[76]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]), were at an unknown risk of bias. In total, 607 participants were analysed, at 2 hours and 6 hours.

At 24 hours, two additional studies (Tunçer 2014[74]; Wang 2012[65]), both at high risk of bias, resulted in a total of twelve studies being combined in a meta-analysis. In total, 964 participants were analysed for 24 hours.

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

- 2 hours (Mean Difference (MD) -15.71, 95% confidence interval (CI) -20.75 to -10.68, P < 0.00001) (Figure 5);
- 6 hours (MD -24.33, 95% CI -30.71 to -17.95, P =< 0.00001) (Figure 6); and
- 24 hours (MD -24.33, 95% CI -30.71 to -17.95, P < 0.00001) (Figure 7) when compared to a control.

However, there was moderate heterogeneity (I^2 = 55%) at 2 hours and substantial (I^2 = 70%) heterogeneity at 6 and 24 hours. It was thought that this may be related in part to the methods relating to the orthodontic intervention carried out; which are explored in more detail in further analyses.

Rescue analgesia

Two studies in this subgroup (Bruno 2011[77]; Tunçer 2014[74]) reported that participants required rescue medication during the study. Tunçer 2014[74] reported that 2 participants required rescue medication; whilst Bruno 2011[77] reported 6 participants required the use of analgesic medication during the study. No further information was available relating to class, dose or timing.

Adverse events

No studies in this subgroup reported any adverse events.

Quality of life and/or patient satisfaction

One study (Wang 2012[65]) reported quality of life assessed using SF-36 and found that, at 30 days, using the there was a significant alleviation in the scale of bodily pain, however there were no significant differences in other variables of the SF-36 results among the three groups. The study also recorded SAS and found that the scores were not significantly different among the groups.

One study (Minor 2009[67]) reported quality of life assessed using STAI and PANAS and found that there were no significant differences between the treatment groups.

Time off school/work

No studies in this subgroup reported this outcome.

Withdrawal from the study

Eight studies in this subgroup experienced withdrawal from the study:

- Polat March 2005[48] reported withdrawal of 22 participants who did not return questionnaires and 8 participants who were too old (>30 years old); n = 30/150, 20%.
- Salmassian 2009[70] reported withdrawal of 4 participants who did not return in a timely manner and 2 participants who withdrew consent after archwire placement; n = 6/66, 9.1%.
- Tunçer 2014[74] reported withdrawal of 3 participants who did not return questionnaires; n = 3/46, 6%.
- Bruno 2011[77] reported withdrawal of 18 participants who had missing or incomplete information, 2 participants who lost their diaries and were unwilling to continue, 6 participants who used analgesic medication during the study, and 10 participants who had discomfort due to elastics and sought treatment elsewhere; n = 36/87, 41.4%.
- Eslamian 2014[59] reported withdrawal of 4 participants; however, the reason is only stated as ‘loss to follow-up’; n = 4/30, 13.3%.
- Kawamoto 2010[69] reported withdrawal of 9 participants who failed to return questionnaires; n = 9/35, 25.7%.
- Nik 2016[72] reported withdrawal of 8 participants who did not take the drug, 3 participants who did not complete the questionnaires and 1 for reasons not discussed in the paper; n = 12/101, 12%.

- Wang 2012[65] reported withdrawal of 7 participants who did not wish to complete the follow-up questionnaire; 7 participants withdrew due to discomfort of orthodontic treatment; 4 who lost the questionnaires, 2 were withdrawn because thought they had not received treatment and 1 was withdrawn for an unknown reason; n = 21/450, 4.7%.

All other studies included in this analysis experienced no withdrawal of participants. This amounted to a total withdrawal of 121 participants from a total of 964 participants in this subgroup.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this subgroup reported this outcome.

Response to treatment

No studies in this subgroup presented data in a way which facilitated assessment of this outcome.

5.3.1.1: Paracetamol versus control

At 2 hours and 6 hours, four studies were combined in a meta-analysis. Three of these studies (Gupta 2014[75]; Nik 2016[72]; Polat March 2005[48]), were at an unknown risk of bias; whilst the remaining study (Kawamoto 2010[69]) was at high risk of bias. In total, 107 participants were included in the meta-analysis, for 2 hours and 4 hours.
At 24 hours, two additional studies were included in the meta-analysis. One of these studies (Tunçer 2014[74]) was at high risk of bias; whilst the other study (Salmassian 2009[70]), was at an unknown risk of bias. In total, 161 participants were included in the meta-analysis for 24 hours.
The meta-analysis showed that paracetamol reduced mean pain intensity during orthodontic treatment at:

- 2 hours (MD -11.90, 95% CI -18.36 to -5.44, P < 0.00001) (Figure 5);
- 6 hours (MD -19.34, 95% CI -24.80 to -13.88, P < 0.00001) (Figure 6); and
- 24 hours (MD -22.09, 95% CI -35.99 to -8.18, P < 0.00001) (Figure 7) when compared to a placebo.

However, although there was no heterogeneity at 2 or 6 hours (I^2 = 0%), at 24 hours there was substantial heterogeneity (I^2 = 65%). It was thought that this may have been due in part to the methods relating to the orthodontic intervention; which have

been broken down further and explored in relation to the effect of the intervention on pain following separator placement and pain following placement of an initial archwire.

In relation to separator placement, paracetamol was shown to be effective at reducing pain at 2 and 6 hours, however there was no difference in comparison with a control at 24 hours. Additionally, there was no heterogeneity at 2 or 6 hours (I^2 = 0%), however, the heterogeneity increased to considerable heterogeneity at 24 hours (I^2 = 76%) (Table 3).

For archwire placement, paracetamol was shown to be effective at reducing pain at 2, 6 and 24 hours. There was no heterogeneity at 2 hours (I^2 = 0%), low heterogeneity, which may not be important, at 6 hours (I^2 = 6%), but again, there was an increase to considerable heterogeneity at 24 hours (I^2 = 85%) (Table 4).

5.3.1.2: Local anaesthetic versus control

One study (Kluemper 2002[61]), at an unknown risk of bias, compared topical benzocaine wax with a placebo wax at initial archwire placement, analysing data from 70 patients. However, the data were recorded at time points not in keeping with those of interest in this review and therefore did not contribute to our analysis.
One study (Eslamian 2014[59]), at an unknown risk of bias, compared topical benzocaine chewing gum with a placebo chewing gum mid-treatment, analysing data from 36 participants. This showed that topical benzocaine chewing gum reduced mean pain intensity following tying-in of an archwire at:

- 2 hours (MD -35.00, 95% CI -49.4 to -20.54, P < 0.00001) (Figure 5);
- 6 hours (MD -24.33, 95% CI -30.71to -17.95, P < 0.00001) (Figure 6); and
- 24 hours (MD -24.33, 95% CI -30.71 to -17.95, P < 0.00001) (Figure 7), when compared to a placebo.

Figure 5: Forest plot of comparison 1: Analgesic versus control, outcome: 1.1 2 hours [Pain(VAS)].

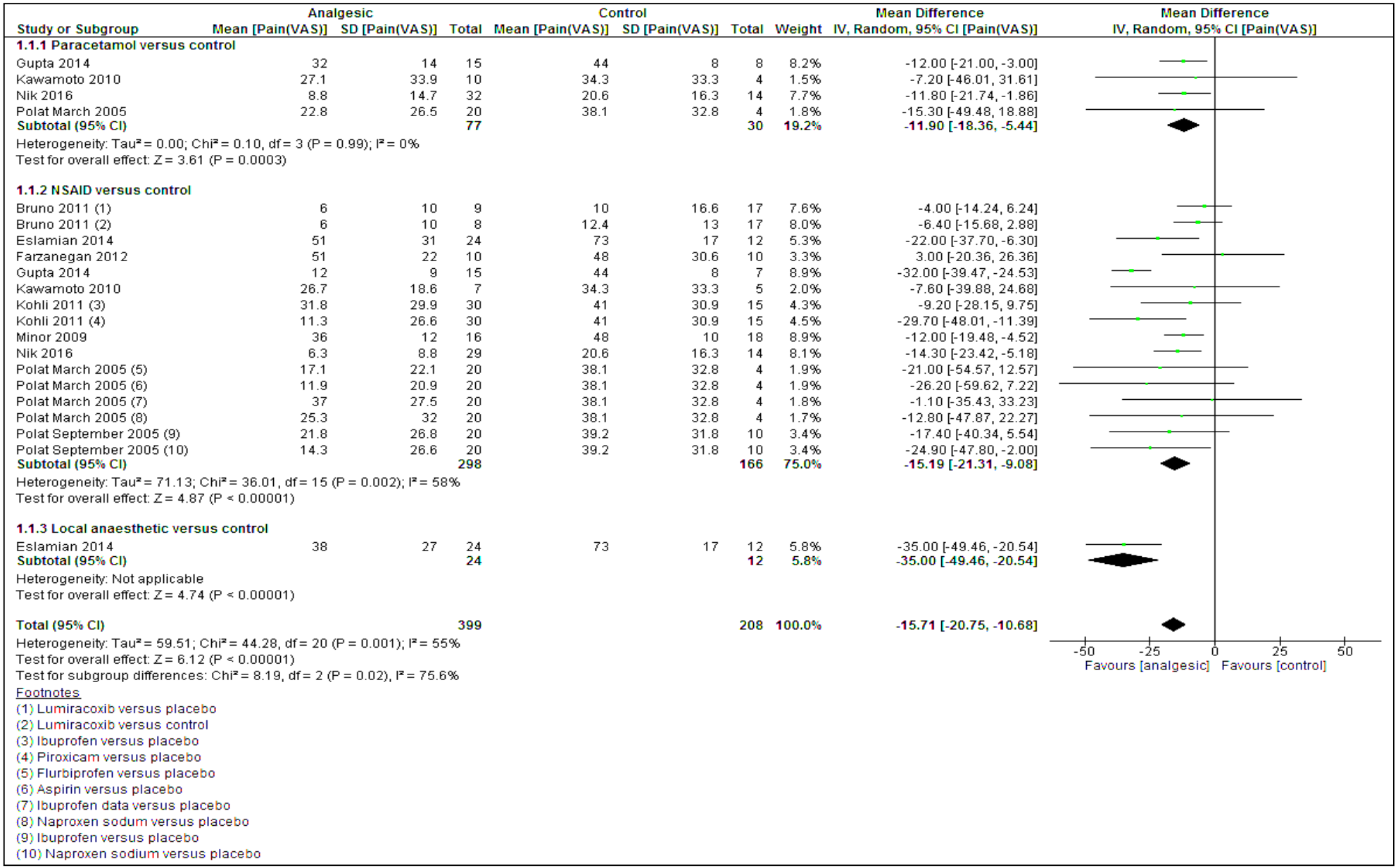


Figure 6: Forest plot of comparison 1: Analgesic versus control, outcome: 1.2 6 hours [Pain(VAS)].

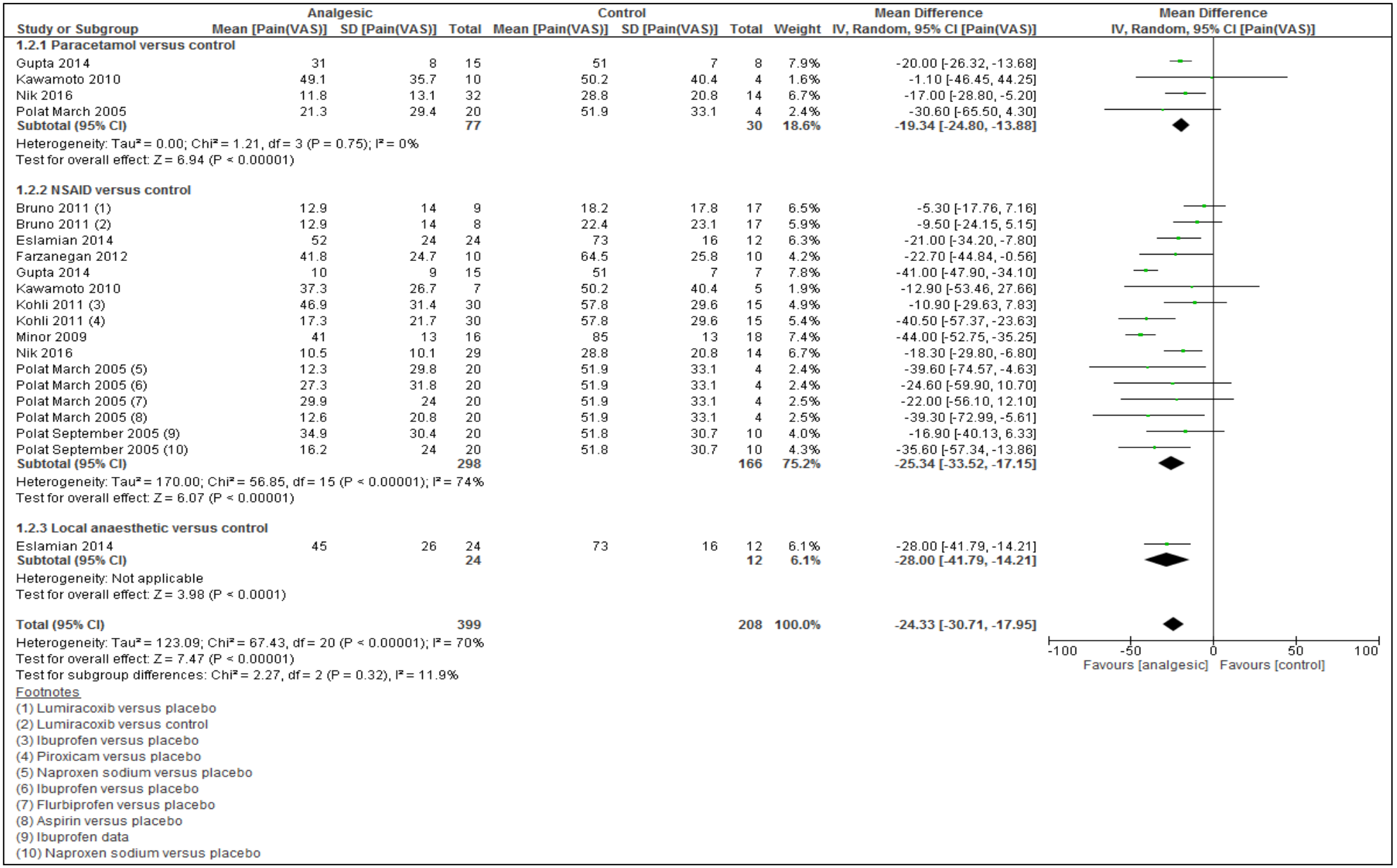


Figure 7: Forest plot of comparison 1: Analgesic versus control, outcome: 1.3 24 hours [Pain(VAS)].

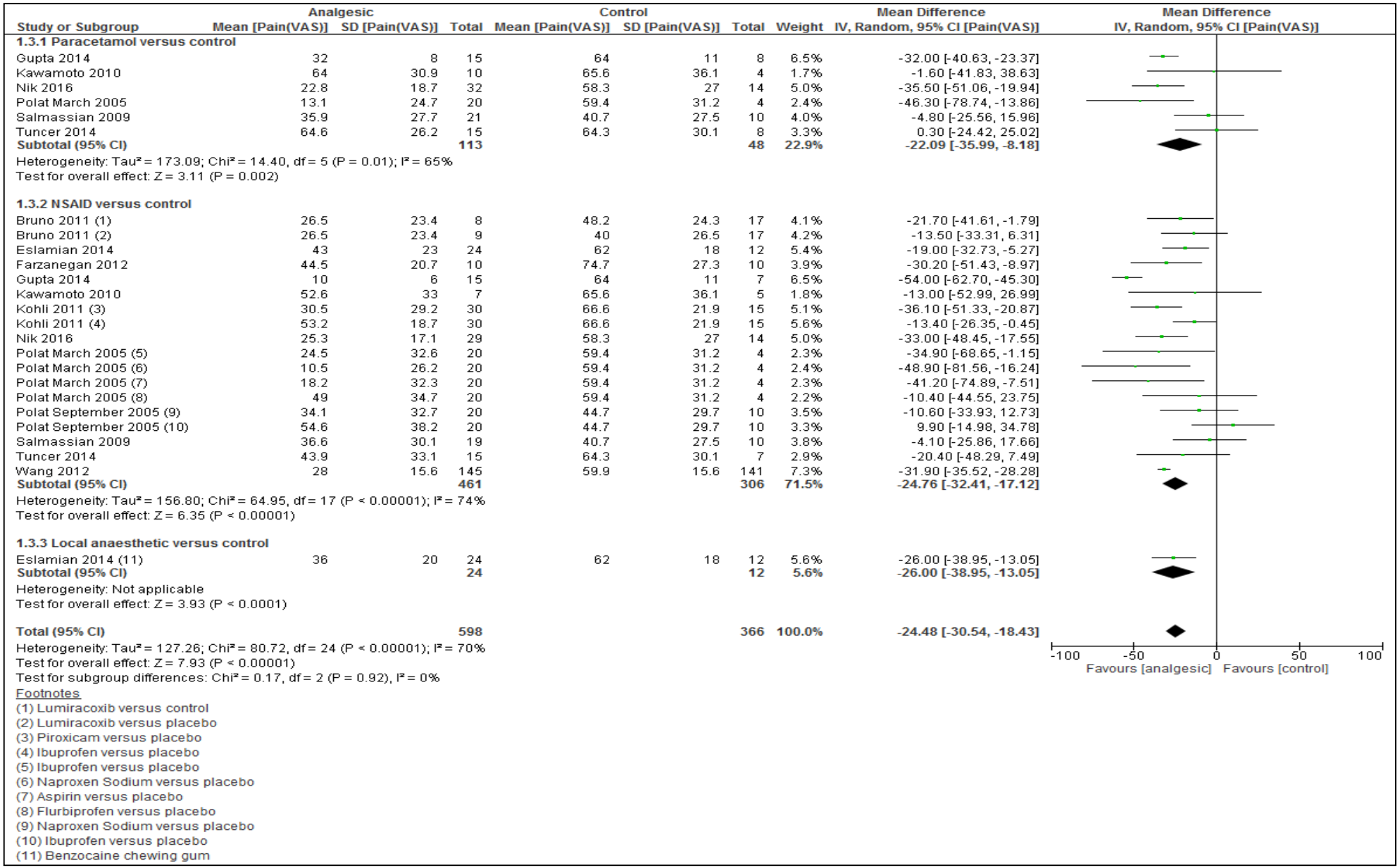


Table 3: Paracetamol versus control – separator placement [Pain(VAS)]

Experimental Intervention	Outcome	No. of studies (no. of participants)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Paracetamol	Pain VAS	2 (79)	-11.51 (-19.15, -3.86)	0.003	0.77	0%
6 hours						
Paracetamol	Pain VAS	2 (79)	-16.00 (-24.65, -7.34)	0.0003	0.38	0%
24 hours						
Paracetamol	Pain VAS	2 (79)	-21.51 (-54.10, 11.09)	0.2	0.04	76%

Table 4: Paracetamol versus control – initial archwire placement [Pain(VAS)]

Experimental Intervention	Outcome	No. of studies (no. of participants)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Paracetamol	Pain VAS	2 (70)	-14.04 (-21.51, -6.58)	0.0002	0.88	0%
6 hours						
Paracetamol	Pain VAS	2 (70)	-21.03 (-27.19, -14.87)	< 0.00001	0.30	6%
24 hours						
Paracetamol	Pain VAS	4 (141)	-21.55 (-40.42, -2.68)	0.03	0.0001	85%

5.3.1:3: Comparison 2: NSAID versus control

At 2 hours and 6 hours, ten studies were combined in a meta-analysis. Four of these studies (Bruno 2011[77]; Farzanegan 2012[68]; Kawamoto 2010[69]; Minor 2009[67]), were all at high risk of bias; whilst the remaining six studies (Eslamian 2014[59]; Gupta 2014[75]; Kohli 2011[76]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]), were at an unknown risk of bias. In total, 506 participants were analysed, for 2 hours and 6 hours.

Eight different classes of NSAID's were investigated across the twelve studies. Seven studies investigated ibuprofen (Farzanegan 2012[68]; Kawamoto 2010[69]; Kohli 2011[76]; Minor 2009[67]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]); two investigated naproxen sodium (Polat March 2005[48]; Polat September 2005[73]); one study investigated aspirin (Polat March 2005[48]); one study investigated etoricoxib (Gupta 2014[75]); one study investigated flurbiprofen (Polat March 2005[48]); one study investigated lumiracoxib (Bruno 2011[77]); one study investigated piroxicam (Kohli 2011[76]), and one investigated Ketoprofen in chewing gum form (Eslamian 2014[59]). For the purposes of this review these have been analysed by subgroup by class and then combined to give an overall meta-analysis for the comparison.

At 24 hours, twelve studies were combined in a meta-analysis. Five of these studies (Bruno 2011[77]; Kawamoto 2010[69]; Farzanegan 2012[68]; Tunçer 2014[74], Wang 2012[65]), were all at high risk of bias; whilst the remaining seven studies (Eslamian 2014[59]; Gupta 2014[75]; Kohli 2011[76]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]), were at an unknown risk of bias. In total, 817 participants were analysed for 24 hours.

Again; eight different classes of NSAID's were investigated across the twelve studies. Nine studies investigated ibuprofen (Kohli 2011[76]; Kawamoto 2010[69]; Farzanegan 2012[68]; Polat March 2005[48]; Polat September 2005[73]; Nik 2016[72]; Salmassian 2009[70]; Tunçer 2014[74], Wang 2012[65]); two investigated naproxen sodium (Polat March 2005[48]; Polat September 2005[73]); one study investigated aspirin (Polat March 2005[48]); one study investigated etoricoxib (Gupta 2014[75]); one study investigated flurbiprofen (Polat March 2005[48]); one study investigated lumiracoxib (Bruno 2011[77]); one study investigated piroxicam (Kohli 2011[76]), and one investigated Ketoprofen in chewing gum form (Eslamian 2014[59]).

The meta-analysis showed that analgesics reduced mean pain intensity during orthodontic treatment at 2 hours (MD -15.22, 95% CI -21.49 to -8.96], P < 0.00001) (Figure 8); 6 hours (MD -15.22, 95% CI -21.49 to -8.96, P =< 0.00001) (Figure 9); and 24 hours (MD -24.33, 95% CI -30.71 to -17.95, P < 0.00001) (Figure 10) when compared to a control. However there was substantial heterogeneity (I^2 = 67%) at 2 hours, and considerable heterogeneity at 6 hours (I^2 = 77%) and at 24 hours (I^2 = 82%). It was again thought that this may have been due in part to the methods relating to orthodontic intervention; which have been broken down further and explored in relation to the effect of the intervention on pain following separator placement, placement of an initial archwire or the effect on pain mid-treatment. In relation to separator placement, NSAIDs were shown to be effective at reducing pain at 2, 6 and 24 hours, in comparison with a control. 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 5). For archwire placement, NSAIDs were shown to be effective at reducing pain at 2, 6 and 24 hours, in comparison with a control. However heterogeneity remained with moderate heterogeneity at 2 hours (I^2 = 47%), low heterogeneity (I^2 = 10%), and considerable heterogeneity at 24 hours (I^2 = 85%) (Table 6). In relation to mid-treatment patients, NSAIDs, in the form of ketoprofen chewing gum, were shown to be effective at reducing pain at 2, 6 and 24 hours, in comparison with a control (Table 7).

Figure 8: Forest plot of comparison 2: NSAID versus control, outcome: 2.1 2 hours [Pain(VAS)].

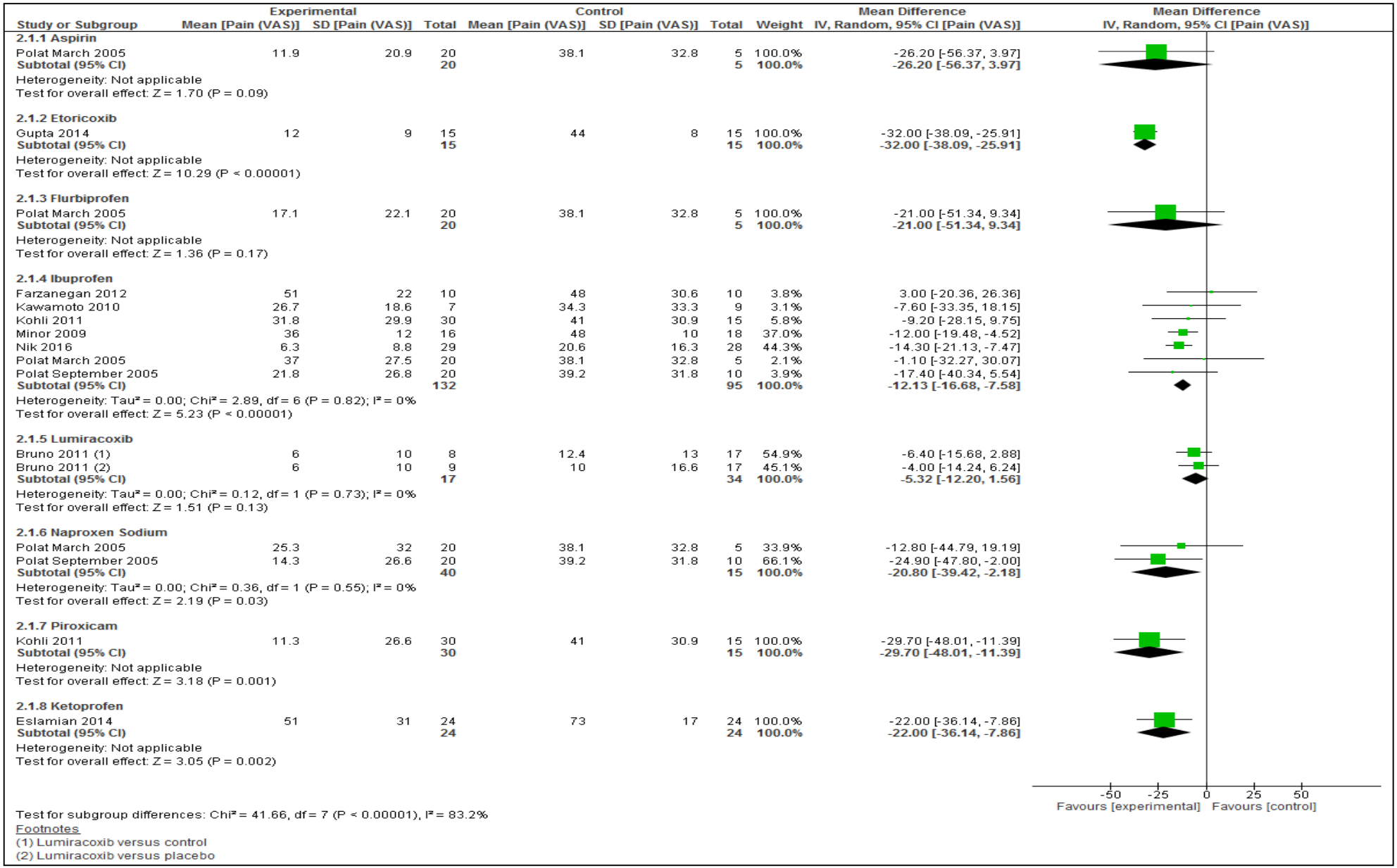


Figure 9: Forest plot of comparison 2: NSAID versus control, outcome: 2.2 6 hours [Pain(VAS)].

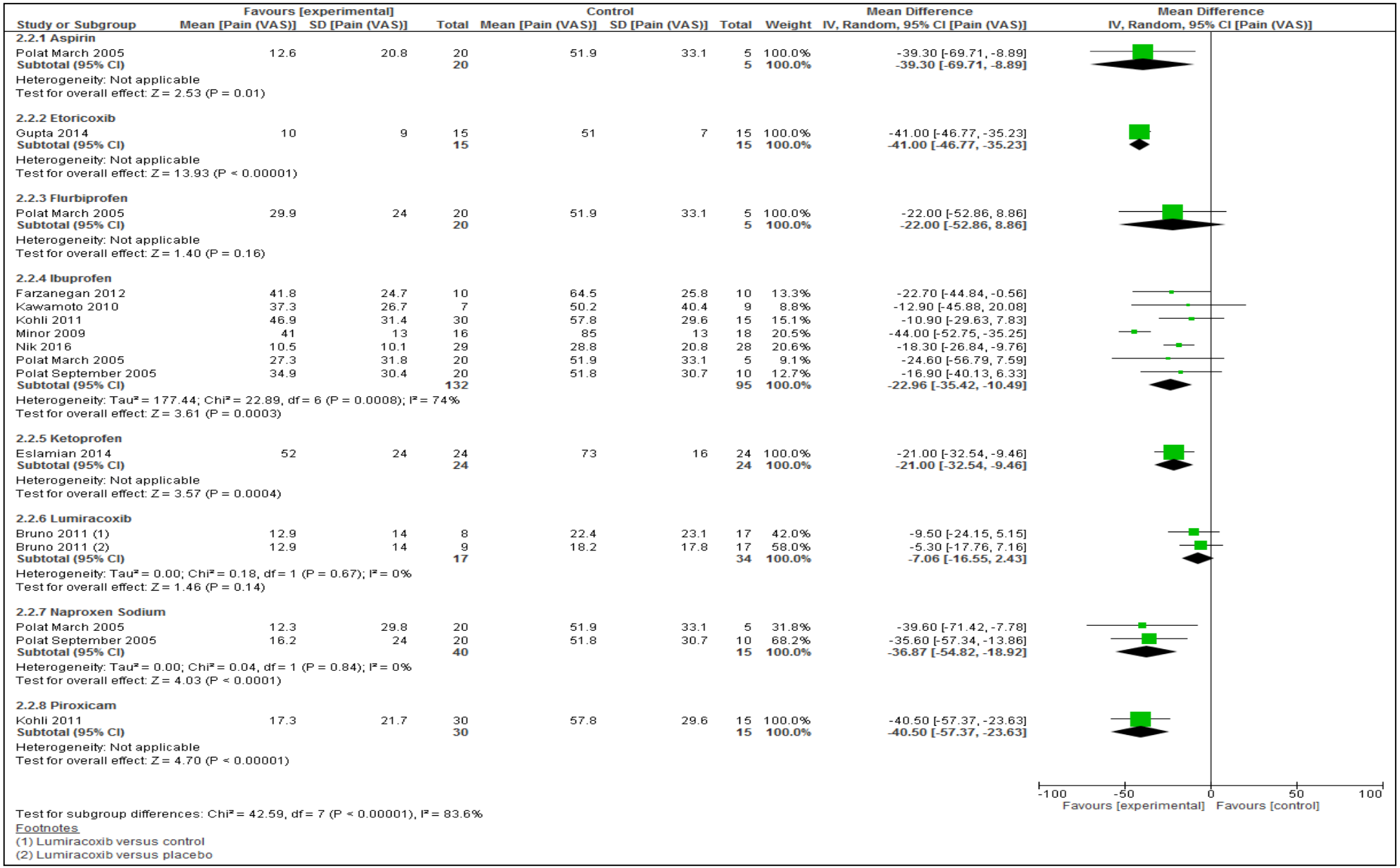


Figure 10: Forest plot of comparison 2: NSAID versus control, outcome: 2.3 24 hours [Pain(VAS)].

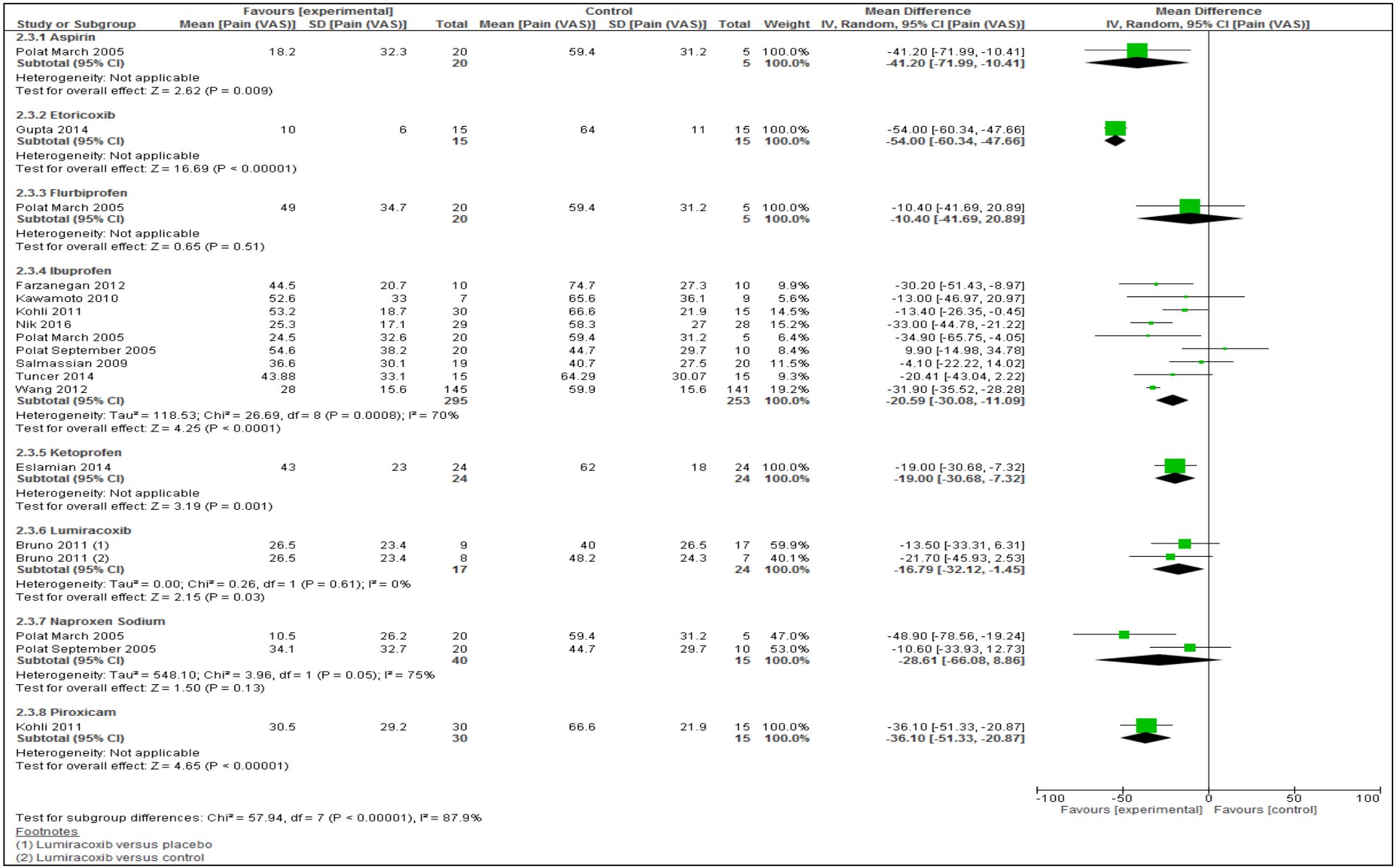


Table 5: Ibuprofen versus control – separator placement [Pain(VAS)]

Experimental Intervention	Outcome	No. of studies (no. of participants)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Ibuprofen	Pain VAS	4 (152)	-12.80 (-17.59 to -8.01)	<0.00001	0.91	0%
Lumiracoxib		1 (51)	-5.32 (-112.20 to 1.56)	0.13	0.73	0%
Piroxicam		1 (45)	-29.70 (-48.01, -11.39)	0.001	N/A	N/A
Subtotal		**5 (248)**	**-11.10 (-15.78, -6.42)**	**<0.00001**	**0.25**	**23%**
6 hours						
Ibuprofen	Pain VAS	4 (150)	-23.41 (-41.43, -5.39)	0.01	0.0001	86%
Lumiracoxib		1 (51)	-7.06 (-16.55, 2.43)	0.14	0.67	0%
Piroxicam		1 (45)	-40.50 (-57.37, -23.63)	<0.00001	N/A	N/A
Subtotal		**5 (248)**	**-8.80 (-13.47 to -4.12)**	**0.0002**	**0.97**	**0%**
24 hours						
Ibuprofen		3 (118)	-21.85 (-37.33, -6.37)	0.006	0.07	62%
Lumiracoxib		1 (51)	-17.58 (-31.62, -3.54)	0.01	0.57	0%
Piroxicam		1 (45)	-36.10 (-51.33, -20.87)	<0.00001	N/A	N/A
Subtotal		**4 (214)**	**-23.66 (-32.81, -14.51)**	**<0.00001**	**0.12**	**42%**

Table 6: Ibuprofen versus control – initial archwire placement [Pain(VAS)]

Experimental Intervention	Outcome	No. of studies (no. of patients)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Aspirin	Pain VAS	1 (25)	-26.20 (-56.37, 3.97)	0.09	N/A	N/A
Etoricoxib		1 (30)	-32.00 (-38.09 to -25.91)	<0.00001	N/A	N/A
Flurbiprofen		1 (25)	-21.00 (-51.34, 9.34)	0.17	N/A	N/A
Ibuprofen		3 (75)	-6.02 (-20.52, 8.47)	0.42	0.45	0%
Naproxen Sodium		2 (55)	-20.80 (-39.42, -2.18)	0.03	0.55	0%
Subtotal		**4 (210)**	**-19.23 (-29.90, -8.56)**	**0.0004**	**0.07**	**47%**
6 hours						
Aspirin	Pain VAS	1 (25)	-39.30 (-69.71, -8.89)	0.01	N/A	N/A
Etoricoxib		1 (30)	-41.00 (-46.77 to -35.23)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	-22.00 (-52.86, 8.86)	0.16	N/A	N/A
Ibuprofen		3 (75)	-20.87 (-35.21, -6.52)	0.004	0.91	0%
Naproxen Sodium		2 (55)	-36.87 (-54.82, -18.92)	< 0.0001	0.84	0%
Subtotal		**4 (210)**	**-35.42 (-42.15, -28.68)**	**< 0.00001**	**0.35**	**10%**
24 hours						
Aspirin	Pain VAS	1 (25)	-41.20 (-71.99, -10.41)	0.09	N/A	N/A
Etoricoxib		1 (30)	-54.00 (-60.34 to -47.66)	<0.00001	N/A	N/A
Flurbiprofen		1 (25)	-10.40 (-41.69, 20.89)	0.51	N/A	N/A
Ibuprofen		6 (420)	-19.71 (-33.60, -5.82)	0.005	0.004	71%
Naproxen Sodium		2 (55)	-28.61 (-66.08, 8.86)	0.13	0.05	75%
Subtotal		**7 (555)**	**-26.26 (-37.81, -14.71)**	**< 0.0001**	**< 0.00001**	**85%**

Table 7: NSAID versus control – mid-treatment [Pain (VAS)]

Experimental Intervention	Outcome	No. of studies (no. of patients)	Effect Measure MD (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, -7.86)	0.002	N/A	N/A
6 hours						
Ketoprofen (chewing gum)	Pain VAS	1 (48)	MD -40.50 (-57.37, -23.63)	<0.00001	N/A	N/A
24 hours						
Ketoprofen (chewing gum)	Pain VAS	1 (48)	MD -40.50 (-57.37, -23.63)	<0.00001	N/A	N/A

5.3.2: Comparison 3: NSAID versus paracetamol

Pain

At 2 hours and 6 hours, seven studies were combined in a meta-analysis. Three of these studies (Kawamoto 2010[69]; Najafi 2015[71]; Ousehal 2009[63]), were at high risk of bias; three studies (Gupta 2014[75]; Nik 2016[72]; Polat March 2005[48]), were at an unknown risk of bias; and one study was assessed as low risk of bias (Bradley 2007[60]). In total, 664 participants were analysed, for 2 hours and 6 hours.

At 24 hours, nine studies were combined in a meta-analysis. Four of these studies (Kawamoto 2010[69]; Najafi 2015[71]; Tunçer 2014[74]; Ousehal 2009[63]), were all at high risk of bias; four studies (Gupta 2014[75]; Nik 2016[72]; Polat March 2005[48]; Salmassian 2009[70]), were at an unknown risk of bias; and one study was assessed as low risk of bias (Bradley 2007[60]). In total, 734 participants were analysed for 24 hours.

Six different classes of NSAIDs were investigated across the nine studies. Eight studies investigated ibuprofen (Bradley 2007[60]; Kawamoto 2010[69]; Najafi 2015[71]; Nik 2016[72]; Ousehal 2009[63]; Polat March 2005[48]; Salmassian 2009[70]; Tunçer 2014[74]). One study investigated each of the following: aspirin (Polat March 2005[48]), Etorixocib (Gupta 2014[75]), Flurbiprofen (Polat March 2005[48]), meloxicam (Najafi 2015[71]), and naproxen sodium (Polat March 2005[48]). For the purposes of this review these have been analysed by subgroup, by class and then combined to give an overall meta-analysis for the comparison.

The meta-analysis showed that, although the results favoured NSAIDs slightly for the reduction of mean pain intensity during orthodontic treatment at 2 hours and 6 hours, there was no significant difference at:

- 2 hours (MD -2.92, 95% CI -8.48 to 2.65, P 0.30) (Figure 11);
- 6 hours (MD -5.17, 95% CI -11.71 to 1.37, P =< 0.12) (Figure 12); and
- 24 hours (MD -0.51, 95% CI -8.93 to 7.92, P < 0.91) (Figure 13) when compared to paracetamol.

However, there was substantial heterogeneity (I^2 = 63%) at 2 hours, and considerable heterogeneity at 6 hours (I^2 = 72%) and at 24 hours (I^2 = 82%). It was, again, thought that this may have been due in part to the methods relating to orthodontic intervention; which have been broken down further and explored in relation to the effect of the intervention on pain following separator placement and placement of an initial archwire.

In relation to separator placement, NSAIDs were shown to be no more effective at reducing pain at 2, 6 and 24 hours, in comparison with paracetamol. 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 8).

For archwire placement, NSAIDs were also shown to be no more effective at reducing pain at 2, 6 and 24 hours, in comparison with paracetamol. 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 9).

Rescue analgesia

Two studies in this subgroup (Bradley 2007[60]; Najafi 2015[71]) reported that participants required rescue medication during the study. Bradley 2007[60] reported that 18 participants required rescue medication. The percentages of subjects who took additional analgesia were 9% (7 patients) in the paracetamol group and 14% (11 patients) in the ibuprofen group (P = 0 37 with the chi-square test for association). The study states 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. Najafi 2015[71] reported 18 patients used other analgesics during the time. No further information was available relating to class, dose or timing.

Adverse events

One study (Bradley 2007[60]) reported one participant (<1%) experienced a suspected adverse reaction. Further information was provided in an additional paper[97] detailing an incident involving a 12-year-old male with no relevant medical history and no history of drug allergy. *"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 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 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. 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.[98]"

Quality of life and/or patient satisfaction

No studies in this subgroup reported this outcome.

Time off school/work

No studies in this subgroup reported this outcome.

Withdrawal from the study

Seven studies in this subgroup experienced withdrawal of participants from the study:

- Polat March 2005[48] reported withdrawal of 22 participants who did not return questionnaires and 8 participants who were too old (>30 years old); n = 30/150, 20%.
- Salmassian 2009[70] reported withdrawal of 4 participants who did not return in a timely manner and 2 participants who withdrew consent after archwire placement; n = 6/66, 9.1%.
- Tunçer 2014[74] reported withdrawal of 3 participants who did not return questionnaires; n = 3/46, 6%.
- Bradley 2007[60] reported withdrawal of 9 participants who did not return questionnaires, and 19 participants who did not fulfil inclusion criteria; n = 28/187, 15%.
- Najafi 2015[71] reported withdrawal of 46 participants who did not complete the questionnaire correctly, 16 who did not return questionnaires and 18 participants who took additional analgesics; n = 80/321, 25%.
- Kawamoto 2010[69] reported withdrawal of 9 participants who failed to return questionnaires; n = 9/35, 25.7%.

- Nik 2016[72] reported withdrawal of 8 participants who did not take the drug, 3 participants who did not complete the questionnaires and 1 for reasons not discussed in the paper; n = 12/101, 12%.

All other studies included in this analysis experienced no withdrawal of participants. This amounted to a total withdrawal of 168 participants from a total of 734 participants in this subgroup.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this subgroup reported this outcome.

Response to treatment

No studies in this subgroup presented data in a way which facilitated assessment of this outcome.

Figure 11: Forest plot of comparison 3: NSAID versus paracetamol, outcome: 3.1 2 hours [Pain(VAS)].

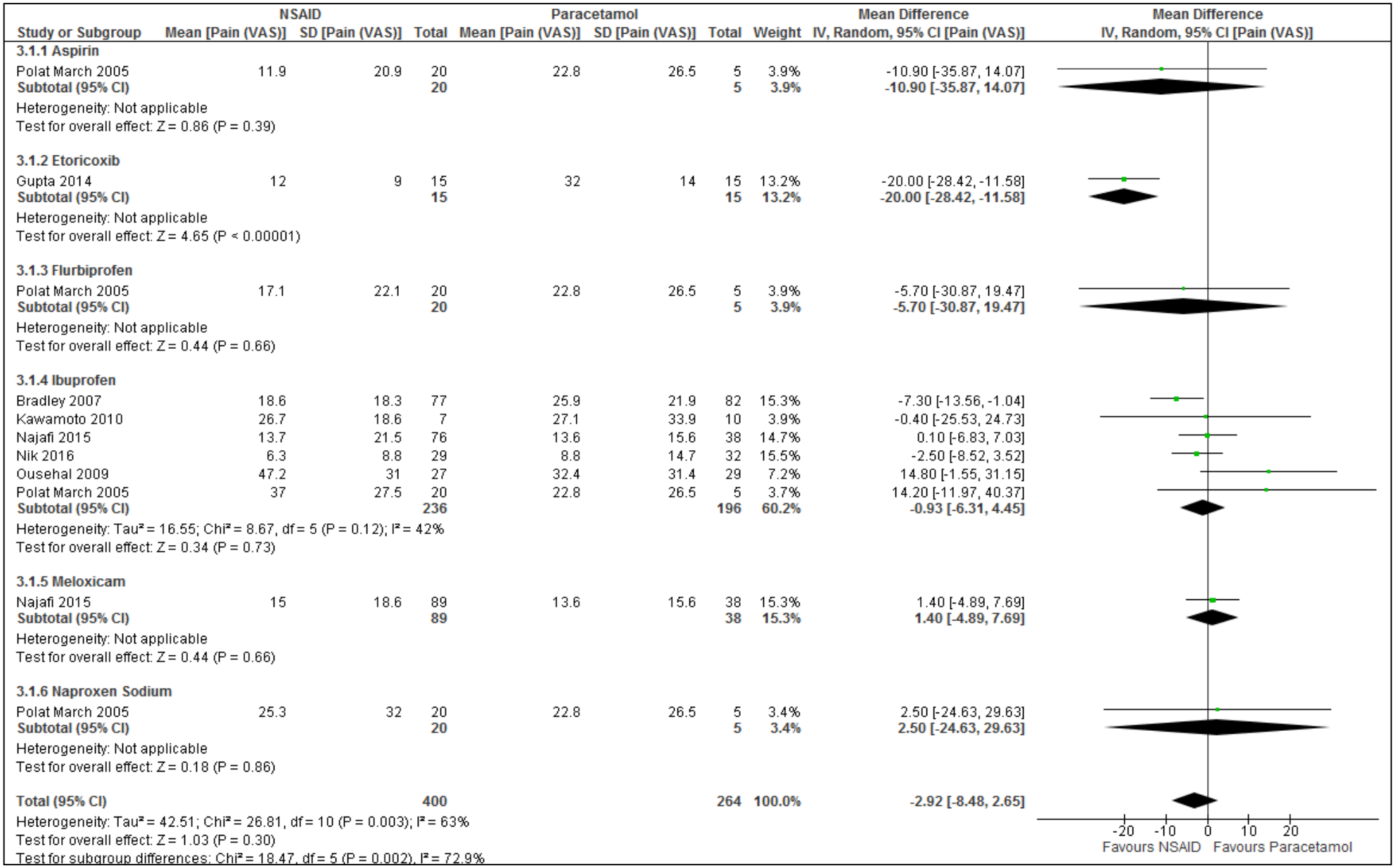


Figure 12: Forest plot of comparison 3: NSAID versus paracetamol, outcome: 3.2 6 hours [Pain(VAS)].

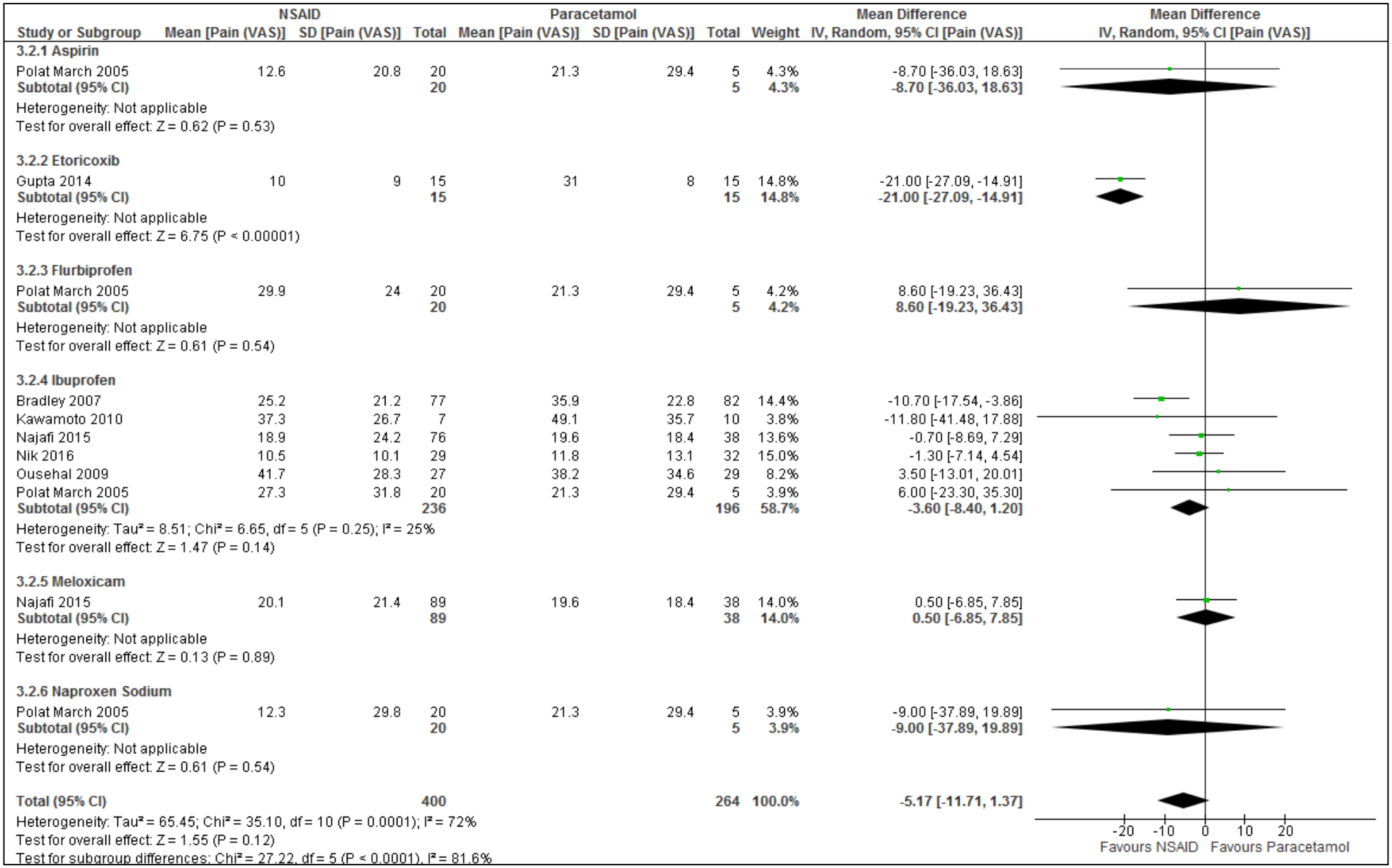


Figure 13: Forest plot of comparison 3: NSAID versus paracetamol, outcome: 3.3 24 hours [Pain(VAS)].

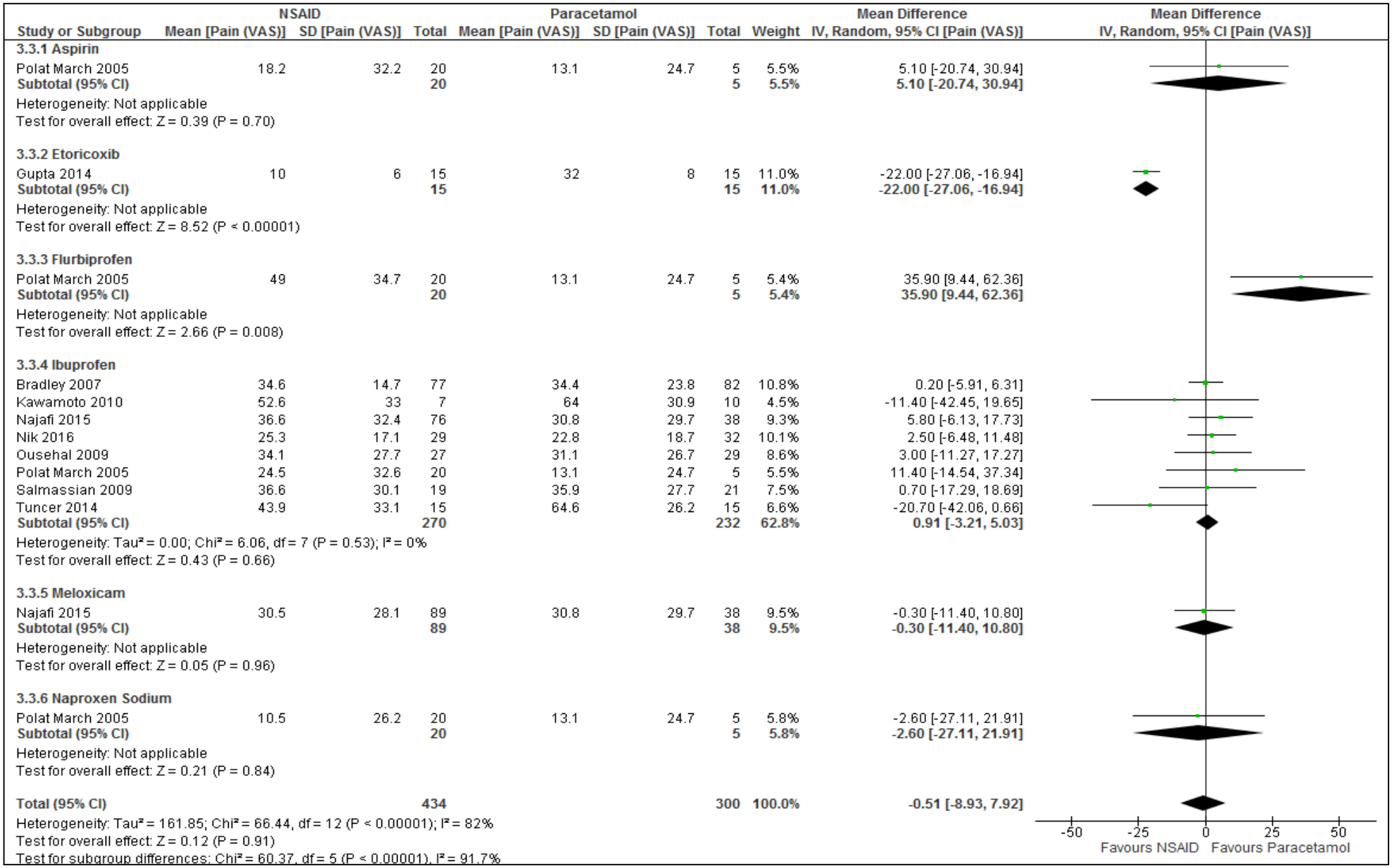


Table 8: NSAID versus paracetamol – separator placement [Pain (VAS)]

Experimental Intervention	Outcome	No. of studies (no. of patients)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Ibuprofen	Pain VAS	4 (351)	-3.36 (-7.00, 0.28)	0.07	0.46	0%
Meloxicam		1 (127)	1.40 (-4.89, 7.69)	0.66	N/A	N/A
Subtotal		**4 (478)**	**-2.16 (-5.44, 1.12)**	**0.20**	**0.37**	**6%**
6 hours						
Ibuprofen	Pain VAS	4 (351)	-4.53 (-10.23, 1.18)	0.12	0.14	44%
Meloxicam		1 (127)	0.50 (-6.85, 7.85)	0.89	N/A	N/A
Subtotal		**4 (478)**	**-3.35 (-8.05, 1.35)**	**0.16**	**0.15**	**40%**
24 hours						
Ibuprofen	Pain VAS	4 (351)	1.38 (-3.22, 5.98)	0.56	0.71	0%
Meloxicam		1 (127)	-0.30 (-11.40, 10.80)	0.96	N/A	N/A
Subtotal		**4 (478)**	**1.14 (-3.11, 5.39)**	**0.60**	**0.83**	**0%**

Table 9: NSAID versus paracetamol – initial archwire placement [Pain (VAS)]

Experimental Intervention	Outcome	Number of studies (number of patients)	Effect Measure MD (95% CI)	P-value for effect	P-value heterogeneity	I^2 (%)
2 hours						
Aspirin	Pain VAS	1 (25)	-10.90 (-35.87, 14.07)	0.39	N/A	N/A
Etoricoxib		1 (30)	-20.00 (-28.42, -11.58)	< 0.00001	N/A	N/A
Flurbiprofen		1 (40)	-5.70 (-20.82, 9.42)	0.46	N/A	N/A
Ibuprofen		2 (81)	14.63 (0.77, 28.50)	0.04	0.97	0%
Naproxen Sodium		1 (25)	2.50 (-24.63, 29.63)	0.86	N/A	N/A
Subtotal		**3 (201)**	**-2.230 (-16.06, 11.61)**	**0.75**	**0.002**	**73%**
6 hours						
Aspirin	Pain VAS	1 (25)	-8.70 (-36.03, 18.63)	0.53	N/A	N/A
Etoricoxib		1 (30)	-21.00 (-27.09, -14.91)	< 0.00001	N/A	N/A
Flurbiprofen		1 (40)	8.60 (-19.23, 36.43)	0.54	N/A	N/A
Ibuprofen		2 (81)	4.10 (-10.28, 18.48)	0.58	0.88	0%
Naproxen Sodium		1 (25)	-9.00 (-37.89, 19.89)	0.54	N/A	N/A
Subtotal		**3 (201)**	**-5.66 (-18.97, 7.64)**	**0.40**	**0.02**	**63%**
24 hours						
Aspirin	Pain VAS	1 (25)	5.10 (-20.77, 30.97)	0.70	N/A	N/A
Etoricoxib		1 (30)	-22.00 (-27.06, -16.94)	< 0.00001	N/A	N/A
Flurbiprofen		1 (25)	35.90 (9.44, 62.36)	0.008	N/A	N/A
Ibuprofen		4 (151)	-1.36 (-13.04, 10.33)	0.82	0.21	33%
Naproxen Sodium		1 (25)	-2.60 (-27.11, 21.91)	0.84	N/A	N/A
Subtotal		**5 (256)**	**-0.37 (-14.41, 13.67)**	**0.96**	**< 0.00001**	**82%**

5.3.3: Comparison 4: NSAID pre-emptive versus NSAID post-treatment

Pain

Two studies (Bernhardt 2001[66]; Steen-Law 2000[34]), at high risk of bias, compared ibuprofen taken pre-emptively with ibuprofen taken post-treatment for the placement of separators, analysing 69 participants. This showed that pre-emptive ibuprofen reduced mean pain intensity following separator placement at 2 hours (MD -11.33, 95% CI -16.09 to -6.58, P < 0.00001) (Figure 14) when compared with ibuprofen taken post-treatment. However there was no difference at 6 hours (MD -8.43, MD -30.37 to 13.50, P < 0.45) (Figure 15); or 24 hours (MD -9.74, 85% CI -47.88 to 28.40, P < 0.62) (Figure 16), when compared to ibuprofen taken post-treatment. 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%).

Rescue analgesia

Both studies in this subgroup reported that participants required rescue medication during the study. One study (Bernhardt 2001[66]) reported 22 participants required additional analgesics during the study. Although the study stated that these 22 patients were evenly distributed among the 3 groups in the study, no further information was available relating to class, dose or timing and participants from group A did not contribute to the analysis in this review.

One study (Steen-Law 2000[34]) reported 17 participants required additional analgesics during the study, 4 in the pre-emptive ibuprofen group; 6 in the post-treatment ibuprofen group and 7 in the control group, who did not contribute to the analysis in this review. No further information was available relating to class, dose or timing.

Adverse events

No studies in this subgroup reported any adverse events.

Quality of life and/or patient satisfaction

No studies in this subgroup reported this outcome.

Time off school/work

No studies in this subgroup reported this outcome.

Withdrawal from the study

One study in this subgroup experienced withdrawal of 3 participants who did not return questionnaires (Steen-Law 2000[34]).

The other study included in this analysis experience no withdrawal of participants.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this subgroup reported this outcome.

Response to treatment

No studies in this subgroup presented data in a way that facilitated assessment of this outcome.

Figure 14: Forest plot of comparison 4: NSAID pre-emptive versus post-treatment, outcome: 4.1 2hrs[Pain (VAS)].

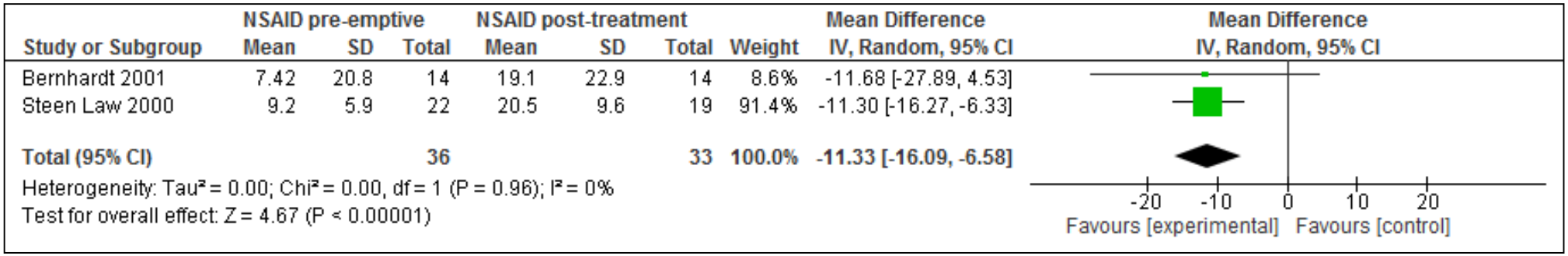


Figure 15: Forest plot of comparison 4: NSAID pre-emptive versus post-treatment, outcome: 4.2 6hrs[Pain (VAS)].

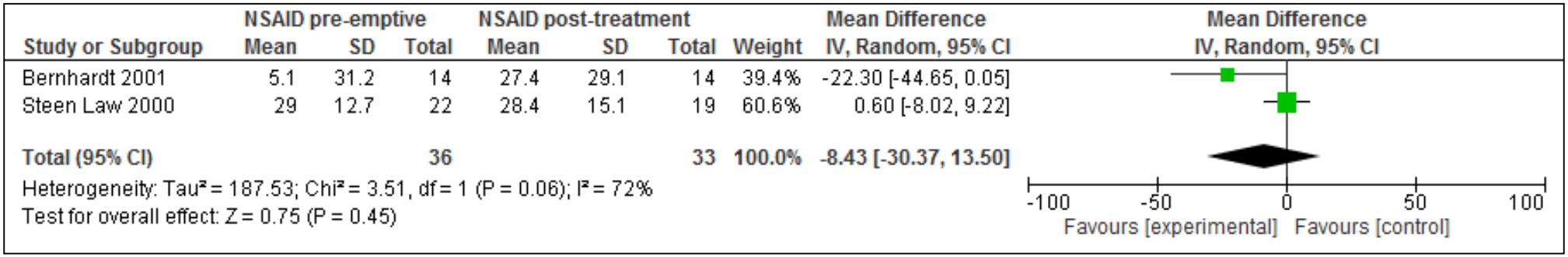
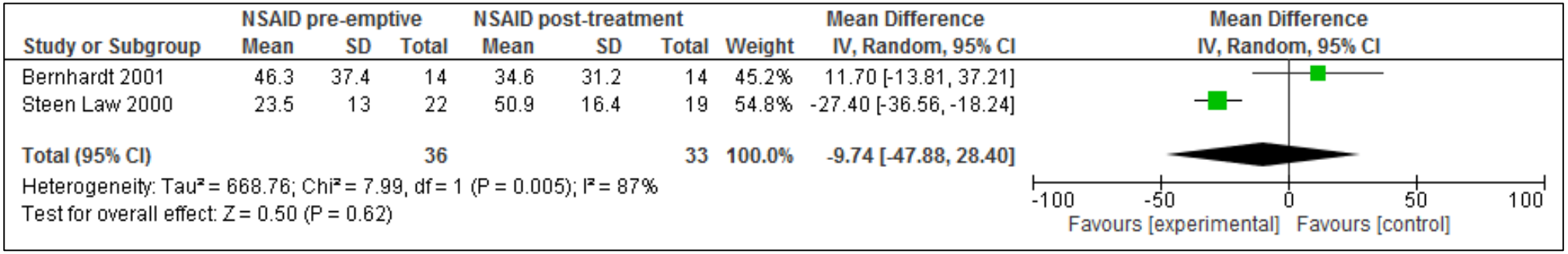


Figure 16: Forest plot of comparison 4: NSAID pre-emptive versus post-treatment, outcome: 4.3 24hrs[Pain (VAS)].



5.3.5: Comparison 5: NSAID versus local anaesthetic

Pain

One study (Eslamian 2014[59]) at unknown risk of bias, compared ketoprofen chewing gum with benzocaine chewing gum, for the relief of pain mid-treatment, analysing 48 participants. This showed that ketoprofen (NSAID) chewing gum did not reduce mean pain intensity mid-treatment at:

- 2 hours (MD -11.33, 95% CI -16.09 to -6.58, P 0.12) (Figure 17);
- 6 hours (MD -8.43,95% CI -30.37 to 13.50, P 0.33) (Figure 18); or
- 24 hours (MD -9.74, 95% CI -47.88 to 28.40, P 0.26) (Figure 19) when compared to benzocaine (local anaesthetic) chewing gum.

Adverse events

No studies in this subgroup reported any adverse events.

Quality of life and/or patient satisfaction

No studies in this subgroup reported this outcome.

Time off school/work

No studies in this subgroup reported this outcome.

Withdrawal from the study

The study included in this subgroup reported withdrawal of 4 participants, however the reason was only stated as lost to follow-up.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this subgroup reported this outcome.

Response to treatment

No studies in this subgroup presented data in a way that facilitated assessment of this outcome.

Figure 17: Forest plot of comparison 5: NSAID versus local anaesthetic, outcome: 5.1 2hrs[Pain (VAS)].

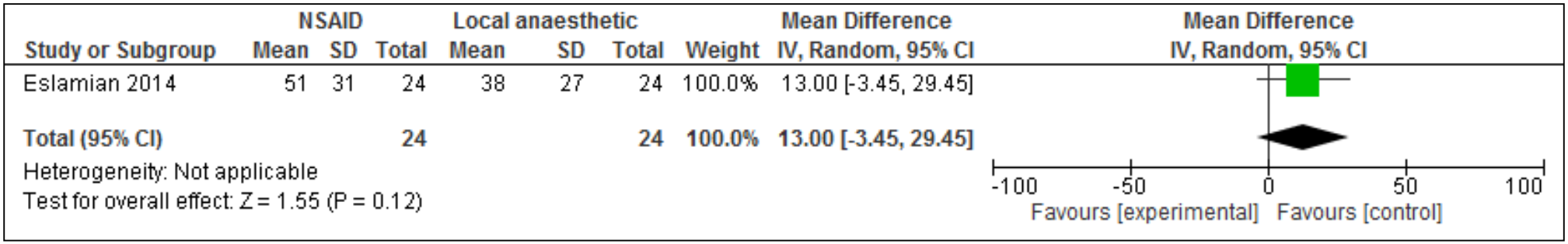


Figure 18: Forest plot of comparison 5: NSAID versus local anaesthetic, outcome: 5.2 6hrs[Pain (VAS)].

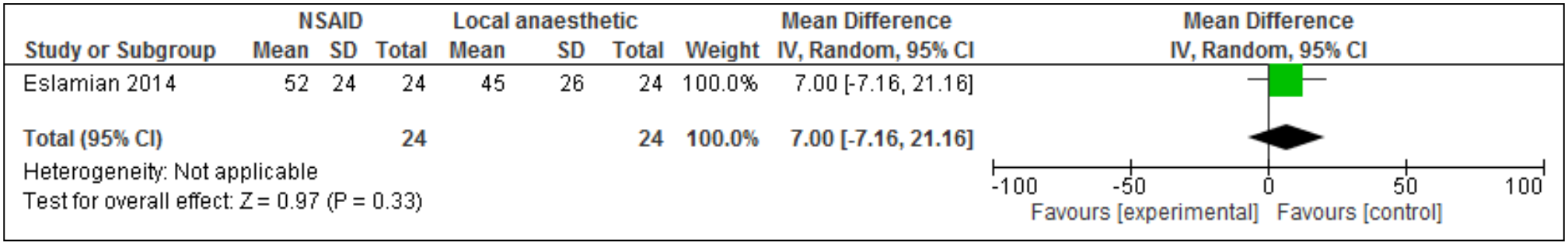
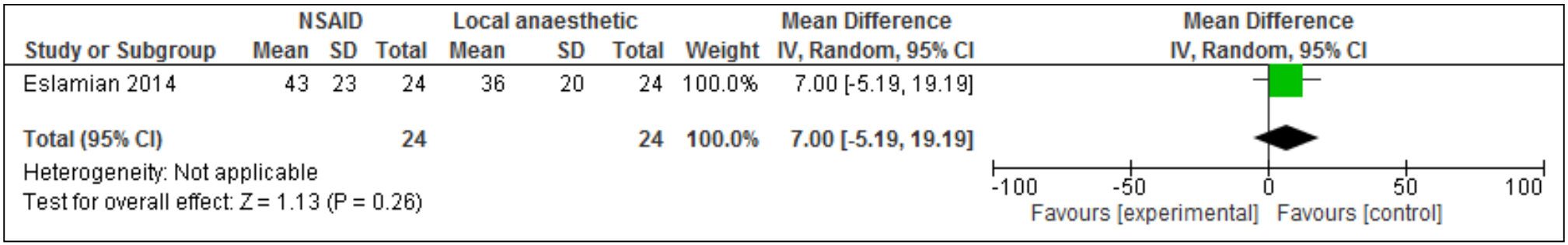


Figure 19: Forest plot of comparison 5: NSAID versus local anaesthetic, outcome: 5.3 24hrs[Pain (VAS)].



5.3.6: Comparison 6: Paracetamol versus calcium

Pain

One study (Yassaei 2012[64]), at high risk of bias, compared paracetamol and calcium for the relief of pain mid-treatment, analysing 40 participants. However data were recorded at baseline and 4 days after treatment and therefore did not contribute to our analysis.

Adverse events

No studies in this subgroup reported any adverse events.

Quality of life and/or patient satisfaction

This study reported psychotic status as measured using the HADS. The reported mean and maximum HADS was 11.28 and 19 in the calcium group. The mean and maximum HADS was 10.52 and 20 in the acetaminophen group. The minimum HADS in both groups was 2. There was no significant difference between the mean HAD scale of the two groups before or after intervention.

Time off school/work

No studies in this subgroup reported this outcome.

Withdrawal from the study

There was no withdrawal from the study included in this analysis.

Failure to complete orthodontic treatment due to the pain experienced

No studies in this subgroup reported this outcome.

Response to treatment

No studies in this subgroup presented data in a way that facilitated assessment of this outcome.

Chapter 6: Discussion

6.1: Summary of main results

Twenty-two randomised controlled trials (RCTs) met our eligibility criteria and were included in this review. We assessed the body of evidence for each comparison and outcome and 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.

Analgesic versus control

We found 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 paracetamol, NSAIDs and local anaesthetic were all effective at reducing pain intensity at 2 hours, 6 hours and 24 hours when compared with either a placebo or control group.

When further subgroup analyses were performed, grouping the data by orthodontic intervention carried out:

- NSAIDs were found to be significantly more effective at reducing pain intensity when compared with a control group at all time points, regardless of the orthodontic intervention.
- Paracetamol was found to be significantly more effective at reducing pain intensity when compared with a control group at all time points when an initial archwire was placed; however, 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 group on pain intensity following the placement of separators.

NSAID versus paracetamol

We found no statistically significant difference between the effective of NSAIDs and paracetamol 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.

Subgroup analysis by class of NSAID found weak evidence based on one study (Gupta 2014[75]) that etoricoxib was significantly better than paracetamol at reducing pain at 2 hours, 6 hours and 24 hours following placement of an initial archwire. However, due to the size of the study and its risk of bias, no recommendation can be made to support one drug over the other.

Similarly, we found weak evidence based on one study (Polat March 2005[48]) that flurbiprofen was significantly better than paracetamol at reducing pain at 2 hours, 6 hours and 24 hours following placement of an initial archwire. However, due to the size of the study and its risk of bias, no recommendation can be made to support one drug intervention over the other.

Pre-emptive NSAID versus post-treatment NSAID

We found some evidence that ibuprofen taken 1 hour prior to separator placement significantly reduces pain intensity at 2 hours when compared to ibuprofen taken post-treatment. Worth noting is that this effect at 2 hours was seen, 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 (Eslamian 2014[59]) compared the use of topical ketoprofen chewing gum (NSAID) with benzocaine chewing gum (local anaesthetic). This small study showed no significant difference between the pain intensity following treatment when either ketoprofen or benzocaine are taken and therefore no recommendation can be made to support one intervention over the other.

Paracetamol versus calcium

There was insufficient evidence to determine whether there was a difference between the outcomes reported in a comparison between paracetamol and calcium from the single small study which evaluated this comparison.

6.2: Potential biases and limitations of the studies

Bias has been reduced in this systematic review by using a broad, sensitive search of multiple databases with no restrictions on language. We have also searched for

unpublished studies and data, and have included studies reported in all languages. However numerous potential biases have been detected, both within and between, individual studies included in this review.

Seven studies had to be excluded from the analysis (Arantes 2009[80]; Ngan 1994[82]; Abtahi 2006[79]; Bird 2007[81]; Patel 2010[83]; Sudhakar 2014[84]; Young 2006[85]) due to inconsistencies or inappropriately presented data which would have otherwise led to inclusion in the meta-analysis of the comparisons relating to analgesics versus control and NSAID versus paracetamol.

Data were not presented in any study to allow for analysis of the secondary outcome of response to treatment. Additionally, data were not presented in any study relating to the class, dose or specific timing of rescue analgesia taken, despite being recorded in six studies. This presents a potential bias and limitation as it may be that one intervention required more additional analgesics than another, ultimately influencing their pain intensity that has otherwise been attributed to the trial intervention.

A number of included studies had small sample sizes, which in some cases did not reach the number required to detect a difference based on the sample size calculations. Additionally, multiple studies with three or more arms required the sample sizes to be split for purposed of comparison. The control arm sample size was split for the comparison of analgesics versus control in ten studies (Bruno 2011[77]; Eslamian 2014[59]; Gupta 2014[75]; Kawamoto 2010[69]; Kohli 2011[76]; Nik 2016[72]; Polat March 2005[48]; Polat September 2005[73]; Salmassian 2009[70]; Tunçer 2014[74]). The paracetamol arm sample size was split for the head-to-head comparison of NSAIDs versus paracetamol in two studies (Najafi 2015[71]; Polat March 2005[48]). This resulted in small numbers of participants and wide confidence intervals in the final analysis which may have impacted on the overall outcome.

Another limitation of the studies was heterogeneity, which was identified in varying degrees across all comparisons. Of note are the:

- Moderate heterogeneity for analgesics versus control at 2 hours;
- Substantial heterogeneity for:
    - analgesics versus control at 6 hours and 24 hours;
    - NSAIDs versus control at 2 hours;
    - NSAID versus paracetamol at 2 hours and

    - pre-emptive versus post-treatment NSAIDs at 6 hours; and
- Considerable heterogeneity for:
    - paracetamol versus control at 24 hours;
    - NSAIDs versus control at 6 hours and 24 hours;
    - NSAID versus paracetamol at 6 hours and 24 hours and
    - pre-emptive versus post-treatment NSAIDs at 24 hours.

The cause of this was thought to be both clinical heterogeneity, relating to individual variations in participant responses to pain, particularly in those studies which recruited only female participants; differences in methodology relating to class and timing of interventions and small sample sizes; and statistical heterogeneity, due to the overall pooling of data and the large number of studies included in the meta-analyses. Further sub-group analyses, by orthodontic intervention, were carried out to determine if this was the cause for the heterogeneity and, although it did account for some heterogeneity, by reducing the I^2 in most cases by some extent, heterogeneity still remained. It was felt that further subgroup analysis to try and account for heterogeneity, for example by timing of intervention, was not appropriate due to the small number of studies. We therefore allowed for the heterogeneity by using a random effects model.

6.3: Agreements and disagreements with other studies or reviews

Three other reviews were found that reported on similar comparisons and outcomes to this review (Angelopoulou 2012[88]; Ashley 2016[89]; Xiaoting 2010[90]). Angelopoulou 2012[88] and Xiaoting 2010[90] report the efficacy of ibuprofen with lower confidence than we have reported. Although each of these reviews found a significant difference between ibuprofen when compared with a control, Angelopoulou 2012[88] found it was only significant at 2 hours and 6 hours following placement of separators or an initial aligning archwire, whilst Xiaoting 2010[90] reported the difference as significant only at 6 hours and 24 hours following placement an initial aligning archwire. The difference in confidence is due to the greater number of studies that we have included in our systematic review when compared to the previous reviews. This is most likely due to the publication of several studies within the last few years since the other reviews were published.

Additionally, Xiaoting 2010[90] reports that there was no difference in pain control between ibuprofen and paracetamol, supporting the findings of this review.
The Cochrane review by Ashley 2016[89] reports the efficacy of pre-emptive ibuprofen at 2 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 additional time points beyond 2 hours.

Chapter 7: Authors Conclusions

7.1: Implications for practice

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

Due to the lack of evidence we remain uncertain as to whether the use of systemic NSAIDs or paracetamol is more effective, or whether the use of topical NSAIDs or local anaesthetic is more effective at reducing pain associated with orthodontic treatment.

There is low quality evidence that the use of pre-emptive ibuprofen, taken 1 hour before orthodontic treatment, significantly reduces pain up to 2 hours after treatment, however the effect appears to reduce over time and is no longer significant at 6 hours and beyond.

7.2: Implications for research

In view of the quality of the studies identified in this systematic review, it has been difficult to draw definitive conclusions as to the best drug to recommend to patients 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 randomised controlled clinical studies to assess the efficacy of drug interventions with relation to NSAIs and paracetamol.

When designing future studies, the following need to be considered:

- Clear inclusion and exclusion criteria should be set, taking into consideration factors which can effect patient's perception of pain, particularly gender.
- An a priori sample size calculation should be carried out.
- Adequate reporting of rescue analgesics taken by participants in each arm of the trial. We recommend the following:
    - Type of drug taken;
    - Dose of drug taken;
    - Time at which drug was taken.
- 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.

Chapter 8: Acknowledgements

We would like to thank Anne Littlewood (Trials Search Co-ordinator, Cochrane Oral Health Group) for developing the search strategy and Helen Worthington (Cochrane Oral Health Group) for her methodological and statistical support.

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

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- *Melissa Bernhardt*: provided details of random sequence generation and allocation concealment (Bernhardt 2001[66]).
- *Sarvraj Kohli*: provided details of random sequence generation, allocation concealment and blinding (Kohli 2011[76]).
- *Sara Yousefinia*: provided details of random sequence generation, allocation concealment and orthodontic intervention (Eslamian 2014[59]).

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Appendix 1: Characteristic of Studies (ordered by ID)

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:** (1) Scheduled to begin comprehensive orthodontic treatment,;(2) No prophylactic antibiotic coverage required; (3) No debilitating systemic diseases; (4) Currently not using antibiotics or analgesics; (5) No contraindication to the use of ibuprofen; and (6) A maximum age of 16 years and a minimum weight requirement of 88 pounds (the weight requirement was based on Food and Drug Administration–approved over-the-counter pediatric dosage labelling guidelines).
	Exclusion criteria: None outlined in the methods however later excluded participants who did not agree to participate, did not return completed questionnaire or those who took additional "rescue" medication.
	Orthodontic intervention: Separator placement.
	Patient Sampling:
	n=114 recruited and randomised;
	n=63 returned their completed questionnaire;
	n=22 excluded from analysis for taking additional medication (evenly distributed between the 3 groups);
	n=41 data analysed for (aged 9 yrs 3 months - 16 yrs 11 months);
	Gp 1 (n=13) 10 male:3 female, mean age 12.1 ± 1.6;
	Gp 2 (n=14) 4 male:10 female, mean age 13.5 ± 1.9;
	Gp 3 (n=14) 6 male:8 female, mean age12.8 ± 1.5.

Interventions	**NSAID versus placebo/pre-emptive versus post-emptive** **Ibuprofen (400mg) vs. control (lactose placebo)**; **Gp 1:** Ibuprofen 1hr before placement, followed by ibuprofen 6hrs after initial dose. **Gp 2:** Ibuprofen 1hr before placement, followed by placebo 6hrs after initial dose. **Gp 3:** Placebo 1hr before placement, followed by ibuprofen 6hrs after initial dose.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 10/bedtime (Primary outcome), 17/awakening, 24 hours and 2, 3 and 7 days (secondary outcome) after separator 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:** 22 participants excluded from analysis for taking additional medication. No harms reported.

	Data handling by review authors: The data presented for the analysis is based on Figure 1 showing mean pain scores (mean + SEM) for chewing. The SEM was used to calculate SD. Data from Gp 1 did not contribute to the analyses, Gp 2 and 3 data were used for the comparison of pre-emptive versus post-emptive analgesia. **Other information of note:** Wide variation in gender at baseline for Gp 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".* 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)	Low 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:** Appears to be adequate randomisation.
Allocation concealment (selection bias)	Low 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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	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)	High risk	73/114 drop-outs = 64% attrition (36% completion). High number of drop-outs, but equally distributed across the groups.
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.

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-December 2005 (23 months).

Participants	**Inclusion criteria:** (1) Age between 12 and 16 years; (2) No history of peptic ulceration, or renal, hepatic, or cardiac impairment; (3) No history of asthma requiring steroid inhalers or unstable asthma in the last year; (4) No history of adverse reactions to ibuprofen or paracetamol; and (5) Currently not using analgesics or antibiotics.
	Exclusion criteria: Not specified.
	Orthodontic intervention: Separator placement.
	Patient Sampling:
	n=208 selected;
	n=21 excluded;
	n=21 refused to participate;
	n=187 randomised (Gp 1 n=92; Gp 2 n=95);
	n=28 drop-outs/excluded from analysis (Lost to follow-up [not returning questionnaire]: Gp 1 n=6, Gp 2 n=3; Did not fulfil inclusion criteria Group 1 n=9, Gp 2 n=10);
	n=159 data analysed for;
	Gp 1 (n=77) male n=28: female n=49, mean age 13.7 $\pm$ 1.0;
	Gp 2 (n=82) male n=29: female n=53, mean age 13.8 $\pm$ 1.2.
	Age *p*=0.38 (independent-samples *t* test)
	Sex: *p*=1.00 (chi-square test for association) male 35.8%: female 64.2%.

Interventions	**NSAID versus paracetamol** **Ibuprofen (400mg; 2x200mg caplet) vs. paracetamol (1g; 2x500mg caplet)**; provided pre-emptively to separator placement, and again post-treatment. **Gp 1:** Ibuprofen 1hr before placement, followed by ibuprofen 6hrs after initial dose. **Gp 2:** Paracetamol 1hr before placement, followed by paracetamol 6hrs after initial dose.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 10/bedtime (primary outcome), 24 hours 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 reference paper by McAlinden et al, "s*ince 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 reports Group 1 as paracetamol arm of trial, and Group 2 as ibuprofen arm. In order to align with this systematic review's own protocol, 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 patients were analysed. An intention-to-treat analysis was carried out on the 18 patients 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.
Blinding of participants and personnel (performance bias)	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)	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)	Low risk	28/187 drop outs = 15% attrition (85% 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.

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:** 1) At least 18 years of age; 2) Presence of second molars and second bicuspids, since separating elastics had to be fixed on the first molars; 3) No clinical signs of gingival inflammation.
	Exclusion criteria: 1)Use of any medication that could interfere with results >2 weeks before the procedure; 2) Any of the following conditions, screened through a questionnaire: cardiopathies, nephropathies, hepatopathies and/or gastrointestinal disorders, diabetes, high cholesterol, blood vessel obstructions, allergy to anti-inflammatory drugs, intolerance to lactose, pregnancy.
	Orthodontic intervention: Separator placement.
	Patient Sampling:
	n=87 recruited and randomised;
	n=38 drop-out/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 analysed;
	Gp A (n=17) 4 male:13 female, mean age 24.64;
	Gp B (n=17) 4 male:13 female, mean age 22.64;
	Gp C (n=17) 5 male:12 female, mean age 22.47.

Interventions	**NSAID versus placebo** **Lumiracoxib (400mg) vs. placebo vs no treatment**; provided pre-emptively to separator placement. **Gp A:** Lumiracoxib 1hr before separator placement. **Gp B:** Placebo 1hr before separator placement. **Gp C:** No intervention.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 24 hours and 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 arm, group B as Lumiracoxib arm and group C as control arm. For the purposes of aligning with this systematic review's own protocol, 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:** Data for means and standard deviations were received 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 was not achieved.
Blinding of participants and personnel (performance bias)	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)	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)	High risk	36/87 drop-out = 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, complaint of pain over 50 based on the VAS in previous sessions, 6-8mm crowding, no use of analgesics during the study period, no history of renal or *river* disease or any other contraindication for the use of understudy medications. Comment: "*river disease*" spelling error present in paper.

	Exclusion criteria: Those not signing the consent form, used analgesics and anti-inflammatory drugs during the study, did not complete the questionnaire, did not use or improperly used benzocaine or ketoprofen chewing gums.
	Orthodontic intervention: Mid-treatment adjustments.
	Patient Sampling:
	n=30 recruited and randomised;
	n=4 drop-out/excluded from analysis;
	n=26 data analysed;
	Gp A (n=26) 12 male:14 female, mean age 18.07 ± 3.19;
	Gp B (n=26) 12 male:14 female, mean age 18.07 ± 3.19;
	Gp C (n=26) 12 male:14 female, mean age 18.07 ± 3.19.	

Interventions	**NSAID versus placebo/local anaesthetic versus placebo/NSAID versus local anaesthetic Ketoprofen chewing gum vs. benzocaine chewing gum vs. placebo chewing gum**; provided post-operatively following appliance adjustments. **Gp A:** Ketoprofen chewing gum every 8 hours for 3 days after treatment. **Gp B:** Benzocaine chewing gum every 8 hours for 3 days after treatment. **Gp C:** Placebo chewing gum every 8 hours for 3 days after treatment.	
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 24 hours and day 2 10am and 6pm, day 3 10am and 6pm and 7 days after appliance adjustment.	
Notes	**Conflict of interests/funding:** Not reported. **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 A has been allocated as the ketoprofen arm, group B as the benzocaine arm and group C as 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 as involving retie of an 0.016" or 0.018" Nickel Titanium archwire through correspondence with the author. 4-week washout period allowed between interventions.	
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 regarding how method of randomisation

		was carried out 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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	Low risk	**Quote:** "*Questionnaires were analysed by a statistician blinded to the group allocation of patients".* **Comment:** Adequate method of blinding.
Incomplete outcome data (attrition bias)	Low risk	4/30 drop-outs = 13.3% attrition (86.7% completion). However, the reason for drop-out is unclear.
Selective reporting (reporting bias)	Low risk	Unclear data presented in paper however clarification received from correspondence with the author.
Other bias	Low risk	Unclear reporting throughout paper however verified by correspondence with the author.

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, the patients had no systemic diseases and were not receiving analgesic therapy. They had moderate crowding (4-8 mm) according to Little's irregularity index. All patients 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 randomised and analysed: Gp 1 (n=10) female only, age data not reported; Gp 2 (n=10) female only, age data not reported; Gp 3 (n=10) female only, age data not reported; Gp 4 (n=10) female only, age data not reported; Gp 5 (n=10) female only, age data not reported.	
Interventions	**NSAID versus placebo** **Ibuprofen (400mg) vs. placebo vs chewing gum vs. soft viscoelastic bite wafer vs. hard viscoelastic bite wafer**; provided after initial archwire placement. **Gp 1:** Ibuprofen immediately after archwire placement and at 8-hour intervals for a week if pain persisted. **Gp 2:** Placebo immediately after archwire placement and at 8-hour intervals for a week if pain persisted. **Gp 3:** Gum chewed for 5mins immediately after archwire placement and at 8 hour intervals for a week if pain persisted. **Gp 4:** Soft bite wafer chewed or bit down on for 5minutes at 8-hour intervals for a week if pain persisted. **Gp 5:** Hard bite wafer chewed or bit down on for 5minutes at 8-hour intervals for a week if pain persisted.	
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, bedtime, 24 hours 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 Group 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 how method of allocation concealment was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	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 Gp 1 and Gp 2. Not possible to blind participants and personnel regarding allocation to Gp 3, 4 or 5.
Blinding of outcome assessment (detection bias)	Unknown risk	Inadequate information regarding method of blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	0/50 drop-outs = 0% attrition (100% completion).
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	High risk	Study carried out on female patients only, therefore subject to sampling bias and not necessarily generalisable to the population.

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 inch NiTi wire in at least in one arch.
	Exclusion criteria: Patients were not allowed to be currently taking any antibiotics or analgesics, they could have no allergy to NSAIDs and no oral pathology nor could they have had a tooth extracted at least 2 weeks before bonding.
	Orthodontic intervention: Initial archwire placement.
	Patient Sampling:
	n=45 recruited and randomised (23 F: 22 M; aged 15-22);
	n=0 loss to follow-up;
	n=45 data analysed;

	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	**NSAID versus paracetamol, NSAID versus Etoricoxib, NSAID versus placebo** **Paracetamol (500mg) vs. etoricoxib (60mg) vs. placebo**; provided 1 hour before initial archwire placement and post-operatively. **Gp 1:** Paracetamol 1 hour before and thrice daily for 3 days after archwire placement. **Gp 2:** Etoricoxib 1 hour before and once daily for 3 days after archwire placement. **Gp 3:** Placebo 1 hour before and thrice daily for 3 days after archwire placement.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, bedtime, 24 hours and 2nd day at night-time, 48 hours after initial archwire placement and 3rd day at night-time.
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 reports 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-time’s are not specified. 1st day bedtime has been assumed to be approximately 10hours, 2nd day night-time has been assumed to be approximately 31hrs and 3rd day night-time as approximately 53hrs.

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:** Appears to be adequate randomisation.
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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	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)	Low risk	0/45 drop-out = 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. **Design:** Parallel (3 arms). **Number of centres:** 2. **Study duration:** Not reported.
Participants	**Inclusion criteria:** (1) Started orthodontic treatment that required banding of posterior teeth and placement of two or more separators; (2) Able to swallow analgesic pills; (3) English speaking; (4) 9 to 17 years of age; (5) Minimum weight requirement of 88 pounds based on mg/kg paediatric dosage recommendations. **Exclusion criteria:** Current orthodontic or space maintenance appliances, if there was a contraindication to the use of acetaminophen or ibuprofen, if they were currently taking antibiotics or analgesics, had 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 drop-outs/excluded from analysis (Gp 1=4, Gp 2=2, Gp 3=3 all failed to return questionnaires); n=26 data analysed for: Gp 1 (n=7) male n=1: female n=6, mean age 12.7 $\pm$ 1.3; Gp 2 (n=10) male n=3: female n=7, mean age 13.0 $\pm$ 1.6; Gp 3 (n=9) male n=5: female n=4, mean age 12.6 $\pm$ 1.8.

Interventions	**NSAID versus placebo; NSAID versus Paracetamol; Paracetamol versus placebo.** **Ibuprofen (400mg) vs. paracetamol (650mg) vs. placebo (640mg Avicel)**; provided pre-emptively and post-treatment to separator placement. **Gp 1:** Ibuprofen 1hr before placement and 6hrs after initial dose. **Gp 2:** Paracetamol 1hr before placement and 6hrs after initial dose. **Gp 3:** Placebo 1hr before placement and 6hrs after initial dose.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded immediately before and after, 2, 6, bedtime, 24 hours 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 Gp 1 as placebo arm and Gp 3 as ibuprofen arm. For the purposes of aligning with this systematic review's own protocol, the figures for Gps 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**
Random sequence generation (selection bias)	Low risk	**Quote:** *"Computer generated random patient coding and group allocation was utilized".* **Comment:** Appears to be adequate randomisation.
Allocation concealment (selection bias)	Low risk	**Quote:** "*The random allocation assignments were concealed and inaccessible to the investigator."* **Comment:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	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)	High risk	9/35 drop-out = 25.7% attrition (74.3% 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.

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 were included. Periodontal tissues were in good health. No systemic disease that would compromise normal healing (e.g., diabetes) was present. No medications were taken at the time of the study. **Exclusion criteria:** None specified. **Orthodontic intervention:** Separator placement. **Patient Sampling:** n=80 randomised (Group 1 n=40; Group 2 n=40); n=10 drop-outs/excluded from analysis (Lost to follow-up: not returning questionnaire=7; did not require pain relief=3); n=70 data analysed for: Group 1 (n=35) male n=18: female n=17, mean age 23.8 ±10.3; Group 2 (n=35) male n=16: female n=19, mean age 25.2 ± 8.6. Age *p*=0.5. Sex: *p*=0.6.
Interventions	**Local anaesthetic wax versus placebo** **Benzocaine wax vs. placebo**; provided post-treatment for topical use, not applied until 24hours after visit. **Gp 1:** Orthodontic menthol wax, medicated with 20% benzocaine. **Gp 2:** Unmedicated orthodontic wax (without menthol).
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at baseline, 1, 17, 29, 41, 53 hours 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 does 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 hours after visit, therefore data from this study has not contributed to analyses in this systematic review. **Other information of note:** Much of the details in the paper relate 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 how method of randomisation was carried out 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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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 possess different tastes, but patients unlikely to recognise if active drug or not, or to discuss with other participants.
Blinding of outcome assessment (detection bias)	Unclear risk	**Quote:** "*Randomised double-blind prospective RCT".* **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)	Low risk	10/80 drop-out = 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:** (1) At least 13 years of age and not older than 20 years of age; (2) Beginning orthodontic treatment for the first time; (3) Reporting no contraindications or adverse reactions related to ibuprofen and piroxicam; (4) Currently not using any antibiotics; and (5) Meeting a minimum weight requirement of 88 pounds, as per Food and Drug Administration–approved-over-the-counter paediatric dosage labelling guidelines. In addition, patients were required to provide written informed consent for participation in the study.
	Exclusion criteria: None specified.
	Orthodontic intervention: Separator placement.
	Patient Sampling:
	n=90 randomised (Group 1 n=30; Group 2 n=30; Group 3 n=30);
	n=0 drop-out/excluded from analysis;
	n=90 analysed (45 males and 45 females);
	Group 1 (n= 30) male n=15: female n=15, mean age 14.7 $\pm$ 3.4;
	Group 2 (n=30) male n=15: female n=15, mean age 14.2 $\pm$ 2.8;
	Group 3 (n=30) male n=15: female n=15, mean age 15.1 $\pm$ 3.6.

Interventions	**NSAID versus placebo versus NSAID** **Ibuprofen (400mg) vs. piroxicam (20mg) vs. placebo**; provided 1 hour pre-emptively. **Gp 1:** Ibuprofen 1 hour before separator placement. **Gp 2:** Placebo 1 hour before separator placement. **Gp 3:** Piroxicam 1 hour before separator placement.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, bedtime, 24 hours 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. “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.

	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 how method of randomisation was carried out 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 how method of allocation concealment was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	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:** 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)	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)	Low risk	0/90 drop-outs =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. **Design:** Parallel (2 arms). **Number of centres:** 1. **Study duration:** Not reported.

Participants	**Inclusion criteria:** 1) Mobile patients, male and female aged between 18-40 were fitted with a brace; 2) Moderate or severe pain in the mouth region was measured using the 'visual analogue scale' as per the protocol; 3) At least 1 of the two signs of inflammation (oedema or hyperaemia) of a moderate intensity, or severe on a point scale from 0 to 3; 4) Written consent was obtained from the patient. **Exclusion criteria:** None specified. **Orthodontic intervention:** Initial archwire placement. **Patient Sampling:** n=120 patients selected and randomised; n=0 drop-outs/excluded from analysis n=120 data analysed for: Group 1 (n=60) gender and age data not reported; Group 2 (n=60) gender and age data not reported.	
Interventions	**NSAID versus NSAID** **Ketoprofen (160mg) vs. benzidamine chloride (22.5mg)**; mouthwash provided post-operatively. **Gp 1:** Ketoprofen 10ml in 100ml of water twice a day (after breakfast and the evening meal) for up to 7 days. **Gp 2:** Benzidamine chloride 15ml 1twice a day (after breakfast and the evening meal) for up to 7 days.	
Outcomes	**Primary outcome:** Pain score (Visual Analogue Scale (VAS)) - Recorded at baseline, day 1, 2, 3, 4, 5, 6, and 7 1 hour after breakfast and 1 hour after the evening meal. **Secondary outcome:** The seriousness of the following signs – oedea 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. The resolution of any signs of inflammation was deducted from the data produced regarding seriousness, flowing 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 measured, data has only been presented at 4 days. Therefore, data from this study has not been used for this systematic review. No information is provided relating to drop-outs, it has been assumed that all participants returned questionnaires and contributed to the final analysis. **Other information of note:** This paper has been translated from Italian with additional correspondence from the author.	
Risk of bias		
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 how method of randomisation was carried out 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 how method of allocation concealment was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	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)	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)	Low risk	0/120 drop-outs =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 was available.
Other bias	Low risk	No other sources of bias detected.

Minor 2009

Methods	**Setting:** University of Florida orthodontic clinic. **Design:** Parallel (3 arms). **Number of centres:** 1. **Study duration:** 37 months.
Participants	**Inclusion criteria:** (1) At least 13 and not older than 30 years of age; (2) Not pregnant; (3) Beginning orthodontic treatment for the first time; (4) Orthodontic treatment required the placement of at least 1 separator in each of the 4 quadrants; (5) No contraindications or adverse reactions to ibuprofen or almonds; and (6) written informed consent to participate. **Exclusion criteria:** None specified. **Orthodontic intervention:** Separator placement. **Patient Sampling:**

	n=51 enrolled;
	n=0 drop-outs/excluded from analysis;
	n=51 data analysed for:
	Gp A (n=16) male n=6: female n=10, mean age 17.6 +/-5.0;
	Gp B (n=17) male n=10: female n=7, mean age 14.9 +/-2.7;
	Gp C (n=18) male n=5: female n=13, mean age 16.4 +/-3.6.

Interventions	**NSAID versus placebo** **Ibuprofen (400mg) vs. placebo**; provided pre- and post-treatment to separator placement, or post-treatment, or both. **Gp A:** Ibuprofen 1hr before placement, 3hrs after and 7hrs after placement. **Gp B:** Placebo 1hr before placement, ibuprofen 3hrs and 7hrs after placement. **Gp C:** Placebo 1hr before placement, placebo 3hrs and 7hrs after placement.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at pre-treatment expectation of pain, 2, 6, 10/bedtime, 17/awakening, 24 hours 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 (Visual Analogue Scale (VAS)) [Not an outcome of this review]. Affective states (State and Trait Anxiety Inventory (STAI)) [Not an outcome of this review].
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 are presented - Table III labelled as chewing but the discussion states that the data for chewing was not included. Mean VAS data for 24 hours shows values of over 10cm, despite a 10cm VAS being used. Therefore, data for 24 hours has been excluded for the purposes of this review. For the purposes of this review, data from Gp B has not been used, data from Gp 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 how method of randomisation

		was carried out 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."* **Comment:** Inadequate information regarding how method of allocation was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	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 carried out therefore unable to make a judgement on appropriateness.
Blinding of outcome assessment (detection bias)	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 carried out therefore unable to make a judgement on appropriateness.
Incomplete outcome data (attrition bias)	Low risk	0/51 drop-outs=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 not recorded. 10cm VAS used but measurements show values of >10cm at 24 hours 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	<u>Patient Sampling:</u> **Inclusion criteria:** 1. Need separator placement to begin orthodontic treatment in the maxillary arch; 2. Aged 15 years or older; 3. Were informed and signed the written informed consent, 4. Not currently using antibiotics, analgesics, anti-inflammatory, anti-coagulative, diuretics, oral anti diabetics, lithium, cyclosporine, and methotrexate; 5. No need for antibiotic prophylaxis; 6. No chronic systemic disease or clotting disorders; 7. Not reporting contraindication for NSAIDs; 8. 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 randomised;
	n=16 drop-outs (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 analysed for:
	Gp 1 (n=76) male n=21: female n=55, mean age 22.1 ± 3.2;
	Gp 2 (n=76) male n=19: female n=57, mean age 21.7 ± 3.5;
	Gp 3 (n=89) male n=21: female n=68, mean age 21.2 ± 3.8.

Interventions	**NSAID versus NSAID; NSAID versus paracetamol** **Ibuprofen (400mg) vs. paracetamol (650mg) vs. meloxicam (7.5mg)**; provided pre-emptively to separator placement. **Gp 1:** Ibuprofen 1hr before separator placement. **Gp 2:** Paracetamol 1hr before separator placement. **Gp 3:** Meloxicam 1hr before separator placement.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at immediately, 2, 6, 24 and 48 hours 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, 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:** Appears to be adequate randomisation.
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 how method of allocation was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	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:** Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	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:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	High risk	80/321=25% drop-out (75% 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.

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:** All patients started orthodontic treatment that required separators, had no systemic or gastrointestinal diseases, had not taken analgesics or any other drugs currently, had no contraindication to the use of either acetaminophen or liquefied ibuprofen, their weight was above 40 kg, and their first molar were without decay or filling or periodontal problem. The last criterion

	was checked through clinical observation, probing, and panoramic radiographs. **Exclusion criteria:** None specified, however later stated they would exclude patients who had taken additional analgesics. **Orthodontic intervention:** Separator placement. **Patient Sampling:** n=101 randomised; n=12 drop-outs/excluded from analysis (Did not take drugs correctly=8; did not complete questionnaire=3); n=89 data analysed for: Gp 1 (n=29) male n=13: female n=16, mean age 15.6 +/- 4.17; Gp 2 (n=32) male n=14: female n=18, mean age 15.8 +/- 3.49; Gp 3 (n=28) male n=12: female n=16, mean age 15.3 +/-3.15.	
Interventions	**NSAID versus placebo; paracetamol versus placebo; NSAID versus paracetamol** **Ibuprofen (400mg) vs. paracetamol (650mg) vs. placebo**; provided pre-emptively to separator placement. **Gp 1:** Ibuprofen 1hr before separator placement and every 6 hours until 24 hours (5 doses). **Gp 2:** Paracetamol 1hr before separator placement and every 6 hours until 24 hours (5 doses). **Gp 3:** Placebo 1hr before separator placement and every 6 hours until 24 hours (5 doses).	
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at immediately, 2, 6, bedtime and 24 hours after separator placement.	
Notes	**Conflict of interests/funding:** Not reported. **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 placebo arm. Although referred to as acetaminophen, this group has been referred to as paracetamol for the purposes of this review. Gender data presented as a percentage, calculated as values for the purposes of this review. **Other information of note:** No baseline information provided about groups before drop-out. Mean age for Gp 2 differs throughout study. For the purposes of the review, the data from Table 1 has 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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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:** Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	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:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	12/101=12% drop-out (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; drop-outs; patient non-compliance. **Orthodontic intervention:** Initial archwire placement. **Patient Sampling:** n=56 randomised and analysed: Gp A (n=27); Gp B (n=29).

	Overall: female n=39 (69.9%): male n=17 (30.4%); age <15=21.4%: aged >15=78.6%.	
Interventions	**NSAID versus paracetamol** **Ibuprofen (600mg; 2x300mg p/day for 5 days) vs. paracetamol (2g; 4x500mg p/day for 7 days)** **Gp A:** Ibuprofen provided immediately post-treatment, daily oral dose thereafter. **Gp B:** Paracetamol provided immediately post-treatment, daily oral dose thereafter.	
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 24 hours 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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	Low risk	**Quote:** *"Drug distribution was done with a single-blind method; single investigators were unaware of the drug".* **Comment:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	0/56=0% drop-out (100% completion).

Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	High risk	Large gender and age variation at baseline, more females in all groups and majority of participants aged >15 years indicating sampling bias.

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; oral membrane lesions from 2-6mm 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 fixed or removable appliance fit. **Patient Sampling:** n=60 selected, randomised and analysed: (<14 years n=30; >14 years n=30; male n=30; female n=30) Gp 1 (n=20) male n=10: female n=101, mean age 14 ± 2; Gp 2 (n=20) male n=10: female n=10, mean age 14 ± 2. Gp 3 (n=20) male=10: female=10, mean age 14 ± 2.
Interventions	**NSAID versus placebo** **Flurbiprofen (10ml 0.25% mouthwash; 3 times daily for 7 days) vs. placebo (10ml mouthwash; 2 minute rinse duration; 3 times daily for 7 days) vs. control**; Gp 1: Flurbiprofen; provided post-operatively to separator placement. Gp 2: Placebo; provided post-operatively to separator placement. Gp 3: Control, no treatment.
Outcomes	Pain score (Visual Analogue Scale (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 has not been used for this systematic review. **Other information of note:** Original paper translated from Italian to English. All patients had pre-existing ulceration and had started orthodontic treatment within the last month.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
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:** Appears to be adequate randomisation.
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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	**Quote:** "*Single blinding: patients were not aware of the treatment received".* **Comment:** Adequate blinding of participants however no randomisation of personnel.
Blinding of outcome assessment (detection bias)	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:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	0/50 drop-outs = 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.

Polat March 2005

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 pediatric dosage labeling 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 randomised; n=30 drop-outs/excluded from analysis (n=22 did not return questionnaires; n=8 over 30 years of age); n=120 data analysed for: Gp 1 (n=20) male n=10: female n=10, mean age 15.0 ± 3.7; Gp 2 (n=20) male n=15: female n=5, mean age 15.0 ± 2.8; Gp 3 (n=20) male n=13: female n=7, mean age 15.0 ± 4.5; Gp 4 (n=20) male n=15: female n=5, mean age 16.0 ± 4.6; Gp 5 (n=20) male n=13: female n=7, mean age 15.0 ± 2.9; Gp 6 (n=20) male n=10: female n=10, mean age 16.0 ± 6.1.
Interventions	**NSAID versus placebo; NSAID versus NSAID; NSAID versus paracetamol; NSAID versus aspirin; NSAID versus placebo Aspirin (300mg) vs. ibuprofen (600mg) vs. flurbiprofen (100mg) vs. paracetamol (500mg) vs. naproxen sodium (550mg) vs. placebo (lactose)**; pre-emptively and post-treatment following archwire placement. **Gp 1:** Aspirin 1 hr before, and 6 hrs after bonding appointment. **Gp 2:** Ibuprofen 1 hr before, and 6 hrs after bonding appointment. **Gp 3:** Flurbiprofen 1 hr before, and 6 hrs after bonding appointment. **Gp 4:** Paracetamol 1 hr before, and 6 hrs after bonding appointment **Gp 5:** Naproxen sodium; provided 1 hr pre-operatively. **Gp 6:** Placebo; provided 1 hr pre-operatively.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, bedtime, 24 hours 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:** Not reported. “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)	Low risk	**Quote:** "*All tablets were identical in color, and the patient and research assistant were both blind*". **Comment:** Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	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 is blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	22/150 drop-outs = 15% attrition (85% 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.

Polat September 2005

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 pediatric dosage labeling 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 randomised;
	n=0 drop-outs/excluded from analysis;
	n=60 data analysed for:
	Gp 1 (n=20) male n=14: female n=6, mean age 15.0 +/- 2.2;
	Gp 2 (n=20) male n=13: female n=7, mean age 17.0 +/- 7.0;
	Gp 3 (n=20) male n=10: female n=10, mean age 16.0 +/-6.1.	

Interventions	**NSAID versus placebo; NSAID versus NSAID** **Naproxen sodium (550mg; 1 dose) vs. ibuprofen (400mg; 1 dose) vs. placebo (lactose; 1 dose)**; pre-emptively before archwire placement. **Gp 1:** Naproxen sodium; provided 1 hr pre-operatively. **Gp 2:** Ibuprofen; provided 1 hr pre-operatively. **Gp 3:** Placebo; provided 1 hr pre-operatively.	
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, bedtime, 24 hours and 2, 3 and 7 days 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:** Not reported. “None of them had taken additional medication”. **Data handling by review authors:** Study reports 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 review'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 is 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)	Low risk	**Quote:** "*The patient and research assistant were blinded to each subject's experimental group*". **Comment:** Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	**Quote:** "*The patient and research assistant were blinded to each subject's experimental group*". **Comment:** Inadequate information regarding assessment, unclear if assessor is blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	0/60 drop-outs = 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:** (1) Scheduled to begin comprehensive orthodontic treatment (banding/bonding of at least 10 teeth in 1 arch and archwire placement in at least 1 arch); (2) Extractions, if required, performed at least 2 weeks before appliance and archwire placement; (3) Healthy with no significant medical findings; (4) No prophylactic antibiotic coverage required; (5) Currently not taking antibiotics or analgesics; (6) No contraindications to the use of acetaminophen or ibuprofen; (7) No lactose intolerance; (8) Minimum age of 12 years and minimum weight of 88 lbs (as required by the FDA for the use of over-the-counter pediatric dosage label guidelines); and (9) 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 analysed for: Group 1 (n=21) male n=9: female n=12, age data not reported;

	Group 2 (n=19) male n=12: female n=7, age data not reported; Group 3 (n=20) male n=10: female n=10, age data not reported.
Interventions	**NSAID versus placebo; NSAID versus paracetamol; Paracetamol versus placebo** **Paracetamol (600mg) vs. ibuprofen (400mg) vs. placebo (2 tablets)**; **Gp 1:** Paracetamol; immediately after each VAS time point, starting 3hrs pre-operatively. **Gp 2:** Ibuprofen; immediately after each VAS time point, starting 3hrs pre-operatively. **Gp 3:** Placebo; immediately after each VAS time point, starting 3hrs pre-operatively.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 3, 7, 19, 24, 31 and 48 hours 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:** Not reported. "No patients took additional analgesics during the study period". **Data handling by review authors:** Although referred to as acetaminophen, 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.
Blinding of participants and personnel (performance bias)	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:** Appears to be adequate blinding.

Blinding of outcome assessment (detection bias)	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:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	6/66 drop-out = 9.1% attrition (90.9% competition).
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:** (1) Was scheduled to begin comprehensive orthodontic treatment, (2) Required no prophylactic antibiotic coverage, (3) Had no debilitating systemic diseases, (4) was not currently using antibiotics or analgesics, (5) Had no contraindication to the use of ibuprofen, and (6) Had a maximum age of 16 years and a minimum weight of 88 pounds. This weight requirement was based on FDA-approved over-the-counter pediatric dosage labeling guidelines.
	Exclusion criteria: None specified.
	Orthodontic intervention: Separator placement.
	Patient Sampling:
	n=115 selected;
	n=4 refused to participate;
	n=111 randomised;
	n=52 drop-out/lost to follow-up (did not receive separators at their next appointment=28, did not take medications and return questionnaires=3);
	n=63 data analysed (male=15: female=38);
	Gp A (n=22) male n=10: female n=12, mean age 13.4 $\pm$ 1.7;
	Gp B (n=19) male n=6: female n=13, mean age 13.3 $\pm$ 1.4;
	Gp C (n=22) male n=9: female n=13, mean age 13.1 $\pm$ 1.8.

Interventions	**Ibuprofen (400mg) pre-emptive vs. ibuprofen (400mg) post-treatment vs. placebo (lactose)**; provided pre-emptively to separator placement, or post-treatment. **Gp A:** Ibuprofen 1 hour before separator placement, placebo immediately after appointment. **Gp B:** Placebo 1 hour before separator placement, ibuprofen immediately after appointment.

	Gp C: Placebo 1 hour before separator placement, placebo immediately after appointment.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at 2, 6, 24 hours 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 requires in 10 patients – n=4/18% Gp A, n=6/32% Gp B. **Data handling by review authors:** The data presented for the analysis is based on Figure 1 showing mean pain scores (mean + SEM) for chewing. The SEM was used to calculate SD. Data from Gp C did not contribute to the analyses, Gp A and B data were used for the comparison of pre-emptive versus post-emptive analgesia. **Other information of note:** Only pain during chewing data is reflected in this systematic review. No baseline information has been 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)	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: Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	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:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	High risk	52/111 drop-outs = 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.

Tuncer 2014

Methods	**Setting:** Unspecified location, Turkey. **Design:** Parallel (3 arms). **Number of centres:** Not reported. **Study duration:** Not reported.

Participants	**Inclusion criteria:** 1. No prophylactic antibiotic coverage required, 2. No history of systemic diseases or allergies, 3. No current use of antibiotics or analgesics, 4. No contraindication to the use of NSAID, 5. No teeth extraction at least 4 weeks before bonding, 6. No history of orthodontic treatment, 7. Not being in the menstrual period for female patients and 8. Minimal crowding of maximum 7 mm that can be treated without extractions.
	Exclusion criteria: Patients with open bites; also have excluded participants who had additional doses of analgesic although not stated in the exclusion criteria.
	Orthodontic intervention: Initial archwire placement.
	Patient Sampling:
	n=60 selected;
	n=12 excluded/refused to participate (reasons not reported);
	n=48 randomised;
	n=3 drop-out/lost to follow-up (Group 1=2 additional dose consumption, Group 2=0, Group 3=1 lost to follow-up).
	n=45 data analysed (male=14: female=31);
	Group 1 (n=15) male n=17: female n=8, mean age 114.66 +/-2.06;
	Group 2 (n=15) male n=4: female n=11, mean age 14.36 +/-1.91;
	Group 3 (n=15) male n=3: female n=12, mean age 14.5 +/-2.0.

Interventions	**NSAID versus placebo; NSAID versus Paracetamol; Paracetamol versus placebo**

	Ibuprofen (400mg) vs. paracetamol (500mg) vs. placebo (lactose); provided pre-emptively and post-treatment following archwire placement. **Gp 1:** Ibuprofen 1 hour before archwire placement, and 6 hours after. **Gp 2:** Paracetamol 1 hour before archwire placement, and 6 hours after. **Gp 3:** Placebo 1 hour before archwire placement, and 6 hours after.
Outcomes	Pain score (Visual Analogue Scale (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 (PGE2) levels in the gingival crevicular fluid (GCF) 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. **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".* **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)	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:** Appears to be adequate blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	**Quote:** "*Prospective, randomized, double-blind, placebo-controlled study*". **Comment:** Inadequate information regarding blinding to make a judgement on appropriateness.
Incomplete outcome data (attrition bias)	Low risk	3/46 drop-out = 6% attrition (94% completion).
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	Low risk	Large gender variation at baseline, more males in Gp A, more females in Gp B and C indicating sampling 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:** (1) patients aged over 10 yrs; (2) patients who were able to comprehend and complete the study; (3) patients who consented to the research procedures and signed an informed consent; and (4) minors with permission from a parent or legal guardian. **Exclusion criteria:** (1) they had undergone previous orthodontic treatment; (2) they had recently experienced a toothache; (3) they were diagnosed concurrently as having infectious diseases and/or systemic diseases; (4) they had used analgesics within 3 days prior to orthodontic treatment or exhibited a contraindication to NSAIDs; (5) they 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); (6) their pain threshold was less than 3 sec or greater than 60 sec; or (7) their endurance time was greater than 5 min according to the cold pressor test (CPT; Johnson and Petrie, 1997). **Orthodontic intervention:** Initial archwire placement. **Patient Sampling:** n=502 assessed for eligibility; n=52 excluded (14 did not meet criteria, 33 declined to participate, 5 other reasons);

	n=450 randomised: n=21 drop-out/lost to follow-up (7 did not wish to complete follow-up questionnaire (Gp 1=3, Gp 2=1, Gp 3=3); 7 withdrew due to discomfort of orthodontic treatment (Gp 1=2, Gp 2=2, Gp 3=3); 4 lost questionnaires (Gp 1=1, Gp 2=1, Gp 3=2); 2 felt they had not received treatment (Gp 1=1, Gp 2=1; 1 unknown Gp 3); n=429: Gp 1 (n=143) male n=36.67%: female n=63.33%, mean age 16.57 ± 5.0; Gp 2 (n=145) male n=25.33%: female n=74.67%, mean age 17.68 ± 5.53; Gp 3 (n=141) male n=40.67%: female n=59.33%, mean age 16.27 ± 5.02.	
Interventions	**NSAID versus placebo** **Cognitive Behavioural Therapy vs. Ibuprofen (300mg) vs. Control (no treatment)**; **Gp 1:** Cognitive Behavioural Therapy; Immediately after archwire placement, structured phone procedure at day 8, 9, 10, 14 and 30. **Gp 2:** Ibuprofen 6hours, 12hours and 24hours after initial archwire placement. **Gp 3:** Placebo; routine diet and hygiene. Calls on day 8, 9,10, 14 and 30 after archwire placement.	
Outcomes	**Primary Outcome:** Pain score (Visual Analogue Scale (VAS)) - Recorded at 1, 2, 3, 7, 14 and 30 days after initial archwire placement. **Secondary Outcome:** Life quality 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 are prior to drop-out, no data available for age after drop-out. Study does not allocate intervention to specific group labels. For the purposes of this systematic review, Gp 1 has been allocated as the CBT arm, Gp 2 as the ibuprofen arm and group 3 as the placebo arm. Data from Gp 1 did not contribute to the analyses, Gp 2 and 3 data were used for the comparison of pharmacological interventions only. 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:** Appears to be adequate randomisation.
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:** Appears to be adequate allocation concealment.
Blinding of participants and personnel (performance bias)	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)	Low risk	**Quote***: "The outcome assessors and statisticians were blinded to the allocation.*" **Comment:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	21/450 drop-outs = 4.67% attrition (95.33% completion)
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately.
Other bias	High risk	Large gender variation in Gp 2, could have resulted in sampling bias.

Yassaei 2012

Methods	**Setting:** Shahid Sadoughi University, Iran. **Design:** Parallel (2 arms). **Number of centres:** 1. **Study duration:** Not reported.
Participants	**Inclusion criteria:** (1) female patients; (2) age 14-19 years; (3) at least 2 months passed from first archwire placement (in first or second stage of comprehensive orthodontic treatment but no first archwire); (4) upper and lower first premolar extraction cases with bialveolar protrusion or crowding; (5) their pain intensity between 40 and 100 mm (VAS); (6) whom signed the written informed consent to participate; (7) no contraindications to the use of acetaminophen or calcium such as ventricular fibrillation, renal calculi, hypopara-thyroidism and calcium supplement intake. **Exclusion criteria:** None specified. **Orthodontic intervention:** Initial archwire placement. **Patient Sampling:** n=40 randomised (although not clear): Gp 1 (n=19) male n=0: female n=19, mean age 17.43 ± 1.69; Gp 2 (n=21) male n=0: female n=21, mean age 16.42 ± 1.74.

Interventions	**Paracetamol versus calcium** **Paracetamol (325mg) vs. Calcium (500mg)**; **Gp 1:** Paracetamol; one tablet nightly until 60 tablets taken. **Gp 2:** Calcium; one tablet nightly until 60 tablets taken.
Outcomes	Pain score (Visual Analogue Scale (VAS)) - Recorded at pre-treatment and 4 days after procedure. Pain and anxiety measurements on HAD scale if pain intensity on VAS was greater than 40mm. 2, 6, 24 hours and 2, 3 and 7 days after separator or initial archwire placement.
Notes	**Conflict of interests/funding:** None reported. **Adverse events/Harm:** Not discussed. **Data handling by review authors:** Study does not allocate intervention to specific group labels. For the purposes of this systematic review, Gp 1 has been allocated as the paracetamol arm and Gp 2 as the calcium arm. Time points measured in this study were pre-treatment and 4 days later. Therefore, data from this study has not been used for this systematic review. No information is provided relating to drop-outs, it has been assumed that all participants returned questionnaires and contributed to the final analysis. **Other information of note:** Although referred to as acetaminophen, this group has been referred to as paracetamol for the purposes of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "*On the basis of a systematic randomised trial, patients were prescribed acetaminophen (325mg) or calcium forte (500mg)."* **Comment:** Inadequate information regarding how randomisation was carried out therefore unable to make a judgement on appropriateness.
Allocation concealment (selection bias)	Unclear risk	**Quote:** "*On the basis of a systematic randomised trial, patients were prescribed acetaminophen (325mg) or calcium forte (500mg)."* **Comment:** Inadequate information regarding how allocation was carried out therefore unable to make a judgement on appropriateness.
Blinding of participants and personnel (performance bias)	Unclear risk	**Quote:** "*The patients and the one who did the VAS measurements were totally blind to the randomization*." **Comment:** Appears to be adequate blinding however does not specify exactly how blinding of participants was achieved.

Blinding of outcome assessment (detection bias)	Low risk	**Quote:** "*The patients and the one who did the VAS measurements were totally blind to the randomization*." **Comment:** Appears to be adequate blinding.
Incomplete outcome data (attrition bias)	Low risk	0/40 drop-out = 0% attrition (100% completion).
Selective reporting (reporting bias)	Unclear risk	Unclear outcome assessment and time points.
Other bias	High risk	Only carried out in females but made generalisable to all patients therefore potential sampling bias. Unclear methodology, not repeatable.

Appendix 2: Characteristic of excluded studies

Study	Reason for exclusion
Abtahi 2006	Insufficient information to allow inclusion of data.
Angelopoulou 2013	Systematic Review.
Arantes 2009	Insufficient information to allow inclusion of data.
Ashley 2016	Systematic Review.
Bird 2007	Insufficient information to allow inclusion of data.
Cherubini 2003	Insufficient information in the abstract record to allow inclusion.
Eslamian 2016	Insufficient information in the abstract record to allow inclusion.
Ireland 2016	Not randomised for specific analgesics - potential for crossover and confounding of analgesic effect between groups.
Moradinejad 2014	Insufficient information in the abstract record to allow inclusion.
Murdock 2010	Not randomised for specific analgesics - potential for crossover and confounding of analgesic effect between groups.
Ngan 1994	Insufficient information to allow inclusion of data.
Ogata 1999	Insufficient information in the abstract record to allow inclusion.
Parks 2001	Insufficient information in the abstract record to allow inclusion.
Patel 2011	Insufficient information to allow inclusion of data.
Rooke 2012	Insufficient information in the abstract record to allow inclusion.
Sudhakar 2014	Insufficient information to allow inclusion of data.
Xiaoting 2010	Systematic Review.
Young 2006	Insufficient information to allow inclusion of data.

Appendix 3: MEDLINE (OVID) search strategy

#1 Explode ORTHODONTICS(ME)

#2 orthodontic*

#3 #1 OR#2

#4 PAIN (ME)

#5 FACIAL PAIN (ME)

#6 HEADACHE (ME)

#7 NEURALGIA (ME)

#8 EARACHE (ME)

#9 TOOTHACHE (ME)

#10 PAIN-MEASUREMENT (ME)

#11 pain* OR discomfort OR headache* OR migraine* OR neuralgi* OR earache* OR toothache Or odontalgi* OR (pain near (manag* OR relief OR reliev OR control*))

#12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 Explode ANALGESICS (ME)

#14 analgesi*

#15 ANESTHETICS-LOCAL (ME)

#16 ((local OR topical) AND (anaesthetic* OR analgesi*)) OR ((local OR topical) AND (anesthetic* OR analgesi*))

#17 ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL (ME)

#18 “Nonsteroidal Anti-Inflammatory Agent*” OR “Anti Inflammatory Agent*” OR “Nonsteroidal Antiinflammatory Agent*” OR “Non Steroidal Antiinflammatory Agent” OR “Nonsteroidal Analgesic*” Or “Anti-Inflammatory” OR “Asprin-Like Agent*” or NSAID*

#19 opioid

#20 aspirin

#21 paracetamol

#22 acetaminophen

#23 medication*

#24 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 #25 #3 AND #12 AND #24

Appendix 4: Title and Abstract Screening

	Authors	NOT an RCT or CCT?			NOT a review with relevant references?			NOT 1^0 to do with pain relief during ortho Rx			Studies where pain intensity / relief or intensity are measured			Notes	EXCLUDE		
		Yes	No	?	Yes	No	?	Yes	No	?	Yes	No	?		Yes	No	?
1.																	
2.																	
3.																	
4.																	
5.																	
6.																	
7.																	
8.																	
9.																	
10.																	

RCT/CCT – human; prospective; 2 or more interventions; random/quasi- random/haphazard allocation.
NOT randomly selected; allocation for clinical reasons; participants selected own intervention; intervention & control groups different e.g. sick vs. healthy, practice vs. hospital; matched unless matched **prior** to randomisation

Appendix 5: Study Eligibility Form

Factors	Assessment	Comments
TYPE OF STUDY		
1. Is the study described as randomized?	Yes ↓ Exclude Unclear ↓ No ↓	
PARTICIPANTS		
2. Were the participants diagnosed as having pain?	Yes ↓ Exclude Unclear ↓ No ↓	
INTERVENTIONS		
3. Did the study contain at least two groups receiving different route/dose/form of pharmacological intervention?	Yes ↓ Exclude Unclear ↓ No ↓	
4. Was the difference in pain the only planned difference between the groups?	Yes ↓ Exclude Unclear ↓ No ↓	
OUTCOMES		
5. Did the study report pain outcomes?	Yes ↓ Exclude Unclear ↓ No ↓	

Appendix 6: Data Extraction Form

Study details

*First Author _____ *Year of publication _____

Number of trials included in this paper _____

If more than one, complete separate extraction forms for each and add letters A, B, C etc. to the paper name

If other papers report further results of this trial, incorporate them onto this form and note what has been done here e.g. time points, outcomes.

_____

_____

_____

Method

Setting: Location of trial centre(s)
Source of participants: Comment
Method of recruitment: Comment
Design: Comment
Study Duration: (Date until Date) (number of months)
Maximum duration of follow-up: (number of months)
Follow-up timepoints reported: Comment
"Detail how measurements were collected"

Details of Comparisons	Tick if YES
Analgesic versus Placebo	_____
Analgesic versus No treatment	_____
Analgesic versus Active treatment	_____
Analgesic versus Same analgesic, different dose	_____
Local anaesthetic versus Placebo	_____
Other notes on comparisons	_____

Participants

Selected n=x
Refused to participate n=x
Excluded n=x
Randomised n=x

Inclusion criteria: (quote/comment)
Exclusion criteria: (quote/comment)
Intention to treat analysis: (quote/comment)

Details of the interventions

	Group 1	Group 2	Group 3	Overall
Group Name (for trial ID)				
Group randomised)	**Yes / No**	**Yes / No**	**Yes / No**	**Yes / No**
Drug / Placebo or No Treatment				
Route & Dose or description of Placebo				
Time of administration of drug / placebo				
Number recruited				
Number of dropouts				

Characteristics of participants

	Group 1	Group 2	Group 3	Overall/Total
Age				
Sex				
Ethnicity				

Outcomes

Primary: _____

Secondary: _____

Notes

Conflict of interests/funding: Quote/Comment

Adverse events/Harm: Quote/Comment

Risk of bias assessment

Please **CIRCLE / HIGHLIGHT** response as appropriate

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High/Low/ Unclear risk	Comment: Quote: "*place corresponding quote here*"
Allocation concealment (selection bias)	High/Low/ Unclear risk	Comment: Quote: "*place corresponding quote here*"
Blinding of participants and personnel (performance bias)	High/Low/ Unclear risk	Comment: Quote: "*place corresponding quote here*"
Blinding of outcome assessment (detection bias)	High/Low/ Unclear risk	Comment: Quote: "*place corresponding quote here*"
Incomplete outcome data (attrition bias)	High/Low/ Unclear risk	Comment:x/x drop outs = x% attrition (x% completion)
Selective reporting (reporting bias)	High/Low/ Unclear risk	Comment: Quote: "*place corresponding quote here*"
Other bias	High/Low/ Unclear risk	Comment: [If nothing else, state "No obvious sources of bias."]

Results

Chewing VAS (score/index)

Results at each time point														
Time point	**2hrs**		**6hrs**		**Bed**		**24hrs**		**2d**		**3d**		**7d**	
CHEWING		SD		SD		SD		SD		SD		SD		SD
Gp 1 Drug name/placebo														
Gp 2 Drug name/placebo														
Gp 3 Drug name/placebo														

Biting VAS (score/index)

Results at each time point														
Time point	**2hrs**		**6hrs**		**Bed**		**24hrs**		**2d**		**3d**		**7d**	
CHEWING		SD		SD		SD		SD		SD		SD		SD
Gp 1 Drug name/placebo														
Gp 2 Drug name/placebo														
Gp 3 Drug name/placebo														

Verbal Descriptive Score

	Results at each time point			
Time point				
Gp 1 Drug name/placebo				
Gp 2 Drug name/placebo				
Gp 3 Drug name/placebo				

Duration of pain

	Time (days/hours/minutes)
Gp 1 Drug name/placebo	
Gp 2 Drug name/placebo	
Gp 3 Drug name/placebo	

Rescue Medication

	Dose required			
Time point				
Gp 1 Drug name/placebo				
Gp 2 Drug name/placebo				
Gp 3 Drug name/placebo				

Comments