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Single dose oral ibuprofen for acute postoperative pain in adults (Review)

Derry CJ, Derry S, Moore RA, McQuay HJ

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[Intervention Review]

Single dose oral ibuprofen for acute postoperative pain in adults

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ABSTRACT

Background

This review updates a 1999 Cochrane review showing that ibuprofen at various doses was effective in postoperative pain in single dose studies designed to demonstrate analgesic efficacy. New studies have since been published. Ibuprofen is one of the most widely used non-steroidal anti-inflammatory (NSAID) analgesics both by prescription and as an over-the-counter medicine. Ibuprofen is used for acute and chronic painful conditions.

Objectives

To assess analgesic efficacy of ibuprofen in single oral doses for moderate and severe postoperative pain in adults.

Search methods

We searched Cochrane CENTRAL, MEDLINE, EMBASE and the Oxford Pain Relief Database for studies to May 2009.

Selection criteria

Randomised, double blind, placebo-controlled trials of single dose orally administered ibuprofen (any formulation) in adults with moderate to severe acute postoperative pain.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Pain relief or pain intensity data were extracted and converted into the dichotomous outcome of number of participants with at least 50% pain relief over 4 to 6 hours, from which relative risk and number-needed-to-treat-to-benefit (NNT) were calculated. Numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, were sought as additional measures of efficacy. Information on adverse events and withdrawals were collected.

Main results

Seventy-two studies compared ibuprofen and placebo (9186 participants). Studies were predominantly of high reporting quality, and the bulk of the information concerned ibuprofen 200 mg and 400 mg. For at least 50% pain relief compared with placebo the NNT for ibuprofen 200 mg (2690 participants) was 2.7 (2.5 to 3.0) and for ibuprofen 400 mg (6475 participants) it was 2.5 (2.4 to 2.6). The proportion with at least 50% pain relief was 46% with 200 mg and 54% with 400 mg. Remedication within 6 hours was less frequent with higher doses, with 48% remedicating with 200 mg and 42% with 400 mg. The median time to remedication was 4.7 hours with 200 mg and 5.4 hours with 400 mg. Sensitivity analysis indicated that pain model and ibuprofen formulation may both affect the result, with dental impaction models and soluble ibuprofen salts producing better efficacy estimates. Adverse events were uncommon, and not different from placebo.

Authors' conclusions

The very substantial amount of high quality evidence demonstrates that ibuprofen is an effective analgesic in treating postoperative pain. NNTs for 200 mg and 400 mg ibuprofen did not change significantly from the previous review even when a substantial amount of new information was added. New information is provided on remedication.

PLAIN LANGUAGE SUMMARY

A single dose of ibuprofen administered orally to treat acute postoperative pain in adults

Ibuprofen at 200 mg and 400 mg produces a high level of pain relief in about half of those with moderate or severe acute postoperative pain. This is a good result compared with most other analgesics tested in a very well researched model of pain used for demonstrating that drugs can actually produce pain relief. There were no more adverse events than with placebo.

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews on 'Single dose oral ibuprofen and diclofenac for postoperative pain' (Collins 1999). In this update it refers to ibuprofen only, and the title now states that the review is limited to adults. An updated review of single dose oral diclofenac in acute postoperative pain in adults has also been published (Derry P 2009).

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care. This is one of a series of reviews whose aim is to present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level.

Recently published reviews include paracetamol (Toms 2008), celecoxib (Derry 2008), naproxen (Derry C 2009) and parecoxib (Lloyd 2009).

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants is small, allowing no reliable conclusions to be drawn about safety. To show that the analgesic is working it is necessary to use placebo (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is hence important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following 4 to 6 hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over 4 to 6 hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first 6 hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Clinicians prescribe non-steroidal anti-inflammatory drugs (NSAIDs) on a routine basis for a range of mild-to-moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Since NSAIDs do not depress respiration and do not impair gastro-intestinal motility as do opioids (BNF 2002) they are clinically useful for treating pain after minor surgery and day surgery, and have an opiate-sparing effect after more major surgery (Grahame-Smith 2002).

Ibuprofen was developed in the 1960s and is used extensively throughout the world for relief of pain and inflammation in both acute and chronic conditions. It is available over the counter in most countries, usually as 200 mg tablets, with 1200 mg as the recommended maximum daily dose for adults. Under medical supervision, up to 3200 mg daily may be taken, divided into three doses. The lysine salt of ibuprofen is more soluble in water, with some theoretical advantage for faster onset after oral administration, and with the possibility that it could be used intravenously. Intravenous ibuprofen lysine has been used for closure of patent ductus arteriosis in newborns (Aranda 2006). Topical formulations are also available over the counter, and are dealt with in other separate reviews.

In UK primary care in 2007 there were 4.5 million prescriptions for ibuprofen, most commonly for 400 mg tablets (2.6 million), but only 6800 for ibuprofen lysine (PACT 2007). These numbers do not include over the counter sales, which are considerable, with over seven million packs sold annually in the UK in 2000, about 46,000 kg by weight (Sheen 2002).

A major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site (because of the inhibition of platelet aggregation) (Forrest 2002) and from the upper gastrointestinal tract, (especially in patients stressed by surgery, the elderly, frail, or dehydrated). Other potentially serious adverse events include acute liver injury, acute renal injury, heart failure, and adverse reproductive outcomes (Hernandez-Diaz 2001). However, such complications are more likely to occur with chronic use and NSAIDs generally present fewer risks if used in the short term, as in the treatment of postoperative pain (Rapoport 1999).

The previous review included 35 studies in 34 reports with 3591 participants. Ibuprofen was shown to be an effective analgesic at 200 mg and 400 mg, with numbers-needed-to-treat-to-benefit (NNTs) for at least 50% pain relief over 4 to 6 hours of 3.3 (95% confidence interval (CI) 2.8 to 4.0) and 2.7 (2.5 to 3.0) respectively. Adverse events were generally mild and transient and did not differ

from placebo. A number of new studies are now available. The increased numbers of studies and participants gives more robust estimates of outcomes, and permits more detailed analysis of subgroups. This review has also looked at use of rescue medication as an additional measure of efficacy.

OBJECTIVES

To evaluate the analgesic efficacy and safety of oral ibuprofen in the treatment of acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, using criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005).

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they were full publications of double blind trials of a single dose oral ibuprofen against placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Multiple dose studies were included if appropriate data from the first dose were available, and cross-over studies were included provided that data from the first arm were presented separately.

Studies were excluded if they were:

- posters or abstracts not followed up by full publication;
- reports of trials concerned with pain other than postoperative pain (including experimental pain);
- studies using healthy volunteers;
- studies where pain relief was assessed by clinicians, nurses or carers (i.e. not patient-reported);
- studies of less than 4 hours' duration or which failed to present data over 4 to 6 hours post-dose.

Types of participants

Studies of adult participants (15 years old or above) with established moderate to severe postoperative pain were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was assumed when the VAS score was greater than 30 mm (Collins 1997). Studies of participants with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp). Studies investigating participants with pain due to uterine cramps alone were excluded.

Types of interventions

Orally administered ibuprofen with matched placebo administered as a single oral dose for post-operative pain.

Types of outcome measures

Data collected included the following.

- characteristics of participants;
- pain model;
- patient-reported pain at baseline (physician, nurse, or carer reported pain will not be included in the analysis);
- patient-reported pain relief and/or pain intensity expressed hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours;
- patient-reported global assessment of treatment (PGE), using a standard five-point scale;
- number of participants using rescue medication, and the time of assessment;
- time to use of rescue medication;
- withdrawals - all cause, adverse event;
- adverse events - participants experiencing one or more, and any serious adverse event, and the time of assessment.

Search methods for identification of studies

For the earlier review the following electronic databases were searched using a sensitive search strategy:

- *The Cochrane Library* (August 1996);
- The Specialised Register of the Cochrane Pain, Palliative and Supportive Care group (December 1996);
- MEDLINE (1966 to December 1996);
- EMBASE (1980 to January 1997);
- Biological Abstracts (Jan 1985 to December 1996;
- Oxford Pain database (Jadad 1996a).

For this update the following electronic databases were searched.

- Cochrane CENTRAL (Issue 2, 2009);
- MEDLINE via Ovid (1996 to May 2009);
- EMBASE via Ovid (1996 to May 2009);

See Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy and Appendix 3 for the CENTRAL search strategy.

Additional studies were sought in reference lists of retrieved articles and reviews.

Language

No language restriction was applied.

Unpublished studies

Abstracts, conference proceedings and other grey literature were not searched, but known unpublished studies from a different review were included.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies that might be included in the updated review. Disagreements were resolved by consensus or referral to a third review author.

Quality assessment

Two review authors independently assessed the included studies for quality using a five-point scale (Jadad 1996b).

The scale used is as follows.
Is the study randomised? If yes give one point.
Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.
Is the study double blind? If yes then add one point.
Is the double blind method reported and is it appropriate? If yes add one point, if no deduct one point.
Are the reasons for patient withdrawals and dropouts described? If yes add one point.

The results are described in the 'Methodological quality of included studies' section below, and 'Characteristics of included studies' table.

Data management

Data were extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling were entered into RevMan 5.

Data analysis

QUOROM guidelines were followed (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used number of participants who received study medication in each treatment group. Analyses were planned for different doses. Sensitivity analyses were planned for pain model (dental versus other postoperative pain), trial size (39 or fewer versus 40 or more per treatment arm), and quality score (two versus three or more), and formulation (standard tablet versus more soluble tablet or liquid preparations). A minimum of two studies and 200 participants were required for any analysis (Moore 1998).

Primary outcome:

Number of participants achieving at least 50% pain relief

For each study, mean TOTPAR (total pain relief) or SPID (summed pain intensity difference) for active and placebo groups were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The proportion of participants in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then converted into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. Information on the number of participants with at least 50%maxTOTPAR for active treatment and placebo was then used to calculate relative benefit (RB) and NNT.
Pain measures accepted for the calculation of TOTPAR or SPID were:

- five-point categorical pain relief (PR) scales with comparable wording to "none, slight, moderate, good or complete";
- four-point categorical pain intensity (PI) scales with comparable wording to "none, mild, moderate, severe";
- Visual analogue scales (VAS) for pain relief;
- VAS for pain intensity.

If none of these measures were available, numbers of participants reporting "very good or excellent" on a five-point categorical global scale with the wording "poor, fair, good, very good, excellent" were taken as those achieving at least 50% pain relief (Collins 2001).

Further details of the scales and derived outcomes are in the glossary (Appendix 4).

Secondary outcomes:

1. Use of rescue medication. Numbers of participants requiring rescue medication were used to calculate relative risk (RR) and numbers needed to treat to prevent (NNTp) use of rescue medication for treatment and placebo groups. Median (or mean) time to use of rescue medication was used to calculate the weighted mean of the median (or mean) for the outcome. Weighting was by number of participants.

2. Adverse events. Numbers of participants reporting adverse events for each treatment group were used to calculate RR and numbers needed to treat to harm (NNH) estimates for:

- any adverse event;
- any serious adverse event (as reported in the study);
- withdrawal due to an adverse event.

3. Withdrawals. Withdrawals for reasons other than lack of efficacy (participants using rescue medication - see above) and adverse events were noted, as were exclusions from analysis where data were presented.

RB or RR estimates were calculated with 95% Confidence Interval (CI) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CI were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the RB did not include the number one.

Homogeneity of studies was assessed visually (L'Abbé 1987). The z test (Tramèr 1997) was used to determine if there was a significant difference between NNTs for different doses of active treatment, or between groups in the sensitivity analyses.

RESULTS

Description of studies

This review included 72 studies in abstract, 9186 participants. The previous review identified 34 reports of 35 studies, in which 2214 participants were treated with ibuprofen and 1377 with placebo. This updated review identified a total of 65 published reports of 67 studies, and one published report of five unpublished studies (Edwards 2002), in which a total of 5804 participants were treated with ibuprofen and 3382 with placebo. Details of the studies are in the 'Characteristics of included studies' table. Three new studies were excluded (Cooper 1996b; Doyle 2002; Schleier 2007), please see the 'Characteristics of excluded studies' table for further details.

In an new search in May 2009, four additional studies were identified. Two were subsequently excluded after reading the full text (Akural 2009; Chopra 2009), and two are awaiting classification (Daniels 2009; Kleinert 2008). These studies are not included in this analysis.

Ibuprofen 50 mg was used in three studies, 100 mg in four studies, 200 mg in 20 studies (25 treatment arms), 400 mg in 61 studies (67

treatment arms), 600 mg in three studies (four treatment arms), and 800 mg in one study.

Most studies had treatment arms using standard formulation tablets, but nine used tablets of a more soluble salt of ibuprofen (lysine or arginine) or a "soluble" or liquid preparation (De Miguel Rivero 1997; Hersh 2000; Laveneziana 1996; Mehlisch 1995; Nelson 1994; Olson 2001; Pagnoni 1996; Parker 1986; Wahl 1997). Six studies included treatment arms using both standard tablets and a more soluble preparation (Black 2002; Desjardins 2002; Mehlisch 2002; Seymour 1991 (study 1); Seymour 1991 (study 2); Seymour 1996).

Fifty-seven studies were in participants with dental pain following surgical extraction of one or more impacted third molars, 10 studies were in participants with pain following obstetric or gynaecological surgery (seven), abdominal or gynaecological surgery (two), and abdominal or pelvic surgery (one), two studies were in participants with pain following orthopaedic surgery, and one study each in general surgery, tonsillectomy, and hernia repair.

Study duration was 4 hours in nine studies, 5 hours in two studies, 6 hours in 42 studies, 7 hours in one study, 8 hours in nine studies, 12 hours in six studies, and 24 hours in three studies.

Risk of bias in included studies

Methodological quality of included studies

All included studies were both randomised and double blind. Twenty-one studies were given a score of five, 32 a score of four, 16 a score of three, and three a score of two. Details are in the 'Characteristics of included studies' table.

Effects of interventions

All studies contributed data for analysis of the primary efficacy outcome.

Number of participants achieving at least 50% pain relief

(Table 1; Summary of results A)

Ibuprofen 50 mg versus placebo

Three studies with 316 participants provided data (Forbes 1991a; Schou 1998; Sunshine 1996) (Analysis 1.1).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with Ibuprofen 50 mg was 31% (50/159; range 14% to 53%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 10% (16/157; range 0% to 29%).
- The RB of treatment compared with placebo was 3.2 (1.9 to 5.1), giving an NNT for at least 50% pain relief over 4 to 6 hours of 4.7 (3.3 to 8.0).

Ibuprofen 100 mg versus placebo

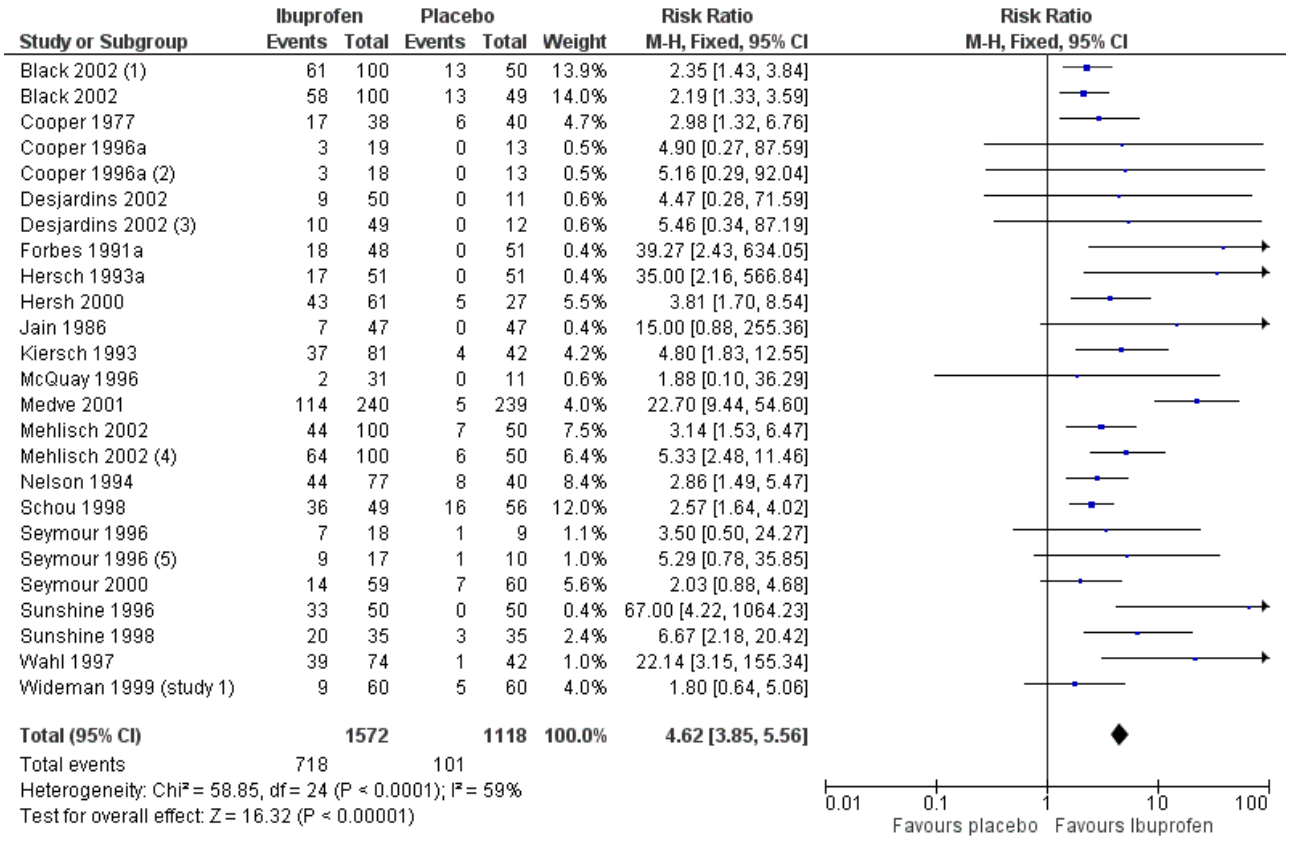
Four studies with 396 participants provided data (Forbes 1991a; Jain 1986; Schou 1998; Sunshine 1996) (Analysis 2.1).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with Ibuprofen 100 mg was 31% (60/192; range 8% to 51%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 8% (16/204; range 0% to 29%).
- The RB of treatment compared with placebo was 3.7 (2.3 to 5.9), giving an NNT for at least 50% pain relief over 4 to 6 hours of 4.3 (3.2 to 6.4).

Ibuprofen 200 mg versus placebo

Twenty studies (25 treatment arms) with 2690 participants provided data (Analysis 3.1; Figure 1)

Figure 1. Forest plot of comparison: 3 Ibuprofen 200 mg versus placebo, outcome: 3.1 Participants with at least 50% pain relief over 4 to 6 hours.



Footnotes
(1) ibuprofen arginine
(2) plus misoprostal 200 mg
(3) ibuprofen arginine
(4) ibuprofen arginine
(5) ibuprofen soluble

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with Ibuprofen 200 mg was 46% (718/1572; range 6% to 73%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 9% (101/1118; range 0% to 29%).
- The RB of treatment compared with placebo was 4.6 (3.9 to 5.6), giving an NNT for at least 50% pain relief over 4 to 6 hours of 2.7 (2.5 to 3.0).

Ibuprofen 400 mg versus placebo

Sixty-one studies (67 treatment arms) with 6475 participants provided data (Analysis 4.1; Figure 2)

Figure 2. Forest plot of comparison: 4 Ibuprofen 400 mg versus placebo, outcome: 4.1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahlstrom 1993	19	32	2	30	0.5%	8.91 [2.26, 35.02]
Arnold 1990	2	15	0	14	0.1%	4.69 [0.24, 89.88]
Bakshi 1994	57	80	31	82	7.3%	1.88 [1.38, 2.57]
Black 2002 (1)	71	99	13	50	4.1%	2.76 [1.70, 4.47]
Black 2002	71	100	13	49	4.2%	2.68 [1.65, 4.34]
Cheung 2007	40	57	5	57	1.2%	8.00 [3.41, 18.79]
Cooper 1977	20	40	6	40	1.4%	3.33 [1.50, 7.42]
Cooper 1982	22	38	5	46	1.1%	5.33 [2.23, 12.72]
Cooper 1988a	19	37	6	43	1.3%	3.68 [1.64, 8.24]
Cooper 1989	37	61	9	64	2.1%	4.31 [2.28, 8.17]
De Miguel Rivero 1997	24	36	15	34	3.7%	1.51 [0.97, 2.35]
Desjardins 2002 (2)	16	49	0	12	0.2%	8.58 [0.55, 133.75]
Desjardins 2002	15	52	0	11	0.2%	7.02 [0.45, 109.31]
Dionne 1998	26	50	2	25	0.6%	6.50 [1.68, 25.22]
Edwards 2002	145	339	11	339	2.6%	13.18 [7.28, 23.88]
Ehrich 1999	14	20	1	32	0.2%	22.40 [3.19, 157.49]
Forbes 1984	21	28	3	28	0.7%	7.00 [2.35, 20.83]
Forbes 1990	15	32	0	34	0.1%	32.88 [2.05, 527.71]
Forbes 1991b	18	37	3	39	0.7%	6.32 [2.03, 19.71]
Forbes 1992	21	38	0	38	0.1%	43.00 [2.70, 685.19]
Frame 1989	26	42	0	38	0.1%	48.07 [3.03, 762.59]
Fricke 1993	40	81	2	39	0.6%	9.63 [2.45, 37.81]
Gay 1996	26	41	7	39	1.7%	3.53 [1.74, 7.19]
Heidrich 1985	15	40	5	40	1.2%	3.00 [1.20, 7.47]
Hersch 1993a	11	49	0	51	0.1%	23.92 [1.45, 395.20]
Hersch 1993b	9	12	6	16	1.2%	2.00 [0.98, 4.08]
Hersh 2000	47	59	5	27	1.6%	4.30 [1.93, 9.59]
Hill 2001	22	49	5	50	1.2%	4.49 [1.85, 10.91]
Jain 1986	9	49	0	47	0.1%	18.24 [1.09, 304.82]
Jain 1988	33	49	17	48	4.1%	1.90 [1.24, 2.92]
Johnson 1997	15	48	9	48	2.2%	1.67 [0.81, 3.43]
Laska 1986	39	39	14	37	3.6%	2.59 [1.72, 3.89]
Laveneziana 1996	29	42	24	41	5.8%	1.18 [0.85, 1.64]
Malmstrom 1999	33	46	4	45	1.0%	8.07 [3.11, 20.93]
Malmstrom 2002	24	45	0	45	0.1%	49.00 [3.07, 781.94]
Malmstrom 2004	32	48	4	49	0.9%	8.17 [3.13, 21.33]
McQuay 1996	6	30	0	11	0.2%	5.03 [0.31, 82.60]
Mehlisch 1990	124	306	5	85	1.9%	6.89 [2.91, 16.30]
Mehlisch 1995	67	98	1	40	0.3%	27.35 [3.93, 190.30]
Mehlisch 2002	57	100	6	50	1.9%	4.75 [2.20, 10.26]
Mehlisch 2002 (3)	62	100	7	50	2.2%	4.43 [2.19, 8.95]
Morrison 1999	20	51	6	50	1.5%	3.27 [1.43, 7.46]
Nørholt 1998	22	26	8	31	1.8%	3.28 [1.77, 6.09]
Olson 2001	57	67	5	39	1.5%	6.64 [2.91, 15.14]
Pagnoni 1996	13	30	5	32	1.2%	2.77 [1.12, 6.84]
Schachtel 1989	27	36	13	38	3.0%	2.19 [1.36, 3.54]
Schou 1998	41	49	16	56	3.6%	2.93 [1.90, 4.51]
Schwartz 2007	5	15	0	16	0.1%	11.69 [0.70, 194.79]
Seymour 1991 (study 1) (4)	22	32	5	16	1.6%	2.20 [1.03, 4.72]
Seymour 1991 (study 1)	20	31	5	16	1.6%	2.06 [0.95, 4.47]
Seymour 1991 (study 2)	20	30	3	15	1.0%	3.33 [1.17, 9.46]
Seymour 1991 (study 2) (5)	8	30	4	15	1.3%	1.00 [0.36, 2.79]
Seymour 1996	11	15	1	9	0.3%	6.60 [1.01, 42.95]
Seymour 1996 (6)	11	16	1	10	0.3%	6.88 [1.04, 45.44]
Seymour 1998	27	76	3	70	0.7%	8.29 [2.63, 26.12]
Seymour 1999	19	41	7	39	1.7%	2.58 [1.22, 5.45]
Singla 2005	77	175	14	60	5.0%	1.89 [1.16, 3.07]
Sunshine 1983	21	30	3	30	0.7%	7.00 [2.33, 21.00]
Sunshine 1987	16	38	11	40	2.6%	1.53 [0.82, 2.86]
Sunshine 1997	17	40	1	39	0.2%	16.57 [2.32, 118.61]
Van Dyke 2004	112	186	9	62	3.2%	4.15 [2.24, 7.67]
Wideman 1999 (study 2)	21	50	3	51	0.7%	7.14 [2.27, 22.44]
Zelenakas 2004	27	51	6	50	1.5%	4.41 [1.99, 9.76]

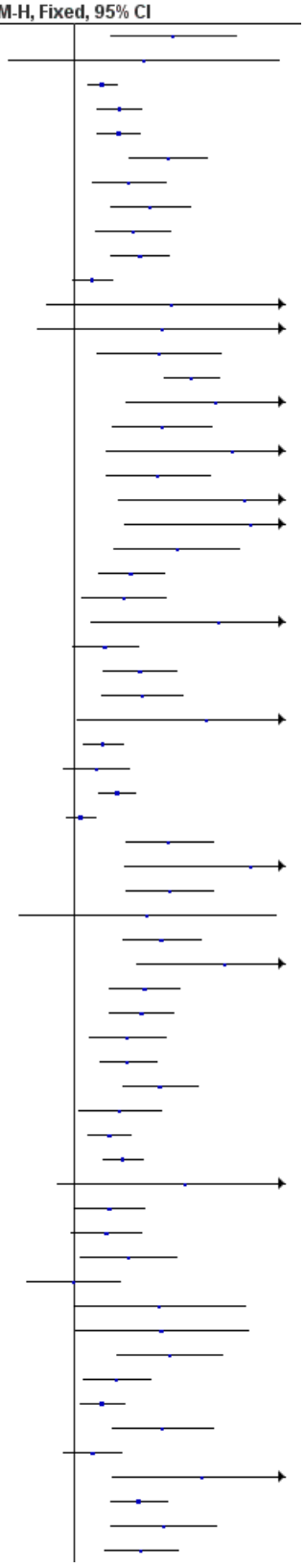
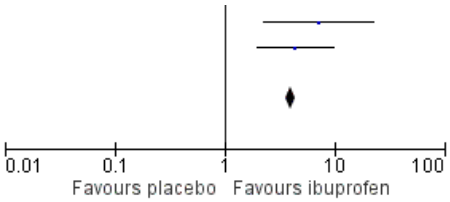


Figure 2. (Continued)



Wideman 1999 (study 2)	21	50	3	51	0.7%	7.14 [2.27, 22.44]
Zelenakas 2004	27	51	6	50	1.5%	4.41 [1.99, 9.76]
Total (95% CI)		**3728**		**2747**	**100.0%**	**3.94 [3.58, 4.35]**
Total events	2013		375			

Heterogeneity: Chi² = 221.50, df = 62 (P < 0.00001); I² = 72%
Test for overall effect: Z = 27.58 (P < 0.00001)

Footnotes
(1) ibuprofen arginate
(2) ibuprofen arginate
(3) ibuprofen arginine
(4) ibuprofen liquigel
(5) ibuprofen liquigel
(6) ibuprofen soluble

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with Ibuprofen 400 mg was 54% (2013/3728; range 13% to 100%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 14% (375/2747; range 0% to 59%).
- The RB of treatment compared with placebo was 3.9 (3.6 to 4.4), giving an NNT for at least 50% pain relief over 4 to 6 hours of 2.5 (2.4 to 2.6).

Ibuprofen 600 mg versus placebo

Three studies (four treatment arms) with 203 participants provided data (Laska 1986; Parker 1986; Seymour 1996) (Analysis 5.1).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with Ibuprofen 200 mg was 77% (88/114; range 47% to 100%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 40% (36/89; range 10% to 61%).
- The RB of treatment compared with placebo was 2.0 (1.5 to 2.6), giving an NNT for at least 50% pain relief over 4 to 6 hours of 2.7 (2.0 to 4.2).

Only one treatment arm used ibuprofen 800 mg (Laska 1986) (Analysis 6.1).

A general trend for better efficacy (lower NNT) with increasing dose was seen. The result for 800 mg ibuprofen was compatible with this trend, and is added for completeness even though there were fewer than 200 participants. (200 mg versus 100 mg z = 3.25, P = 0.001; 400 mg versus 200 mg z = 1.74, P = 0.082; 400 mg versus 100 mg z = 4.15, P < 0.0001).

Summary of results A: Number of participants with ≥ 50% pain relief over 4 to 6 hours

Dose	Studies	Participants	Ibuprofen (%)	Placebo (%)	NNT (95%CI)
50 mg	3	316	31	10	4.7 (3.3 to 8.0)
100 mg	4	396	31	8	4.3 (3.2 to 6.4)
200 mg	20	2690	46	9	2.7 (2.5 to 3.0)
400 mg	61	6475	54	14	2.5 (2.4 to 2.6)
600 mg	3	203	77	40	2.7 (2.0 to 4.2)
800 mg	1	76	100	38	1.6 (1.3 to 2.2)

Sensitivity analysis of primary outcome

(Summary of results B)

Methodological quality

Only three studies (Cooper 1996a; Heidrich 1985; Hersch 1993a) were given quality scores of two, so no sensitivity analysis was carried out for this criterion. Removing these three studies from the analyses did not alter the results.

Pain model; dental versus other surgery

Ibuprofen 200 mg

(Analysis 3.2)

Eighteen studies reporting the primary outcome were in dental pain (Analysis 3.2.1). The proportion of participants with at least 50% pain relief was 47% (680/1462) for ibuprofen 200 mg, and 10% (100/1008) for placebo. The RB was 4.5 (3.7 to 5.4), and the NNT was 2.7 (2.5 to 3.0).

Two studies reporting the primary outcome were in other types of surgery (episiotomy, abdominal and gynaecological surgery) (Analysis 3.2.2). The proportion of participants with at least 50% pain relief was 38% (42/110) for ibuprofen 200 mg, and 5% (5/110) for placebo. The RB was 7.7 (3.2 to 18), and the NNT was 3.0 (2.3 to 4.2).

The 95% CI for NNT in dental and other surgery overlap, indicating that there was no significant difference for this outcome between dental and other types of surgery in these studies at this dose.

Ibuprofen 400 mg

(Analysis 4.2; Figure 3)

Figure 3. Forest plot of comparison: 4 Ibuprofen 400 mg versus placebo, outcome: 4.2 Participants with at least 50% pain relief over 4 to 6 hours: type of surgery.

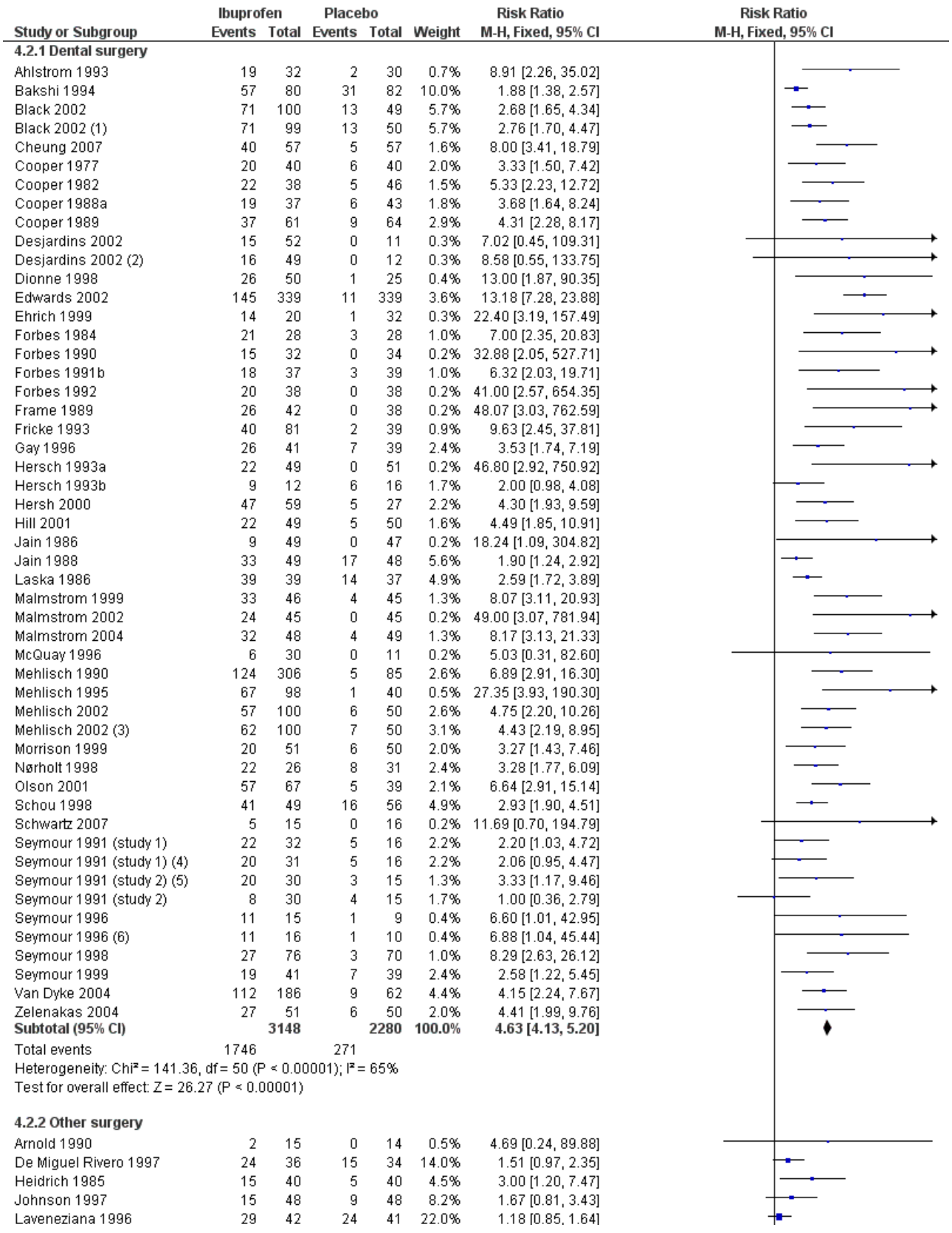
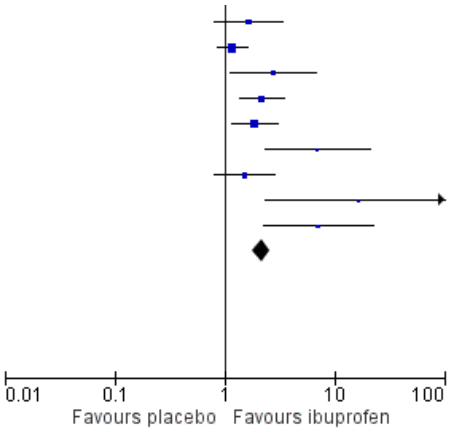


Figure 3. (Continued)

Johnson 1997	15	48	9	48	8.2%	1.67 [0.81, 3.43]
Laveneziana 1996	29	42	24	41	22.0%	1.18 [0.85, 1.64]
Pagnoni 1996	13	30	5	32	4.4%	2.77 [1.12, 6.84]
Schachtel 1989	27	36	13	38	11.5%	2.19 [1.36, 3.54]
Singla 2005	77	175	14	60	18.9%	1.89 [1.16, 3.07]
Sunshine 1983	21	30	3	30	2.7%	7.00 [2.33, 21.00]
Sunshine 1987	16	38	11	40	9.7%	1.53 [0.82, 2.86]
Sunshine 1997	17	40	1	39	0.9%	16.57 [2.32, 118.61]
Wideman 1999 (study 2)	21	50	3	51	2.7%	7.14 [2.27, 22.44]
Subtotal (95% CI)		**580**		**467**	**100.0%**	**2.18 [1.81, 2.62]**
Total events	277		103			

Heterogeneity: Chi² = 31.72, df = 11 (P = 0.0008); I² = 65%
Test for overall effect: Z = 8.23 (P < 0.00001)



Footnotes
(1) Ibuprofen arginine
(2) Ibuprofen arginine
(3) ibuprofen arginine
(4) ibuprofen liquigel
(5) Ibuprofen soluble
(6) ibuprofen soluble

Forty-nine studies reporting the primary outcome were in dental pain (Analysis 4.2.1). The proportion of participants with at least 50% pain relief was 55% (1746/3148) for ibuprofen 400 mg, and 12% (271/2280) for placebo. The RB was 4.3 (3.8 to 4.9), and the NNT was 2.3 (2.2 to 2.4).

Twelve studies reporting the primary outcome were in other types of surgery (including general, orthopaedic, abdominal, obstetric and gynaecological surgery) (Analysis 4.2.2). The proportion of participants with at least 50% pain relief was 48% (277/580) for ibuprofen 400 mg, and 22% (103/467) for placebo. The RB was 2.2 (1.8 to 2.6), and the NNT was 3.9 (3.2 to 5.0).

The 95% CIs for RB and NNT in dental and other surgery do not overlap, indicating that there was a significant difference for this outcome between dental and other types of surgery in these studies at 400 mg (z = 5.86, P < 0.0001).

There were insufficient data to compare different pain models at other doses of ibuprofen.

Dose response in dental studies

A significant difference was seen in dental studies between ibuprofen 200 mg and 400 mg (z = 3.52, P < 0.0005) and also between 400 mg and 600/800 mg (z = 2.02, P = 0.04), although with limited data.

Salt preparation: standard ibuprofen versus ibuprofen lysine, arginine and "soluble"

Ibuprofen 200 mg

(Analysis 3.3; Analysis 3.4)

In all types of surgery, 17 studies used standard ibuprofen (Analysis 3.3.1). The proportion of participants with at least 50% pain relief was 41% (448/1094) for ibuprofen 200 mg, and 7% (67/1009) for placebo; the RB was 6.1 (4.8 to 7.7), and the NNT was 2.9 (2.7 to 3.2). In dental surgery only, 15 studies used standard ibuprofen (Analysis 3.4.1). The proportion of participants with at least 50% pain relief was 41% (406/984) for ibuprofen 200 mg, and 7% (62/899) for placebo; the RB was 5.9 (4.7 to 7.6), and the NNT was 2.9 (2.6 to 3.2).

Seven studies, all in dental surgery, used the lysine or arginine salts, or a preparation described as "soluble", all of which are thought to be more soluble and more readily absorbed (Analysis 3.3.2, Analysis 3.4.2). The corresponding proportion of participants with at least 50% pain relief was 56% (270/478) for ibuprofen 200 mg, and 10% (34/350) for placebo; the RB was 5.7 (4.2 to 7.9), and the NNT was 2.1 (1.9 to 2.4).

The more soluble salts of ibuprofen had significantly lower (better) NNTs than the standard preparation when all surgery was combined (z = 3.85, P < 0.0001) and in dental studies only (z = 3.77, P < 0.0002).

Ibuprofen 400 mg

(Analysis 4.3; Figure 4; Analysis 4.4; Figure 5)

Figure 4. Forest plot of comparison: 4 Ibuprofen 400 mg versus placebo, outcome: 4.3 Participants with at least 50% pain relief over 4 to 6 hours, all surgery: formulation.

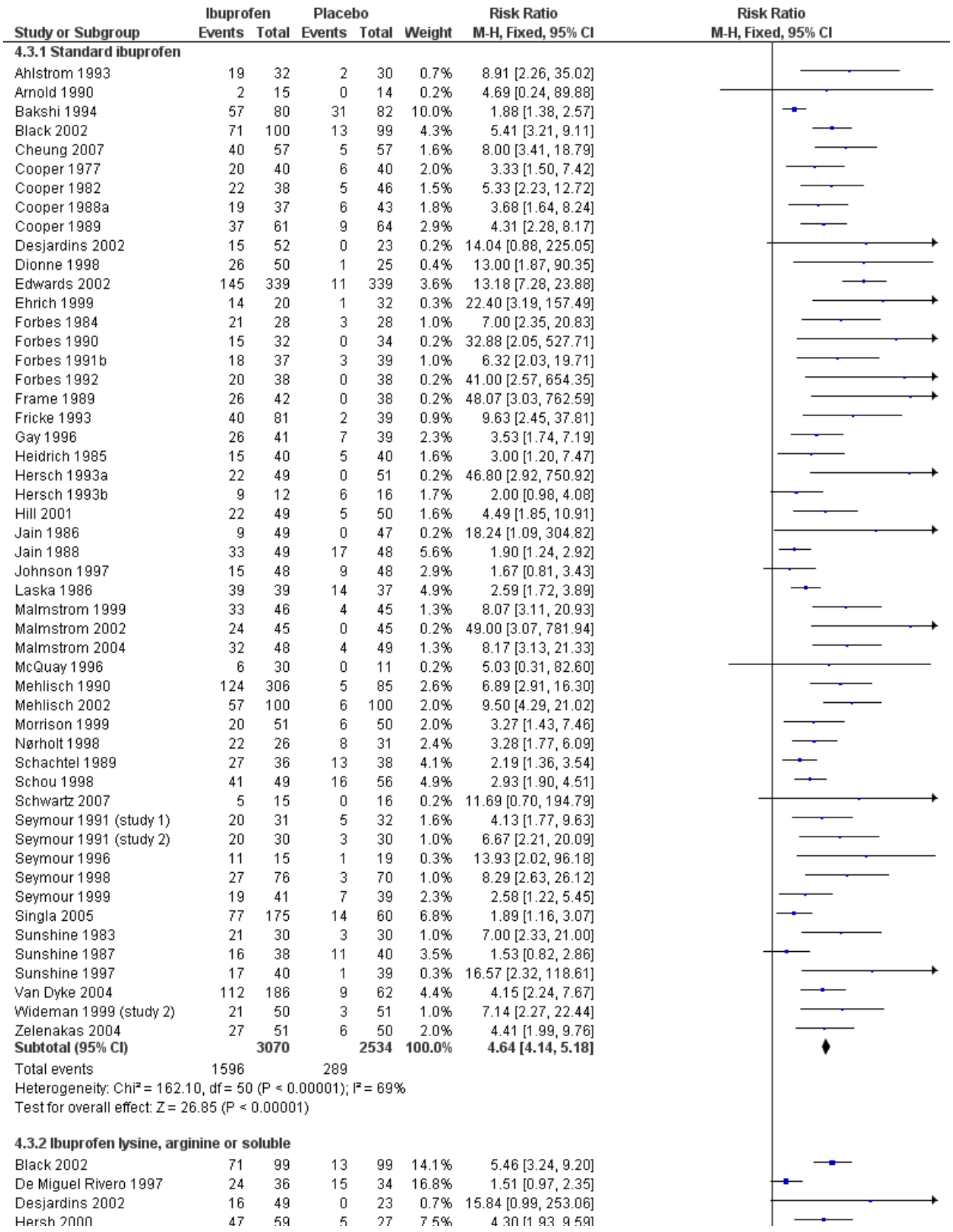


Figure 4. (Continued)

Desjardins 2002	16	49	0	23	0.7%	15.84 [0.99, 253.06]
Hersh 2000	47	59	5	27	7.5%	4.30 [1.93, 9.59]
Laveneziana 1996	29	42	24	41	26.4%	1.18 [0.85, 1.64]
Mehlisch 1995	67	98	1	40	1.5%	27.35 [3.93, 190.30]
Mehlisch 2002	62	100	7	50	10.1%	4.43 [2.19, 8.95]
Olson 2001	57	67	5	39	6.9%	6.64 [2.91, 15.14]
Pagnoni 1996	13	30	5	32	5.3%	2.77 [1.12, 6.84]
Seymour 1991 (study 1)	22	32	5	32	5.4%	4.40 [1.90, 10.18]
Seymour 1991 (study 2)	8	30	4	30	4.3%	2.00 [0.67, 5.94]
Seymour 1996	11	16	1	19	1.0%	13.06 [1.88, 90.54]
Subtotal (95% CI)		**658**		**466**	**100.0%**	**3.70 [3.00, 4.56]**
Total events	427		85			

Heterogeneity: Chi² = 75.44, df = 11 (P < 0.00001); I² = 85%
Test for overall effect: Z = 12.27 (P < 0.00001)

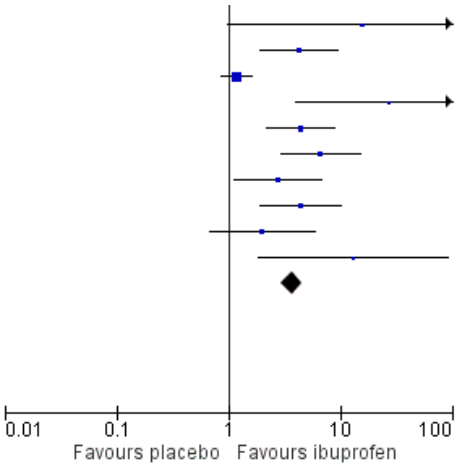


Figure 5. Forest plot of comparison: 4 Ibuprofen 400 mg versus placebo, outcome: 4.4 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: formulation.

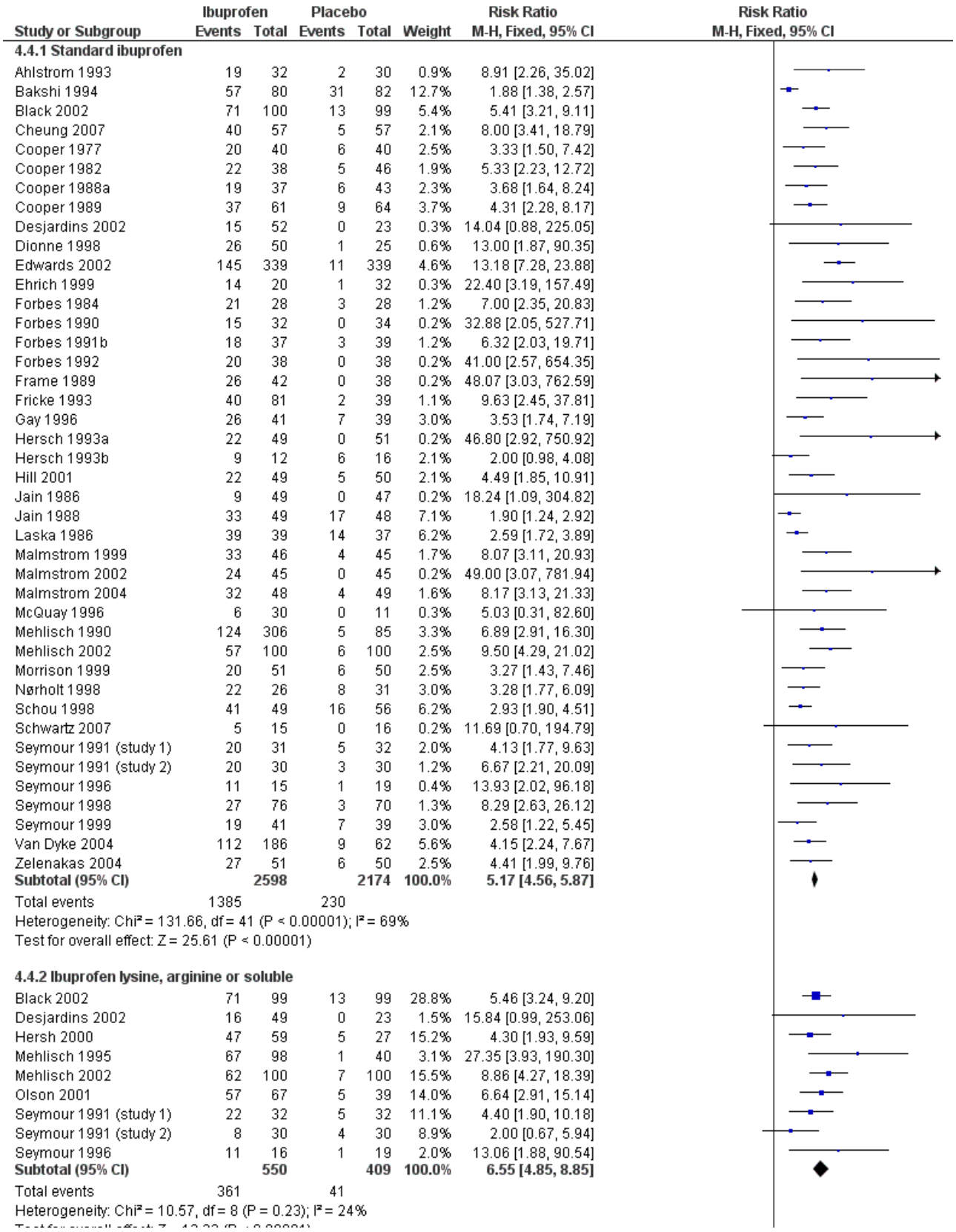


Figure 5. (Continued)

In all types of surgery, 55 studies used standard ibuprofen (Analysis 4.3.1). The proportion of participants with at least 50% pain relief was 52% (1596/3070) for ibuprofen 400 mg, and 11% (289/2534) for placebo; the RB was 4.6 (4.1 to 5.2), and the NNT was 2.5 (2.4 to 2.7). In dental surgery only, 46 studies used standard ibuprofen (Analysis 4.4.1). The proportion of participants with at least 50% pain relief was 53% (1385/2598) for ibuprofen 400 mg, and 11% (230/2174) for placebo; the RB was 5.2 (4.6 to 5.9), and the NNT was 2.3 (2.2 to 2.5).

In all types of surgery, 12 studies used the lysine or arginine salts, or a preparation described as "soluble" (Analysis 4.3.2). The corresponding proportion of participants with at least 50% pain relief was 65% (427/658) for ibuprofen 400 mg, and 18% (85/466) for placebo; the RB was 3.7 (3.0 to 4.6), and the NNT was 2.1 (1.9 to 2.4). In dental surgery, nine studies used lysine, arginine or "soluble" salts (Analysis 4.4.2). The corresponding proportion of participants with at least 50% pain relief was 66% (361/550) for ibuprofen 400 mg, and 10% (41/409) for placebo; the RB was 6.5 (4.8 to 8.9), and the NNT was 1.8 (1.7 to 2.0).

The more soluble salts of ibuprofen had significantly lower (better) NNTs than the standard preparation when all surgery was combined (z = 2.16, P = 0.03) and in dental studies only (z = 4.64, P < 0.0001).

There were insufficient data to analyse the salt preparation for other doses of ibuprofen.

Study size: 40 or more participants per treatment arm versus fewer than 40

The two largest data sets, ibuprofen 200 mg and 400 mg, were used to investigate the effect of study size on the primary outcome. The analysis was further restricted to dental studies only, since these are clinically the most homogeneous studies.

Ibuprofen 200 mg

(Analysis 3.5)

Eleven studies had 40 or more participants in both treatment arms (Black 2002; Forbes 1991a; Hersch 1993b; Jain 1986; Kiersch 1993; Medve 2001; Mehlisch 2002; Nelson 1994; Schou 1998; Seymour 2000; Wahl 1997) (Analysis 3.5.1). The proportion of participants with at least 50% pain relief was 49% (553/1126) for ibuprofen 200 mg, and 10% (80/827) for placebo; the RB was 4.6 (3.7 to 5.6), and the NNT was 2.5 (2.3 to 2.8). Four studies had fewer than 40 participants in both treatment arms (Cooper 1996a; McQuay 1996; Seymour 1996; Sunshine 1998) (Analysis 3.5.2). The proportion of participants with at least 50% pain relief was 34% (44/138) for ibuprofen 200 mg, and 5% (5/91) for placebo; the RB was 5.1 (2.4 to 11), and the NNT was 3.9 (2.8 to 6.1).

Ibuprofen 400 mg

(Analysis 4.5)

Nineteen studies had 40 or more participants in both treatment arms (Bakshi 1994; Black 2002; Cheung 2007; Cooper 1977; Cooper 1989; Hill 2001; Mehlisch 1990; Mehlisch 1995; Mehlisch 2002; Morrison 1999; Schou 1998; Seymour 1998; Edwards 2002; Van Dyke 2004; Zelenakas 2004) (Analysis 4.5.1). The proportion of participants with at least 50% pain relief was 54% (1000/1842) for ibuprofen 400 mg, and 12% (152/1244) for placebo; the RB was 4.4 (3.8 to 5.2), and the NNT was 2.4 (2.2 to 2.6). Fourteen studies had fewer than 40 participants in both treatment arms (Ahlstrom 1993; Ehrich 1999; Forbes 1984; Forbes 1990; Forbes 1991b; Forbes 1992; Hersch 1993b; Laska 1986; McQuay 1996; Nørholt 1998; Schwartz 2007; Seymour 1991 (study 1); Seymour 1991 (study 2); Seymour 1996) (Analysis 4.5.2). The proportion of participants with at least 50% pain relief was 60% (280/463) for ibuprofen 400 mg, and 14% (56/393) for placebo; the RB was 4.1 (3.2 to 5.2), and the NNT was 2.2 (1.9 to 2.5).

There was no consistent or statistically significant effect of study size in this group of studies, using 40 participants per treatment arm as the cut-off.

Summary of results B: Sensitivity analyses using number of participants with ≥ 50% pain relief over 4 to 6 hours

Criterion	Studies	Participants	Ibuprofen (%)	Placebo (%)	NNT (95%CI)
Dental surgery 200 mg	18	2470	47	10	2.7 (2.5 to 3.0)
Other surgery 200 mg	2	220	39	5	3.0 (2.3 to 4.2)
Dental surgery 400 mg	49	5428	55	12	2.3 (2.2 to 2.4)
Other surgery 400 mg	12	1047	48	22	3.9 (3.2 to 5.0)

Dental 600/800 mg	2	165	86	29	1.7 (1.4 to 2.3)
Standard 200 mg, all surgery	17	2103	41	7	2.9 (2.6 to 3.2)
"Soluble" salts 200 mg, all surgery	7	828	56	10	2.1 (1.9 to 2.4)
Standard 400 mg, all surgery	55	5604	52	11	2.5 (2.4 to 2.7)
"Soluble" salts 400 mg, all surgery	12	1124	65	18	2.1 (1.9 to 2.4)
Standard 200 mg, dental surgery	15	1883	41	7	2.9 (2.6 to 3.2)
"Soluble" salts 200 mg, dental surgery	7	828	56	10	2.1 (1.9 to 2.4)
Standard 400 mg, dental surgery	46	4772	53	11	2.3 (2.2 to 2.5)
"Soluble" salts 400 mg, dental surgery	9	959	66	10	1.8 (1.7 to 2.0)
40 + participants, dental surgery 200 mg	11	1953	49	10	2.5 (2.3 to 2.8)
< 40 participants, dental surgery 200 mg	4	229	32	5	3.9 (2.8 to 6.1)
40 + participants, dental surgery 400 mg	19	3086	54	12	2.4 (2.2 to 2.6)
< 40 participants, dental surgery 400 mg	14	856	60	14	2.2 (1.9 to 2.5)

Use of rescue medication

Proportion of participants using rescue medication (Summary of results C)

The majority of studies reporting this outcome did so after 6 hours. A minority reported at shorter times (4 and 5 hours) or longer times (8, 12 and 24 hours) (Table 1). We analysed data for 6 hours because there were sufficient data to permit analysis by dose, and because longer times are likely to exceed the expected duration of effect of ibuprofen (plasma half life 2 hours).

- Two studies using ibuprofen 50 mg reported the proportion of participants using rescue medication over 6 hours (Schou 1998; Sunshine 1996). The weighted mean proportion was 29% (30/102) with ibuprofen and 50% (53/106) with placebo, giving an NNTp of 4.9 (3.0 to 13) (Analysis 1.2).
- Three studies using ibuprofen 100 mg reported the proportion of participants using rescue medication over 6 hours (Jain 1986; Schou 1998; Sunshine 1996). The weighted mean proportion was 38% (54/143) with ibuprofen and 64% (88/153) with placebo, giving an NNTp of 3.8 (2.7 to 6.5) (Analysis 2.2). In the two studies in dental pain, the weighted mean proportion was 59% (54/92) with ibuprofen and 80% (82/103) with placebo, giving an NNTp of 4.8 (2.3 to 12).
- Eight studies using ibuprofen 200 mg reported the proportion of participants using rescue medication over 6 hours. The weighted mean proportion was 48% (215/452) with ibuprofen and 76% (259/342) with placebo, giving an NNTp of 3.6 (2.9 to 4.6) (Analysis 3.6). In the seven studies in dental pain, the weighted mean proportion was 53% (215/402) with ibuprofen and 83% (243/292) with placebo, giving an NNTp of 3.4 (2.8 to 4.3) (Analysis 3.7).
- Twenty-eight studies using ibuprofen 400 mg reported the proportion of participants using rescue medication over 6 hours. The weighted mean proportion was 42% (737/1756) with ibuprofen and 79% (975/1227) with placebo, giving an NNTp of 2.7 (2.5 to 2.9) (Analysis 4.6). In the 22 studies in dental pain, the weighted mean proportion was 41% (628/1541) with ibuprofen and 80% (814/1013) with placebo, giving an NNTp of 2.5 (2.3 to 2.8) (Analysis 4.7).

Only one study (Seymour 1996) using ibuprofen 600 mg reported the proportion of participants using rescue medication, so no analysis was possible for the higher doses.

There was a trend towards a lower (better) NNTp with higher dose for all surgery combined, and for the dental studies alone (200 mg versus 400 mg all surgery: z = 2.53, P = 0.01; 200 mg versus 400 mg dental surgery z = 2.63, P = 0.009).

Dental surgery: effect of formulation

(Analysis 3.8; Analysis 4.8)

- In four dental studies using standard ibuprofen 200 mg, the weighted mean proportion of participants using rescue medication over 6 hours was 67% (116/173) with ibuprofen and 87% (150/172) with placebo, giving an NNTp of 5.0 (3.5 to 8.7) (Analysis 3.8.1). In four dental studies using soluble preparations of ibuprofen 200 mg, the weighted mean proportion of participants using rescue medication over 6 hours was 43% (99/229) with ibuprofen and 78% (93/120) with placebo, giving an NNTp of 2.9 (2.3 to 4.1) (Analysis 3.8.2).
- In 18 dental studies using standard ibuprofen 400 mg, the weighted mean proportion of participants using rescue medication over 6 hours was 42% (455/1053) with ibuprofen and 80% (693/866) with placebo, giving an NNTp of 2.7 (2.4 to 3.0) (Analysis 4.8.1). In six dental studies using soluble preparations of ibuprofen 400 mg, the weighted mean proportion of participants using rescue medication over 6 hours was 34% (102/302) with ibuprofen and 78% (121/147) with placebo, giving an NNTp of 2.1 (1.8 to 2.5) (Analysis 4.8.2).

At both doses fewer participants needed rescue medication over 6 hours with the soluble preparations than the standard preparation. The difference in NNTp was statistically significant for the 400 mg dose (z = 2.39, P = 0.017).

Summary of results C: Weighted mean proportion using rescue medication over 6 hours

Dose	Studies	Participants	Ibuprofen (%)	Placebo (%)	NNTp (95%CI)
50 mg	2	208	29	50	4.9 (3.0 to 13)
100 mg	3	296	38	64	3.8 (2.7 to 6.5)
200 mg	8	794	48	76	3.6 (2.9 to 4.6)
400 mg	28	2983	42	79	2.7 (2.5 to 3.0)
100 mg, dental surgery	2	195	59	80	4.8 (2.3 to 12)
200 mg, dental surgery	7	694	53	83	3.4 (2.8 to 4.3)
400 mg, dental surgery	22	2554	41	80	2.5 (2.3 to 2.8)
Standard 200 mg, dental surgery,	4	345	67	87	5.0 (3.5 to 8.7)
"Soluble" salts 200 mg, dental surgery	4	349	43	78	2.9 (2.3 to 4.1)
Standard 400 mg, dental surgery,	18	1857	43	80	2.7 (2.5 to 3.1)
"Soluble" salts 400 mg, dental surgery	6	449	34	82	2.1 (1.8 to 2.5)

Time to use of rescue medication (Summary of results D)

Thirty-four studies reported the median time, and 17 the mean time to use of rescue medication (Table 1).

- In 10 studies (1807 participants) the weighted mean of the median time to use of rescue medication was 4.7 hours for ibuprofen 200 mg and 2.1 hours for placebo.
- In 31 studies (3548 participants) the weighted mean of the median time to use of rescue medication was 5.6 hours for ibuprofen 400 mg and 1.9 hours for placebo.
- In four studies (345 participants) the weighted mean of the mean time to use of rescue medication was 3.9 hours for ibuprofen 200 mg and 2.2 hours for placebo.
- In 16 studies (1313 participants) the weighted mean of the median time to use of rescue medication was 4.6 hours for ibuprofen 400 mg and 2.8 hours for placebo.

Summary of results D: Weighted median and mean time to use of rescue medication

			Median time	
Dose	**Studies**	**Participants**	**Ibuprofen**	**Placebo**
200 mg	10	1807	4.7	2.1
400 mg	31	3548	5.6	1.9
			Mean time	
200 mg	4	345	3.9	2.2
400 mg	16	1313	4.6	2.8

Adverse events (Summary of results E)

Any adverse event

Most studies collected adverse event data over 4 to 8 hours, but a few collected at 12 and 24 hours, and one at 14 days (Malmstrom 2004). Adverse events were generally described as mild and transient (Table 2).

- Two studies using ibuprofen 50 mg reported on the number of participants with at least one adverse event (Forbes 1991a; Sunshine 1996): 10% (11/114) with ibuprofen, and 7% (8/111) with placebo (Analysis 1.3).
- Three studies using ibuprofen 100 mg reported on the number of participants with at least one adverse event (Forbes 1991a; Jain 1986; Sunshine 1996): 14% (22/152) with ibuprofen, and 13% (20/158) with placebo (Analysis 2.3).
- Fourteen studies using ibuprofen 200 mg reported on the number of participants with at least one adverse event (Black 2002; Desjardins 2002; Forbes 1991a; Hersch 1993a; Hersh 2000; Jain 1986; McQuay 1996; Mehlisch 2002; Nelson 1994; Seymour 2000; Sunshine 1996; Sunshine 1998; Wahl 1997; Wideman 1999 (study 1)): 19% (208/1102) with ibuprofen, and 19% (137/706) with placebo (Analysis 3.9).
- Forty studies using ibuprofen 400 mg reported on the number of participants with at least one adverse event: 17% (476/2870) with ibuprofen, and 16% (326/1997) with placebo (Analysis 4.9).

For doses of ibuprofen of 50 mg to 400 mg there was no significant difference in participants experiencing any adverse event compared with placebo. Two studies using 600 mg and 800 mg ibuprofen also showed no difference from placebo, but these had small amounts of data.

Summary of results E: Participants with at least one adverse event

Dose	Studies	Participants	Ibuprofen (%)	Placebo (%)	NNH (95%CI)
50 mg	2	225	10	7	not calculated
100 mg	3	310	14	13	not calculated
200 mg	14	1808	19	19	not calculated
400 mg	40	4867	17	16	not calculated

Serious adverse event

Two studies reported serious adverse events. Black 2002 reported one participant treated with ibuprofen arginine 200 mg who had dysphagia and pharyngitis after the 60 minute assessment, and Zelenakas 2004 reported one participant treated with placebo who had deep vein thrombosis (DVT).

Withdrawals

(Table 2)

Participants who took rescue medication were classified as withdrawals due to lack of efficacy, and details are reported under "Use of rescue medication" above.

Withdrawals and exclusions were not reported consistently, particularly in older studies. Exclusions may not be of any particular consequence in single dose acute pain studies, where most exclusions result from patients not having moderate or severe pain (McQuay 1982). Withdrawals were sometimes reported without stating which treatment groups these referred to, or when withdrawals occurred, i.e., before assessment of analgesia at 4 to 6 hours, or at some other point before the end of the trial.

Where details were given, withdrawals or exclusions were usually due to protocol violations or adverse events related to the surgical procedure.

A small number of withdrawals due to adverse events were reported. Amongst participants treated with ibuprofen 400 mg, two withdrew due to postoperative bleeding (Malmstrom 1999; Zelenakas 2004), one due to soreness and swelling (Fricke 1993), and two due to vomiting (Malmstrom 2004; Singla 2005). One participant treated with ibuprofen 200 mg withdrew due to a headache, although the headache was present before dosing with the study drug (Kiersch 1993). In the five unpublished studies (Edwards 2002), no more than three participants per treatment group withdrew because of adverse events; no further details were given. Amongst participants treated with placebo, three withdrew due to vomiting and anxiety (Cheung 2007) and one due to postoperative bleeding (Frame 1989). One other placebo participant withdrew due to an adverse event that probably occurred during the multiple dose phase of the study (Parker 1986).

DISCUSSION

The original review of 35 studies in 34 reports included 2214 participants on ibuprofen and 1377 on placebo. This updated review doubles the number of studies, and more than doubles the number of participants, with 72 studies in 66 reports including 5804 participants on ibuprofen and 3382 on placebo. Most of the additional information came from 200 mg and 400 mg ibuprofen doses, and the bulk of the information is for these doses. There was a small amount of additional data for 50 mg and 100 mg, but not for doses higher than 400 mg, although 600 mg is a common dose of ibuprofen in some countries. The new information does not substantially change the result for the primary efficacy outcome, but provides more robust estimates with narrower confidence intervals, and permits more detailed subgroup analysis. Additionally, more attention has been paid to use of and time to additional analgesic requirement.

Overall studies were of good methodological quality. Three studies scored only the minimum for inclusion, one point each for stating they were randomised and double blind. It is possible that additional points were lost because of poor reporting rather than poor methods, and excluding these studies from the primary analysis did not change the results. No formal sensitivity analysis was possible. Almost all of the trials were of sufficiently high reporting quality to minimise reporting bias, and the amount of information such as to minimise any possible effect of publication bias.

NNTs for the primary outcome of at least 50% pain relief over 4 to 6 hours showed a trend for increasing efficacy with increasing dose over the range 100 to 400 mg. At doses of 50 and 100 mg, around 30% of those treated experience at least 50% pain relief, compared to about 10 to 15% with placebo. At 200 mg and 400 mg 46% and 55% experience this level of pain relief, giving NNTs of 2.7 (2.5 to 3.0) and 2.5 (2.4 to 2.7) respectively. Limited data for 600 mg and 800 mg are compatible with this trend. In dental studies only, the dose response was more marked, with a statistically significant difference between 200 mg and 400 mg ($P < 0.0005$), and between 400 mg and 600/800 mg ($P = 0.04$), although with limited data. Dose response from indirect analyses like these has been confirmed by dose response within trials (McQuay 2007).

Indirect comparisons of NNTs for at least 50% pain relief over 4 to 6 hours in reviews of other analgesics using identical methods indicate that ibuprofen 200 mg has equivalent efficacy to naproxen 500/550 mg (2.7 (2.3 to 3.2)) (Derry C 2009) and lumiracoxib 400 mg (2.7 (2.2 to 3.5)) (Roy 2007), while ibuprofen 400 mg has equivalent efficacy to aspirin 1200 mg (2.4 (1.9 to 3.2)) (Oldman 1999) and oxycodone 10 mg plus paracetamol 650 mg (2.5 (2.0 to 3.3)) (Edwards 2000). Both doses are better than paracetamol 1000 mg (3.6 (3.2 to 4.1)) (Toms 2008), but worse than rofecoxib (2.2 (1.9 to 2.4) (Barden 2005). A current listing of reviews of analgesics in the single dose postoperative pain model can be found at www.medicine.ox.ac.uk/bandolier/index.html.

Comparison of dental and other types of surgery demonstrated lower (better) NNTs for at least 50% pain relief compared with placebo in dental studies. This difference was statistically significant for ibuprofen 400 mg ($P < 0.0001$), but not 200 mg, where there were only two studies (220 participants) in non-dental surgery. It has previously been difficult to demonstrate a difference in efficacy between dental and other types of surgery (Barden 2004), although a recent review of diclofenac did demonstrate a similar difference with limited amounts of data (Derry P 2009). It may be that there is indeed a difference, but previous data sets have been too small to show statistical significance. In this review "other" types of surgery were diverse, including orthopaedic, abdominal and hernia surgery, tonsillectomy and episiotomy. Both the extent of the surgery and the context (e.g. perinatal hormonal changes) may influence the perception of pain and make this a highly heterogeneous group. There have never been sufficient data for any one type of "other" surgery to compare with dental surgery.

We carried out all further sensitivity analyses on the large and clinically more homogenous data set of dental studies using ibuprofen 200 and 400 mg. Study size had no statistically significant or consistent effect on efficacy, although as expected, smaller studies gave more variable results (Moore 1998).

A number of studies used ibuprofen preparations that are more soluble than standard ibuprofen, and were developed primarily to speed up absorption and onset of action. We combined these preparations for comparison of efficacy with standard ibuprofen. At both 200 mg and 400 mg the soluble preparations had better efficacy in dental studies ($P < 0.0002$ and $P < 0.0001$ respectively). Whether soluble formulations provide important clinical benefits, and whether the pharmacodynamic results accord with pharmacokinetic properties of the different formulations is beyond the scope of this review, but it is important to note the power of the systematic review to reveal these differences.

It has been suggested that data on use of rescue medication, whether as a proportion of participants requiring it, or the median time to use of it, might be helpful in assessing the usefulness of an analgesic, and possibly distinguishing between different doses (Moore 2005). This review demonstrated a non-significant trend for fewer participants to need rescue medication within 6 hours with higher doses of ibuprofen over the range 50 to 400 mg. For dental studies only, the trend was more obvious, with about 60% using rescue medication with ibuprofen 100 mg, 50% with 200 mg, and 40% with 400 mg, compared with about 80% with placebo over the 6 hour period. It was also possible to demonstrate that the proportion of participants using rescue medication was lower in those treated with "soluble" salts than with standard ibuprofen for the 200 mg and 400 mg doses.

Additionally, the median time to use of rescue medication increased with higher doses, from 4.7 hours with 200 mg to 5.6 hours with 400 mg. Both of these results indicate that the higher doses give more prolonged pain relief than lower doses. Longer duration of action may be advantageous in some circumstances. In a postoperative setting, where patients may feel nauseated, a longer time before remedication is needed may be of benefit to the patient, and it may also reduce demands on time for nursing staff. Duration of action may also be a useful outcome with which to compare different analgesics. The full implications of the importance of remedication as an outcome awaits completion of other reviews, allowing examination of a substantial body of evidence.

Reporting of data for adverse events, withdrawals (other than lack of efficacy) or exclusions, and handling of missing data was not always complete, although it did appear to be better in the more recent studies. Adverse events were collected using various methods (questioning, patient diary) over different periods of time. This may have included periods after the use of rescue medication, which may cause its own adverse events. Poor reporting of adverse events in acute pain trials has been noted before (Edwards 1999). The usefulness of single dose studies for assessing adverse events is questionable, but it is non-the-less reassuring that there was no difference between ibuprofen (at any dose) and placebo for occurrence of any adverse event, and that serious adverse events and adverse event withdrawals were rare, and generally not thought to be related to the test drug. Long term multiple dose studies should be used for meaningful analysis of adverse events since, even in acute pain settings, analgesics are likely to be used in multiple doses. The difficulty will be that the postoperative setting is one in which there are many sequelae of surgery and anaesthesia that manifest as adverse events, like nausea, vomiting, or abdominal discomfort, while others, like headache, can be caused by acute caffeine withdrawal over the postoperative period. The main issue is that of rare but serious adverse events, and these are more likely to be found in large observational studies.

Lack of information about withdrawals or exclusions may have led to an overestimate of efficacy, but the effect is probably not significant because it is as likely to be related to poor reporting as poor methods. In single dose studies most exclusions occur for protocol violations such as failing to meet baseline pain requirements, or failing to return for post treatment visits after the acute pain results are concluded. Where patients are treated with a single dose of medication and observed, often "on site" for the duration of the trial, it might be considered unnecessary to report on "withdrawals" if there were none. For missing data it has been shown that over the 4 to 6 hour period, there is no difference between baseline observation carried forward, which gives the more conservative estimate, and last observation carried forward (Moore 2005).

AUTHORS' CONCLUSIONS

Implications for practice

This updated review does not change the overall primary estimate of efficacy, the NNT for at least 50% pain relief over 4 to 6 hours compared with placebo, but does demonstrate differences in efficacy with different formulations, and provides additional estimates of efficacy in terms of use of rescue medication.

A single dose of ibuprofen 400 mg is an effective analgesic, providing at least 50% pain relief to over half of the treated patients with acute, moderate to severe, postoperative pain. The NNT of 2.5 for at least 50% pain relief compares favourably with other analgesics commonly used for postoperative pain. In single dose, it is associated with a low rate of adverse events, similar to that with placebo. Lower doses provide slightly lower levels of analgesia. The 200 mg dose has a shorter duration of action. The more soluble salts of ibuprofen appear to offer better analgesia for a longer time. The amount of information available for 200 mg and 400 mg dwarfs almost all other analgesics except paracetamol and aspirin.

Implications for research

The most important implication for research is to clarify the apparent difference in efficacy between the standard and more soluble preparations of ibuprofen. A preparation with better efficacy than standard ibuprofen may present an opportunity to provide equivalent analgesia at a reduced dose, and potentially improve safety in longer term use. It should always be the goal to use the lowest dose of a drug that provides the desired clinical effect, and lower doses are likely to be associated with fewer adverse events in clinical practice.

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CHARACTERISTICS OF STUDIES

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

Ahlstrom 1993

Methods	RCT, DB, DD, single oral dose, 3 parallel groups Medication administered when baseline pain was of least moderate intensity Pain assessed at 0, 20, 40, 60 mins then hourly up to 6 hours.
Participants	Third molar extraction N = 127 (97 valid for analysis) M/F not given Mean age 25 years
Interventions	Ibuprofen 400 mg, n = 32 Diclofenac (drinkable) 50 mg, n= 35 Placebo n= 30
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Arnold 1990

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins then hourly up to 6 hours.
Participants	General surgery (including gynaecological and orthopaedic) N = 59 M = 35, F = 24 Age: 22 - 70 years
Interventions	Ibuprofen 400 mg, n = 15 Ketoprofen 25 mg, n = 14 Ketoprofen 100 mg, n = 16 Placebo, n = 14
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals due to AE
Notes	Oxford Quality Score: R2, DB2, W0 Rescue medication permitted - no further details.

Bakshi 1994

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of severe intensity Pain assessed at 0, 20, 40, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 257 (245 valid for analysis) M = 151, F = 94 Mean age 28 years
Interventions	Ibuprofen 400 mg, n = 80 Diclofenac (dispersible) 50 mg, n = 83

Bakshi 1994 *(Continued)*

	Placebo, n = 82
Outcomes	PI: std 100 mm VAS PR: std 5 point scale PGE: non-std 4 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Rescue medication of patient's choice permitted after 1 hour.

Black 2002

Methods	RCT, DB, DD, single then multiple oral dose, 5 parallel groups multicentre Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 498 M = 219, F = 279 Mean age 22 years
Interventions	Ibuprofen 200 mg, n = 100 Ibuprofen 400 mg, n = 100 Ibuprofen arginate 200 mg, n = 100 Ibuprofen arginate 400 mg, n = 99 Placebo, n = 99
Outcomes	PI: std 5 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication was 2nd dose (or active treatment if in placebo group) as required.

Cheung 2007

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity (≥ 50 mm) Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 12 hours, then at 16, 24 hours.
Participants	Third molar extraction N = 171 M = 77, F = 94 Mean age 22 years
Interventions	Ibuprofen 440 mg, n = 57 Celecoxib 400 mg, n = 57 Placebo, n = 57
Outcomes	PI: std 4 point scale PR: std 5point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication (not ibuprofen or celecoxib) permitted after 1 hour.

Cooper 1977

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline then hourly up to 4 hours.
Participants	Third molar extraction N = 245 (192 analysed) M = 83, F = 109 Age 16-35 years
Interventions	Ibuprofen 200 mg n = 38 Ibuprofen 400 mg, n = 40 Aspirin 325 mg, n = 37 Aspirin 650 mg, n = 37

Cooper 1977 *(Continued)*

	Placebo, n= 40
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Cooper 1982

Methods	RCT, DB, single oral dose, 6 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline then hourly up to 4 hours.
Participants	Third molar extraction N = 316 (249 analysed) M = 83, F = 166 Mean age 23 years
Interventions	Ibuprofen 400 mg, n =38 Ibuprofen 400 mg + Codeine 60 mg, n = 41 Aspirin 650 mg, n = 38 Aspirin 650 mg + codeine 60 mg, n = 45 Codeine 60 mg, n = 41 Placebo, n = 46
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Cooper 1988a

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline then hourly up to 4 hours.
Participants	Third molar extraction N = 201 M = 59, F = 102 (161 analysed) Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 37 Ketoprofen 100 mg, n = 39 Ketoprofen 25 mg, n = 42 Placebo, n = 43
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Cooper 1989

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 4 hours.
Participants	Third molar extraction N = 194 (184 analysed for efficacy, 190 for safety) M = 51, F = 133 Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 61 Paracetamol 1000 mg, n = 59 Placebo, n = 64

Cooper 1989 *(Continued)*

Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 1 hour.

Cooper 1996a

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 70 M = 31, F = 39 Mean age 22 years
Interventions	Ibuprofen 200 mg, n = 19 Misoprostal 200 mg, n = 18 Ibuprofen 200 mg + misoprostal 200 mg, n = 20 Placebo, n = 13
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication
Notes	Oxford Quality Score: R1, DB1, W0 Rescue medication permitted after 2 hours.

De Miguel Rivero 1997

Methods	RCT, DB, DD, single oral or intramuscular dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity

De Miguel Rivero 1997 *(Continued)*

	Pain assessed at 0, 10, 20, 30, 45, 60, 90, 120 mins, then hourly up to 5 hours.
Participants	Total hip replacement N = 103 (106 randomised, 3 did not need medication) M = 47, F = 56 Mean age 62 years
Interventions	Ibuprofen arginine 400 mg, n = 36 Magnesic dipyrone, 2 g (IM), n = 33 Placebo, n = 34
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Desjardins 2002

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 5, 10, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 225 M = 103, F = 122 Mean age 25 years
Interventions	Ibuprofen 200 mg, n = 50 Ibuprofen 400 mg, n = 52 Ibuprofen arginate 200 mg, n = 49 Ibuprofen arginate 400 mg, n = 50 Placebo, n = 24
Outcomes	PI: std 4 point scale PR: std 5 point scale

Desjardins 2002 *(Continued)*

	PGE: std 5 point scale
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication (paracetamol plus codeine) permitted after 1.5 hours.

Dionne 1998

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 45, 60 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 181 (176 analysed for efficacy)
	M = 50, F = 126
	Mean age 22 years
Interventions	S(+)-Ibuprofen 200 mg, n = 51
	S(+)-Ibuprofen 400 mg, n = 50
	Ibuprofen (racemic) 400 mg, n = 50
	Placebo, n = 25
Outcomes	PI: std 4 point scale and 100 mm VAS
	PR: std 5 point scale and 100 mm VAS
	Time to use of rescue medication
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication permitted - no further details.

Edwards 2002

Methods	Five RCTs, DB, single oral dose, parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60 mins, then hourly up to 8 hours.
Participants	Third molar extraction
	N = 339

Edwards 2002 *(Continued)*

	M/F nor given
	Age not given
Interventions	Ibuprofen 400 mg, n = 338
	Placebo, n = 339
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	R2, DB2, W1
	Rescue medication permitted - no further details.

Ehrich 1999

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 104
	M = 97, F = 5
	Mean age 25 years
Interventions	Ibuprofen 400 mg, n = 20
	Rofecoxib 50 mg, n = 32
	Rofecoxib 500 mg, n = 20
	Placebo, n = 32
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W0

Ehrich 1999 *(Continued)*

	Rescue medication (paracetamol) permitted at any time.

Forbes 1984

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline, then hourly up to 12 hours.
Participants	Third molar extraction N = 113 M = 52, F = 57 Mean age 21 years
Interventions	Ibuprofen 400 mg, n = 28 Fendosal 200 mg, n = 29 Aspirin 650 mg, n = 24 Placebo, n= 28
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Forbes 1990

Methods	RCT, DB, single then multiple oral dose, 6 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline, then hourly up to 6 hours
Participants	Third molar extraction N = 269 (206 analysed for efficacy, 244 for safety) M = 104, F = 102 Mean age 23 years

Forbes 1990 *(Continued)*

Interventions	Ibuprofen 400 mg, n = 32 Ketorolac 10 mg, n = 31 Ketorolac 20 mg, n = 35 Paracetamol 600 mg, n = 36 Paracetamol 600 mg + codeine 60 mg, n = 38 Placebo, n = 34
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Forbes 1991a

Methods	RCT, DB, single oral dose, 6 parallel groups, multicentre Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 8 hours.
Participants	Third molar extraction N = 362 (298 analysed for efficacy, 362 for safety) M = 121, F = 177 Mean age 22 years
Interventions	Ibuprofen 50 mg, n = 57 Ibuprofen 100 mg, n = 49 Ibuprofen 200 mg, n = 48 Ibuprofen 100 mg + Caffeine 100 mg, n = 49 Ibuprofen 200 mg + Caffeine 100 mg, n = 44 Placebo, n = 51
Outcomes	PI: std 4 point scale PR: std 5 point scale

Forbes 1991a *(Continued)*

	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication permitted after 2 hours.

Forbes 1991b

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at baseline, then hourly up to 8 hours
Participants	Third molar extraction
	N = 276 (241 analysed for efficacy, 269 for safety)
	M = 100, F = 141
	Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 37
	Bromfenac 5 mg, n = 39
	Bromfenac 10 mg, n = 43
	Bromfenac 25 mg, n = 42
	Aspirin 650 mg, n = 41
	Placebo, n = 39
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication permitted after 2 hours.

Forbes 1992

Methods	RCT, DB, single oral dose, 7 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline, then hourly up to 8 hours.
Participants	Third molar extraction N = 324 (280 analysed for efficacy, 317 for safety) M = 119, F = 161 Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 38 Bromfenac 10 mg, n = 43 Bromfenac 25 mg, n = 41 Bromfenac 50 mg, n = 42 Bromfenac 100 mg, n = 40 Aspirin 650 mg, n = 38 Placebo, n = 38
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Frame 1989

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 5 hours
Participants	Third molar extraction N = 139 (123 analysed for efficacy) M = 56, F = 92

Frame 1989 *(Continued)*

	Mean age 24 years
Interventions	Ibuprofen 400 mg, n = 42 Dihydrocodeine 30 mg, n = 43 Placebo, n = 38
Outcomes	PI: non-std 9 point scale PR: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Rescue medication (2nd dose or active drug if placebo group) permitted after 2 hours.

Fricke 1993

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 20, 30, 40, 60 mins, then hourly up to 12 hours.
Participants	Third molar extraction N = 202 (201 analysed for efficacy) M = 77, F = 124 Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 81 Naproxen Na 440 mg, n = 81 Placebo, n = 39
Outcomes	PI: std 4 point scale and 100 mm VAS PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1

Fricke 1993 *(Continued)*

	Rescue medication permitted after 2 hour.

Gay 1996

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at "regular intervals" up to 6 hours.
Participants	Third molar extraction N = 206 (204 analysed for efficacy) M = 86, F = 118 Mean age 24 years
Interventions	Ibuprofen 400 mg, n = 41 Dexketoprofen 5 mg, n = 41 Dexketoprofen 10 mg, n = 42 Dexketoprofen 20 mg, n = 41 Placebo, n = 39
Outcomes	PI: std 4 point scale and 100 mm VAS PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Heidrich 1985

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Orthopaedic surgery N = 120 M = 72, F = 48

Heidrich 1985 *(Continued)*

	Mean age 31 years
Interventions	Ibuprofen 400 mg, n = 40 Paracetamol 300 + codeine 30 mg, n = 40 Placebo, n = 40
Outcomes	PI: std 4 point scale and 100 mm VAS PR: std 5 point scale and 100 mm VAS Numbers of participants using rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB1, W0 No details about rescue medication.

Hersch 1993a

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 8 hours.
Participants	Third molar extraction N = 254 M/F not given Age 16+ years
Interventions	Ibuprofen 200 mg, n = 51 Ibuprofen 400 mg, n = 49 Meclofenamate 100 mg, n = 52 Meclofenamate 50 mg, n = 51 Placebo, n = 51
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB1, W0

Hersch 1993a *(Continued)*

	Rescue medication permitted after 1 hour.

Hersch 1993b

Methods	RCT, DB, pre-surgery placebo then single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30 60 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 103 (81 analysed) M/F not given Age not given
Interventions	All participants received preoperative placebo, then: Ibuprofen 400 mg, n = 12 Codeine 60 mg, n = 16 Placebo, n = 16
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Hersh 2000

Methods	RCT, DB, DD, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity (≥50 mm) Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 210 M = 66, F = 144 Mean age 24 years
Interventions	Ibuprofen liquigel 200 mg, n = 61 Ibuprofen liquigel 400 mg, n = 59

Hersh 2000 *(Continued)*

	Paracetamol 1000 mg, n = 63
	Placebo, n = 27
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication (paracetamol+hydrocodone) permitted after 1 hour

Hill 2001

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60, mins, then hourly up to 12 hours.
Participants	Third molar extraction
	N = 198
	M = 82, F = 116
	Mean age 26 years
Interventions	Ibuprofen 400 mg, n = 49
	Pregabalin 50 mg, n = 49
	Pregabalin 300 mg, n = 50
	Placebo, n = 50
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1

Hill 2001 *(Continued)*

	Rescue medication permitted - no further details

Jain 1986

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline, then hourly up to 6 hours.
Participants	Third molar extraction N = 241 (227 analysed for efficacy) M = 100, F = 127 Mean age 24 years
Interventions	Ibuprofen 400 mg, n = 49 Ibuprofen 200 mg, n = 47 Ibuprofen 100 mg, n = 39 Aspirin 650 mg, n = 45 Placebo, n = 47
Outcomes	PI: non-std 4 point scale and 100 mm VAS PR: non-std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 1 hr.

Jain 1988

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Episiotomy N = 161 (147 analysed) All F

Jain 1988 *(Continued)*

	Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 49 Ibuprofen 200 mg + caffeine 100 mg, n = 50 Placebo, n = 48
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Johnson 1997

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 60 mins, then hourly up to 6 hours.
Participants	Obstetric and gynaecological surgery N = 238 (236 analysed) All F Mean age 41 years
Interventions	Ibuprofen 400 mg, n = 48 Paracetamol 650 mg + oxycodone 10 mg, n = 47 Bromfenac 100 mg, n = 48 Bromfenac 50 mg, n = 47 Placebo, n = 48
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event

Johnson 1997 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication (2nd dose or investigator's choice) permitted after 1 hour.

Kiersch 1993

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 20, 30, 40, 60 mins, then hourly up to 12 hours.
Participants	Third molar extraction
	N = 205 (203 analysed for efficacy)
	M = 90, F = 113
	Mean age 25 years
Interventions	Ibuprofen 200 mg, n = 81
	Naproxen Na 220 mg, n = 80
	Placebo, n = 42
Outcomes	PI: std 4 point scale and 100 mm VAS
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1
	Rescue medication permitted after 2 hours.

Laska 1986

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 200 (191 analysed for efficacy)
	M/F not given

Laska 1986 *(Continued)*

	Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 39 Ibuprofen 600 mg, n = 36 Ibuprofen 800 mg, n = 39 Aluminium ibuprofen 400 mg, n = 39 Placebo, n = 37
Outcomes	PI: std 4 point scale PR: std 5 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Laveneziana 1996

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Inguinal hernia N = 124 All M Mean age 50 years
Interventions	Ibuprofen arginine soluble 400 mg, n = 42 Ketorolac 30 mg, n = 41 Placebo, n = 41
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

Laveneziana 1996 *(Continued)*

	Rescue medication permitted after 1 hour.

Malmstrom 1999

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 272 M = 100, F = 172 Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 46 Rofecoxib 50 mg, n = 90 Celecoxib 200 mg, n = 91 Placebo, n = 45
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication (paracetamol ±hydrocodone) permitted after 1.5 hours.

Malmstrom 2002

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 8 hours, then at 10, 12 and 24 hours.
Participants	Third molar extraction N = 482 M = 124, F = 358 Mean age 22 years
Interventions	Ibuprofen 400 mg, n = 45

Malmstrom 2002 *(Continued)*

	Rofecoxib 50 mg, n = 151
	Celecoxib 400 mg, n = 151
	Celecoxib 200 mg, n = 90
	Placebo, n = 45
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication (paracetamol ± hydrocodone) permitted after 1.5 hours.

Malmstrom 2004

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 8 hours, then at 12 and 24 hours.
Participants	Third molar extraction
	N = 398
	M = 147, F = 251
	Mean age 25 years
Interventions	Ibuprofen 400 mg, n = 48
	Etoricoxib 60 mg, n = 75
	Etoricoxib 120 mg, n = 76
	Etoricoxib 180 mg, n = 74
	Etoricoxib 240 mg, n = 76
	Placebo, n = 49
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication

Malmstrom 2004 *(Continued)*

	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication (paracetamol ± hydrocodone) permitted at any time.

McQuay 1996

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed up to 6 hours (time points not specified).
Participants	Third molar extraction
	N = 161
	M = 59, F = 102
	Mean age 25 years
Interventions	Ibuprofen 200 mg, n = 31
	Ibuprofen 400 mg, n = 30
	Ibuprofen 200 mg + caffeine 50 mg, n = 30
	Ibuprofen 200 mg + caffeine 100 mg, n = 30
	Ibuprofen 200 mg + caffeine 200 mg, n = 29
	Placebo, n = 11
Outcomes	PI: std 4 point scale and 100 mm VAS
	PR: std 5 point scale and 100 mm VAS
	PGE: std 5 point scale
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication permitted after 45 mins.

Medve 2001

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60 mins, then hourly up to 8 hours.
Participants	Third molar extraction

Medve 2001 *(Continued)*

	N = 1197
	M = 476, F = 721
	Mean age 21 years
Interventions	Ibuprofen 200 mg, n = 240
	Tramadol 37.5 mg, n = 238
	Paracetamol 325 mg, n = 240
	Tramadol 37.5 mg + paracetamol 325 mg, n = 240
	Placebo, n = 239
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Time to use of rescue medication
Notes	Oxford Quality Score: R1, DB2, W0
	Rescue medication permitted after 2 hours.

Mehlisch 1990

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Various oral surgery procedures
	N = 705 (697 analysed for efficacy)
	M = 277, F = 420
	Mean age 31 years
Interventions	Ibuprofen 400 mg, n = 306
	Paracetamol 1000 mg, n = 306
	Placebo, n = 85
Outcomes	PI: std 4 point scale
	PR: non-std 4 point scale
	Numbers of participants using rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1

Mehlisch 1990 *(Continued)*

	Rescue medication permitted (time not specified).

Mehlisch 1995

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 240 (239 analysed for efficacy)
	M = 85, F = 155
	Mean age 25 years
Interventions	Ibuprofen lysine 400 mg, n = 98
	Paracetamol 1000 mg, n = 101
	Placebo, n = 40
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication permitted after 1 hour (but were encouraged to wait for 4 hrs).

Mehlisch 2002

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 500
	M/F not given
	Mean age 26 years
Interventions	Ibuprofen 200 mg, n = 100

Mehlisch 2002 *(Continued)*

	Ibuprofen 400 mg, n = 100
	Ibuprofen arginine 200 mg, n = 100
	Ibuprofen arginine 400 mg, n = 100
	Placebo, n = 100
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication permitted after 1 hour.

Morrison 1999

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 151
	M = 75, F = 76
	Mean age 18 years
Interventions	Ibuprofen 400 mg, n = 51
	Rofecoxib 50 mg, n = 50
	Placebo, n = 50
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals

Morrison 1999 *(Continued)*

Notes	Oxford Quality Score: R2, DB1, W1 Rescue medication (paracetamol+hydrocodone) permitted after 1.5 hours.

Nelson 1994

Methods	RCT, DB, DD, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 183 (180 analysed for efficacy) M = 72, F = 111 Mean age 24 years
Interventions	Ibuprofen lysine 200 mg, n = 77 Aspirin 500 mg, n = 65 Placebo, n = 40
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 2 hours.

Nørholt 1998

Methods	RCT, DB, single oral dose, 2 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at baseline, then hourly up to 4 hours.
Participants	Third molar extraction N = 57 M = 21, F = 36

Nørholt 1998 *(Continued)*

	Mean age 24 years
Interventions	Ibuprofen 400 mg, n = 26 Placebo, n = 31
Outcomes	PI: non-std 5 point scale PR: 5 point scale - reverse wording Numbers of participants using rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (paracetamol) permitted.

Olson 2001

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 239 M = 76, F = 163 Mean age 23 years
Interventions	Ibuprofen liquigel 400 mg, n = 67 Ketoprofen 25 mg, n = 67 Paracetamol 1000 mg, n = 66 Placebo, n = 39
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication (standard analgesic) permitted.

Pagnoni 1996

Methods	RCT, DB, DD, single oral dose, 3 parallel groups Medication administered when baseline pain intensity was at least 55 mm Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Caesarean section N = 92 All F Mean age 32 years
Interventions	Ibuprofen arginine soluble 400 mg, n = 30 Ketorolac (IM) 30 mg, n = 30 Placebo, n = 32
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (ketoprofen IM) permitted after 1 hour.

Parker 1986

Methods	RCT, DB, single oral dose then multiple doses, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 4 hours.
Participants	Tonsillectomy N = 139 (110 analysed) M/F not given Age range 16 - 66 years
Interventions	Ibuprofen syrup 600 mg, n = 44 Aspirin syrup 600 mg, n = 33 Placebo, n = 33
Outcomes	PI: non-std 9 point scale

Parker 1986 *(Continued)*

	PR: std 5 point scale
	PGE: std 5 point scale
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W0
	Rescue medication (oral or IM) permitted.

Schachtel 1989

Methods	RCT, DB, single oral dose then multiple doses, 3 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 30, 60 mins, then hourly up to 4 hours.
Participants	Episiotomy
	N = 115 (111 analysed)
	Mean age 27 years
Interventions	Ibuprofen 400 mg, n = 36
	Paracetamol 1000 mg, n = 37
	Placebo, n = 38
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1
	Rescue medication permitted after 1 hour.

Schou 1998

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at baseline, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 280 (258 analysed for efficacy)
	M = 132, F = 126

Schou 1998 *(Continued)*

	Mean age 26 years
Interventions	Ibuprofen 50 mg, n = 51 Ibuprofen 100 mg, n = 53 Ibuprofen 200 mg, n = 49 Ibuprofen 400 mg, n = 49 Placebo, n = 56
Outcomes	PI: non-std 5 point scale PR: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (paracetamol) permitted after 1 hour.

Schwartz 2007

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity. Pain assessed at 0, 15, 30, 75, 120 mins, then hourly up to 8 hours, then at 12 and 24 hours.
Participants	Third molar extraction N = 121 M = 65, F = 56 Mean age 23 years
Interventions	Ibuprofen 400 mg, n = 15 MK-0703 12.5 mg, n = 31 MK-0703 50 mg, n = 28 MK-0703 100 mg, n = 31 Placebo, n = 16 [MK-0703 is a Cox-2 selective inhibitor]
Outcomes	PI: std 4 point scale PR: non-std 4 point scale PGE: std 5 point scale Numbers of participants using rescue medication

Schwartz 2007 *(Continued)*

	Time to use of rescue medication
	Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1
	Rescue medication (hydrocodone bitartrate plus paracetamol as needed) permitted after 1.5 hours

Seymour 1991 (study 1)

Methods	RCT, DB, DD, single oral dose, 3 parallel groups
	Medication administered when baseline pain was more than 30 mm.
	Pain assessed at 0, 10, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 187 (study 1 and study 2)
	M = 60, F = 127
	Mean age 26 years
Interventions	Ibuprofen tablets 400 mg, n = 31
	Ibuprofen liquid in gelatin capsules 400 mg, n = 32
	Placebo n = 32
Outcomes	PI: std 100 mm VAS
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals due to adverse events
Notes	Oxford Quality Score: R1, DB2, W0
	Rescue medication (Co-codamol) permitted.

Seymour 1991 (study 2)

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain intensity was more than 30 mm.
	Pain assessed at 0, 10, 20, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 187 (study 1 and study 2)
	M = 60, F = 127

Seymour 1991 (study 2) *(Continued)*

	Mean age 26 years
Interventions	Ibuprofen tablets 400 mg, n = 30 Ibuprofen soluble 400 mg, n = 32 Placebo, n = 30
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals due to adverse events
Notes	Oxford Quality Score: R1, DB2, W0 Rescue medication (Co-codamol) permitted.

Seymour 1996

Methods	RCT, DB, single oral dose, 7 parallel groups Medication administered when baseline pain intensity was at least 30 mm Pain assessed at 0, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 123 (119 analysed) M = 41, F = 78 age range 18-40 years
Interventions	Ibuprofen tablets 200 mg, n = 18 Ibuprofen soluble 200 mg, n = 17 Ibuprofen tablets 400 mg, n = 15 Ibuprofen soluble 400 mg, n = 16 Ibuprofen tablets 600 mg, n = 17 Ibuprofen soluble 600 mg, n = 17 Placebo, n = 19
Outcomes	PI: std 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication

Seymour 1996 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (paracetamol) permitted.

Seymour 1998

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120, 150 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 217 M = 102, F = 115 Mean age 25 years
Interventions	Ibuprofen 400 mg, n = 76 Aceclofenac 150 mg, n = 71 Placebo, n = 70
Outcomes	PI: std 100 mm VAS PR: std 100 mm VAS PGE: non-std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals due to adverse events
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (Co-proxamol) permitted.

Seymour 1999

Methods	RCT, DB, DD, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 122 M = 40, F = 82

Seymour 1999 *(Continued)*

	Mean age 26 years
Interventions	Ibuprofen 400 mg, n = 41 WAG 994 1 mg, n = 42 Placebo, n = 39 (WAG is an adenosine agonist)
Outcomes	PI: std 100 mm VAS PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication
Notes	Oxford Quality Score: R1, DB2, W0 Rescue medication permitted.

Seymour 2000

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 180 M = 58, F = 122 Mean age 27 years
Interventions	Ibuprofen 200 mg, n = 59 Buffered ketoprofen 12.5 mg, n = 61 Placebo, n = 50
Outcomes	PI: std 4 point scale and 100 mm VAS PR: std 5 point scale PGE: non-std 4 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

Seymour 2000 *(Continued)*

	Rescue medication (co-codamol) permitted after 1 hour.

Singla 2005

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Abdominal or pelvic surgery N = 455 All F Mean age 42 years
Interventions	Ibuprofen 400 mg, n = 175 Ibuprofen 400 mg + oxycodone 5 mg, n = 169 Oxycodone 5 mg, n = 52 Placebo, n = 60
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1 Rescue medication permitted.

Sunshine 1983

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 4 hours.
Participants	Episiotomy N = 120 All F Mean age 24 years

Sunshine 1983 *(Continued)*

Interventions	Ibuprofen 400 mg, n = 30 Aspirin 600 mg, n = 30 Zomepirac 100 mg, n = 30 Placebo, n = 30
Outcomes	PI: std 4 point scale PR: non-std 5 point scale PGE: non-std 4 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Sunshine 1987

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 4 hours.
Participants	Episiotomy , caesarean section or gynaecological surgery N = 200 All F Mean age 26 years
Interventions	Ibuprofen 400 mg, n = 38 Ibuprofen 200 mg + codeine 30 mg, n = 40 Ibuprofen 400 mg + codeine 60 mg, n = 40 Codeine 60 mg, n = 37 Placebo, n = 40
Outcomes	PI: std 4 point scale PR: non-std 5 point scale PGE: non-std 4 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals

Sunshine 1987 *(Continued)*

Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Sunshine 1996

Methods	RCT, DB, single oral dose, 6 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Episiotomy N = 305 All F Mean age 23 years
Interventions	Ibuprofen 50 mg, n = 51 Ibuprofen 100 mg, n = 51 Ibuprofen 200 mg, n = 50 Ibuprofen 100 mg + caffeine 100 mg, n = 50 Ibuprofen 200 mg + caffeine 100 mg, n = 50 Placebo, n = 50
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non-std 4 point scale Numbers of participants using rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted after 1 hour.

Sunshine 1997

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly up to 6 hours.
Participants	Caesarian section or gynaecological surgery N = 120

Sunshine 1997 *(Continued)*

	All F
	Mean age 28 years
Interventions	Ibuprofen 400 mg, n = 40
	Ibuprofen 400 mg + hydrocodone 15 mg, n = 40
	Placebo, n = 39
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication permitted.

Sunshine 1998

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction
	N = 179 (175 analysed for efficacy)
	M = 58, F = 117
	Mean age 22 years
Interventions	Ibuprofen 200 mg, n = 35
	Ketoprofen 6.25 mg, n = 35
	Ketoprofen 12.5 mg, n = 35
	Ketoprofen 25 mg, n = 35
	Placebo, n = 35
Outcomes	PI: std 4 point scale
	PR: std 5 point scale and 100 mm VAS
	PGE: non-std 4 point scale
	Time to use of rescue medication
	Numbers with any adverse event

Sunshine 1998 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (paracetamol) permitted after 1 hour.

Van Dyke 2004

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 498 M = 219, F = 279 Mean age 25 years
Interventions	Ibuprofen 400 mg, n = 186 Ibuprofen 400 mg + oxycodone 5 mg, n = 187 Oxycodone 5 mg, n = 63 Placebo, n = 62
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 2 hours.

Wahl 1997

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 6 hours.
Participants	Third molar extraction N = 164 (163 analysed for efficacy)

Wahl 1997 *(Continued)*

	M = 88, F = 75
	Mean age 27 years
Interventions	Ibuprofen lysinate 342 mg (=200 mg Ibu), n = 74
	Paracetamol 200 mg + aspirin 250 mg + caffeine 50 mg, n = 73
	Placebo, n = 42
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: non-std 6 point scale
	Numbers of participants using rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1
	Rescue medication permitted.

Wideman 1999 (study 1)

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 20, 40, 60, 80, 100, 120, 150, 180 mins, then hourly up to 7 hours.
Participants	Abdominal or gynaecological surgery
	N = 240
	All F
	Mean age 39 years
Interventions	Ibuprofen 200 mg, n = 60
	Ibuprofen 200 mg, + hydrocodone 7.5 mg, n = 59
	Hydrocodone 7.5 mg, n = 61
	Placebo, n = 60
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

Wideman 1999 (study 1) *(Continued)*

	Rescue medication permitted after 1 hour.

Wideman 1999 (study 2)

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 20, 40, 60, 80, 100, 120, 150, 180 mins, then hourly up to 8 hours.
Participants	Abdominal or gynaecological surgery
	N = 201
	All F
	Mean age 40 years
Interventions	Ibuprofen 400 mg, n = 50
	Ibuprofen 400 mg + hydrocodone 15 mg, n = 50
	Hydrocodone 15 mg, n = 50
	Placebo, n = 51
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale
	Numbers of participants using rescue medication
	Time to use of rescue medication
	Numbers with any adverse event
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1
	Rescue medication permitted after 1 hour.

Zelenakas 2004

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain was of moderate to severe intensity
	Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly up to 12 hours.
Participants	Third molar extraction
	N = 202
	M = 77, F = 125
	Mean age 22 years

Zelenakas 2004 *(Continued)*

Interventions	Ibuprofen 400 mg, n = 51 Lumiracoxib 100 mg, n = 51 Lumiracoxib 400 mg, n = 50 Placebo, n = 50
Outcomes	PI: std 4 point scale PR: std 5 point scale and 100 mm VAS PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication (paracetamol+hydrocodone) permitted after 1 hour.

DB - double blind; DD - double dummy; PGE - patient global evaluation of efficacy; PI - pain intensity; PR - pain relief; R - randomised; RCT - randomised controlled trial; std - standard; W - withdrawals

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

Study	Reason for exclusion
Ahlstrom 1989	No placebo control.
Akural 2009	Medication administered preoperativley.
Anaokar 1993	No placebo control.
Apaydin 1994	No placebo control.
Apiou 1988	No placebo control.
Aranda 1989	No placebo control.
Averbuch 2000	Not an original report of trials, and unable to ensure that participants (total of 75 treated with ibuprofen) were not in another included study.
Bailey 1993	No placebo control.
Behotas 1992	Baseline pain intensity was not moderate to severe.
Bhounsule 1990	Did not state whether patients had a baseline pain of at least moderate intensity.
Biehl 1981	No placebo control.
Bloomfield 1974	Used 5 point pain intensity scale which is not validated for the data extraction method.

Study	Reason for exclusion
Calanchini 1991	No placebo control.
Carlos 1984	Could not be obtained despite attempts to contact the authors, ordering through the British Library and help from the librarians at Novartis and Knoll pharmaceuticals.
Carrillo 1990	Did not state when the interventions were administered but as the pain levels were recorded for the first 4 hours following surgery it may be assumed that they were given immediately postoperatively. Therefore insufficient baseline pain.
Chopra 2009	Medication administered at 1 hour, irrespective of baseline pain.
Cooper 1984	Inadequate description of method. Did not state whether interventions were randomly allocated or studies were double-blind.
Cooper 1988b	Inadequate description of method. Did not state whether interventions were randomly allocated.
Cooper 1993	No placebo control.
Cooper 1996b	Intervention administered irrespective of postoperative baseline pain.
Darsow 1988	No direct pain outcome measured over the first 4-6 hours (recorded motility etc in the days following surgery).
Dorfmann 1991	Inadequate description of method. Did not say whether the allocation was randomised, did not say when the interventions were administered postoperatively, no mention of the level of baseline pain and did not define the pain measurement used.
Doyle 2002	No usable data for ibuprofen treatment arm.
El-Tanany 1993	No placebo control.
Fleiss 1979	Take medication "if experience pain". Cannot assume that all the patients included had a baseline pain of >moderate intensity.
Forbes 1991	Used a controlled release formulation of ibuprofen.
Frezza 1985	Could not be obtained despite attempts to contact the authors, ordering through the British Library and help from the librarians at Novartis and Knoll pharmaceuticals.
Gallardo 1980	Baseline pain intensity not moderate to severe.
Gallardo 1981	Data was only collected for three hours.
Garwood 1983	No placebo control.
Giles 1981	No placebo control.
Giles 1985	Did not state which scale was used.
Hazra 1982	Baseline pain intensity not moderate to severe.
Henderson 1994	No placebo control.
Henrikson 1982	Only presented the data for the placebo arm for the first hour.

Study	Reason for exclusion
Henrikson 1985	No placebo control.
Hopkinson 1980	Five point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Hultin 1978	Cross-over study with the first dose administered exactly 1 hour after the local anaesthetic rather than when the patient experienced at least moderate pain.
Hyrkas 1992	Intervention administered preoperatively. Therefore inadequate baseline pain.
Hyrkas 1993	Intervention administered preoperatively. Therefore inadequate baseline pain.
Hyrkas 1994	Intervention administered preoperatively. Therefore inadequate baseline pain.
Iles 1980	Data was only presented for one hour after administration of the interventions.
Iqbal 1986	Could not be obtained despite attempts to contact the authors, ordering through the British Library and help from the librarians at Novartis and Knoll pharmaceuticals.
Iwabuchi 1980	No placebo control.
Joubert 1977	Could not be obtained despite attempts to contact the authors, ordering through the British Library and help from the librarians at Novartis and Knoll pharmaceuticals.
Katharia 1992	Multiple dose study with no separate analysis of the first dose.
Khan 1992	No placebo control.
Kittala 1972	Intervention routinely administered to all participants irrespective of level of baseline pain.
Klein 1994	Abstract.
Mastronardi 1988	No placebo control.
Matthews 1984	First dose was administered immediately postoperatively irrespective of patients level of pain.
McEvoy 1996	No placebo control.
McQuay 1993	No placebo control.
Movilia 1990	First dose was administered immediately postoperatively irrespective of patients level of pain.
Nakanishi 1990	No placebo control.
Negm 1989	Included participants who took the medication when they were experiencing only mild pain.
Rondeau 1980	Baseline pain intensity not moderate to severe.
Rossi 1981	Inadequate description of method. Did not state whether study was double blind. Also data was only recorded for three hours.
Schleier 2007	No placebo control.
Shimura 1981	No placebo control.

Study	Reason for exclusion
Squires 1981	Intervention administered preoperatively. Therefore inadequate baseline pain.
Tai 1992	No placebo control.
Tani 1974	No placebo control.
Tesseroli 1986	The only measure of pain which was in the opinion of the patient rather than the investigator was the pain intensity VAS. At baseline, the mean VAS minus 1.96 x SD was less than 30 mm, therefore some patients included may have had a baseline pain intensity of less than moderate.
Troullos 1990	Intervention administered preoperatively. Therefore inadequate baseline pain.
Turcotte 1986	Baseline pain intensity not moderate to severe.
Van Der Zwan 1982	No direct pain outcome measurement used, pain assessed by analgesic intake.
Van Wering 1972	No placebo control.
Vigneron 1977	Could not be obtained despite attempts to contact the authors, ordering through the British Library and help from the librarians at Novartis and Knoll pharmaceuticals.
Vogel 1984	Combined the data from separate arms of a cross-over trial into one data set.
Von Mayer 1980	Multiple dose study with no mention of the level of baseline pain.
Walker 1976	No placebo control.
Walton 1990	Intervention administered preoperatively. Therefore inadequate baseline pain.
Walton 1993	First dose was given im during surgery, then oral doses were given postoperatively at specified times rather than when patients had baseline pain of at least moderate intensity.
Weber 1990	No placebo control.
Winter 1978	Baseline pain intensity not moderate to severe.
Wuolijoki 1987	Interventions were administered either pre-operatively or immediately post-operatively. Therefore insufficient baseline pain.

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

Daniels 2009

Methods	RCT, DB, DD single dose
Participants	Third molar extraction, experiencing moderate to severe postoperative pain
Interventions	Sodium ibuprofen 512 mg, ibuprofen/poloxamer 400 mg/60 mg, paracetamol 1000 mg, placebo
Outcomes	Pain intensity and pain relief, onset of pain relief, tolerability
Notes	

Kleinert 2008

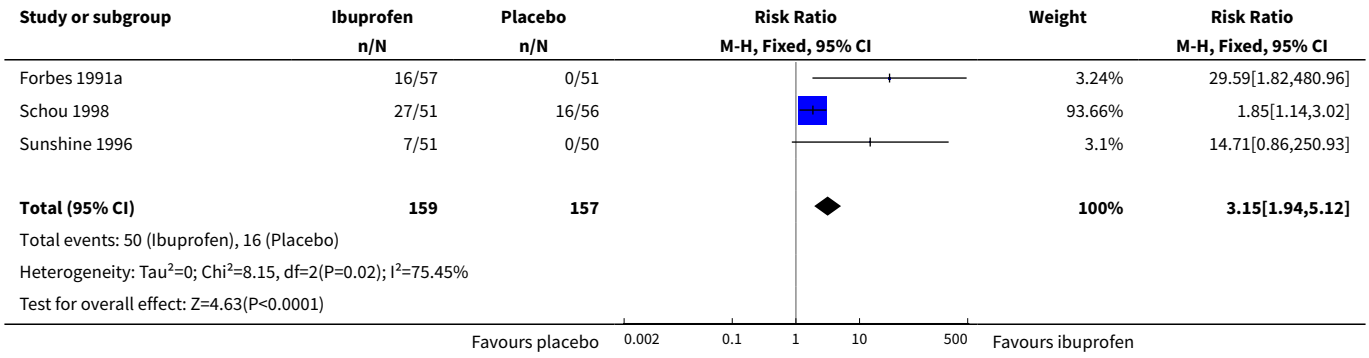
Methods	RCT, DB, single dose
Participants	Mandibular third molar extraction, experiencing moderate to severe postoperative pain
Interventions	Tapentodol HCl 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, morphine sulphate 60 mg, ibuprofen 400 mg, placebo
Outcomes	Pain relief, adverse events
Notes	

DATA AND ANALYSES

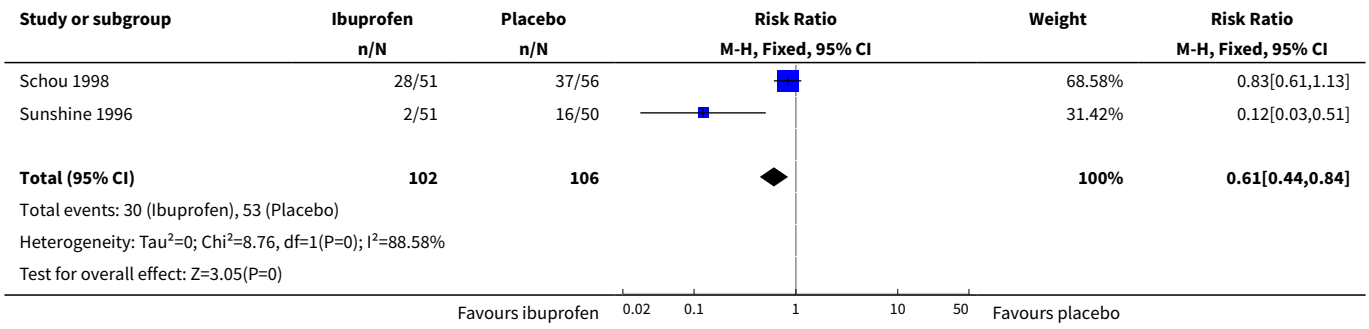
Comparison 1. Ibuprofen 50 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	3	316	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [1.94, 5.12]
2 Participants using rescue medication over 6 hours	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.84]
3 Participants with any adverse event	2	225	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.57, 3.00]

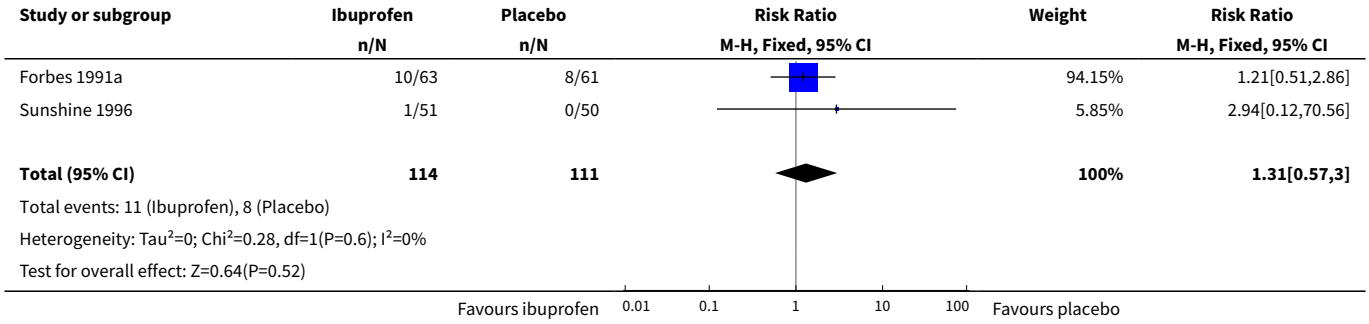
Analysis 1.1. Comparison 1 Ibuprofen 50 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.



Analysis 1.2. Comparison 1 Ibuprofen 50 mg versus placebo, Outcome 2 Participants using rescue medication over 6 hours.



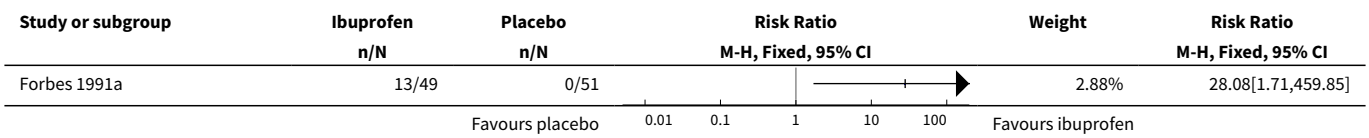
Analysis 1.3. Comparison 1 Ibuprofen 50 mg versus placebo, Outcome 3 Participants with any adverse event.

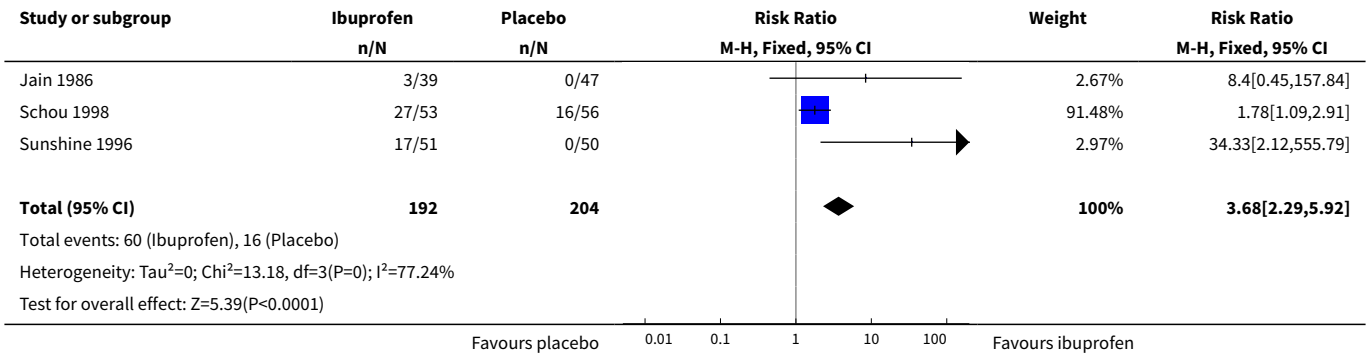


Comparison 2. Ibuprofen 100 mg versus placebo

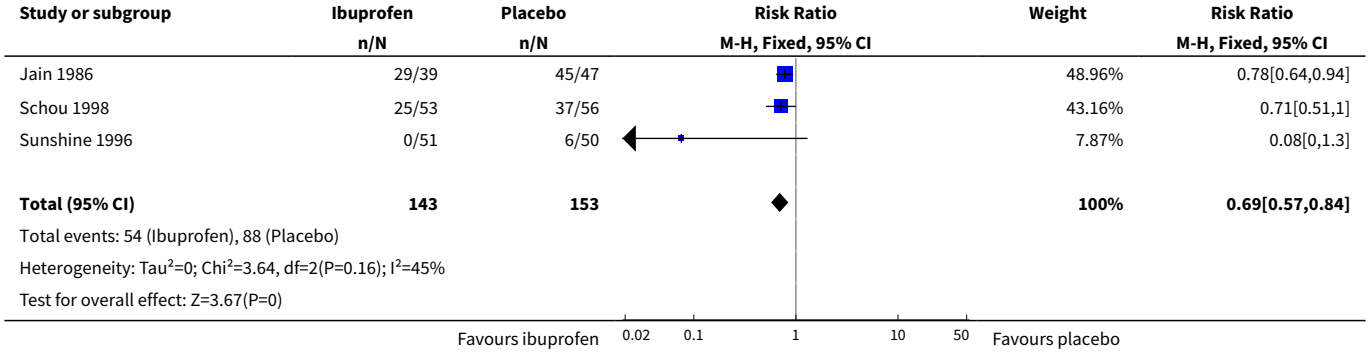
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	4	396	Risk Ratio (M-H, Fixed, 95% CI)	3.68 [2.29, 5.92]
2 Participants using rescue medication over 6 hours	3	296	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.57, 0.84]
3 Participants with any adverse event	3	310	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.71, 2.07]

Analysis 2.1. Comparison 2 Ibuprofen 100 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

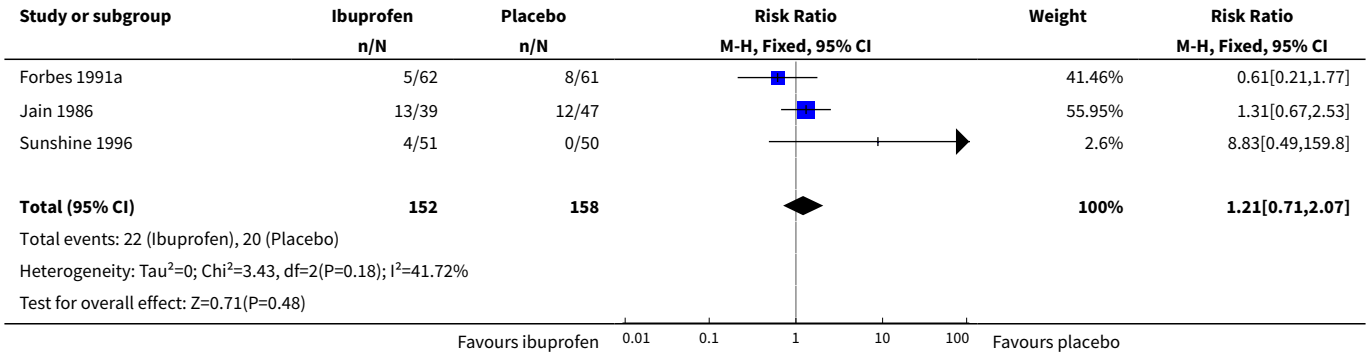




Analysis 2.2. Comparison 2 Ibuprofen 100 mg versus placebo, Outcome 2 Participants using rescue medication over 6 hours.



Analysis 2.3. Comparison 2 Ibuprofen 100 mg versus placebo, Outcome 3 Participants with any adverse event.



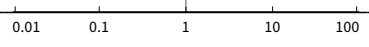
Comparison 3. Ibuprofen 200 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	20	2690	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [3.85, 5.56]
2 Participants with at least 50% pain relief over 4 to 6 hours: type of surgery	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Dental surgery	18	2470	Risk Ratio (M-H, Fixed, 95% CI)	4.48 [3.71, 5.41]
2.2 Other surgery	2	220	Risk Ratio (M-H, Fixed, 95% CI)	7.73 [3.24, 18.41]
3 Participants with at least 50% pain relief over 4 to 6 hours, all surgery: formulation	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Standard ibuprofen	17	2103	Risk Ratio (M-H, Fixed, 95% CI)	6.11 [4.84, 7.73]
3.2 ibuprofen lysine, arginine, or soluble	7	828	Risk Ratio (M-H, Fixed, 95% CI)	5.73 [4.15, 7.90]
4 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: formulation	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Standard ibuprofen	15	1883	Risk Ratio (M-H, Fixed, 95% CI)	5.98 [4.69, 7.62]
4.2 Ibuprofen lysine, arginine or soluble	7	828	Risk Ratio (M-H, Fixed, 95% CI)	5.73 [4.15, 7.90]
5 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: study size	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 40 or more participants	11	1953	Risk Ratio (M-H, Fixed, 95% CI)	4.56 [3.71, 5.61]
5.2 Fewer than 40 participants	4	229	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [2.41, 11.00]
6 Participants using rescue medication over 6 hours	8	794	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.57, 0.70]
7 Participants using rescue medication over 6 hours, dental surgery	7	694	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.60, 0.73]
8 Participants using rescue medication over 6 hours, dental surgery: formulation	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Standard ibuprofen	4	345	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.66, 0.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Ibuprofen lysine, arginine or soluble	4	349	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.48, 0.68]
9 Participants with any adverse event	14	1808	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.02]

Analysis 3.1. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Black 2002	61/100	13/50		13.87%	2.35[1.43,3.84]
Black 2002	58/100	13/49		13.97%	2.19[1.33,3.59]
Cooper 1977	17/38	6/40		4.68%	2.98[1.32,6.76]
Cooper 1996a	3/19	0/13		0.47%	4.9[0.27,87.59]
Cooper 1996a	3/18	0/13		0.46%	5.16[0.29,92.04]
Desjardins 2002	9/50	0/11		0.65%	4.47[0.28,71.59]
Desjardins 2002	10/49	0/12		0.64%	5.46[0.34,87.19]
Forbes 1991a	18/48	0/51		0.39%	39.27[2.43,634.05]
Hersch 1993a	17/51	0/51		0.4%	35[2.16,566.84]
Hersh 2000	43/61	5/27		5.55%	3.81[1.7,8.54]
Jain 1986	7/47	0/47		0.4%	15[0.88,255.36]
Kiersch 1993	37/81	4/42		4.22%	4.8[1.83,12.55]
McQuay 1996	2/31	0/11		0.58%	1.88[0.1,36.29]
Medve 2001	114/240	5/239		4.01%	22.71[9.44,54.6]
Mehlisch 2002	44/100	7/50		7.47%	3.14[1.53,6.47]
Mehlisch 2002	64/100	6/50		6.4%	5.33[2.48,11.46]
Nelson 1994	44/77	8/40		8.43%	2.86[1.49,5.47]
Schou 1998	36/49	16/56		11.95%	2.57[1.64,4.02]
Seymour 1996	7/18	1/9		1.07%	3.5[0.5,24.27]
Seymour 1996	9/17	1/10		1.01%	5.29[0.78,35.85]
Seymour 2000	14/59	7/60		5.56%	2.03[0.88,4.68]
Sunshine 1996	33/50	0/50		0.4%	67[4.22,1064.23]
Sunshine 1998	20/35	3/35		2.4%	6.67[2.18,20.42]
Wahl 1997	39/74	1/42		1.02%	22.14[3.15,155.34]
Wideman 1999 (study 1)	9/60	5/60		4%	1.8[0.64,5.06]
Total (95% CI)	**1572**	**1118**		**100%**	**4.62[3.85,5.56]**
Total events: 718 (Ibuprofen), 101 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=58.85, df=24(P<0.0001); I^2=59.22%					
Test for overall effect: Z=16.32(P<0.0001)					



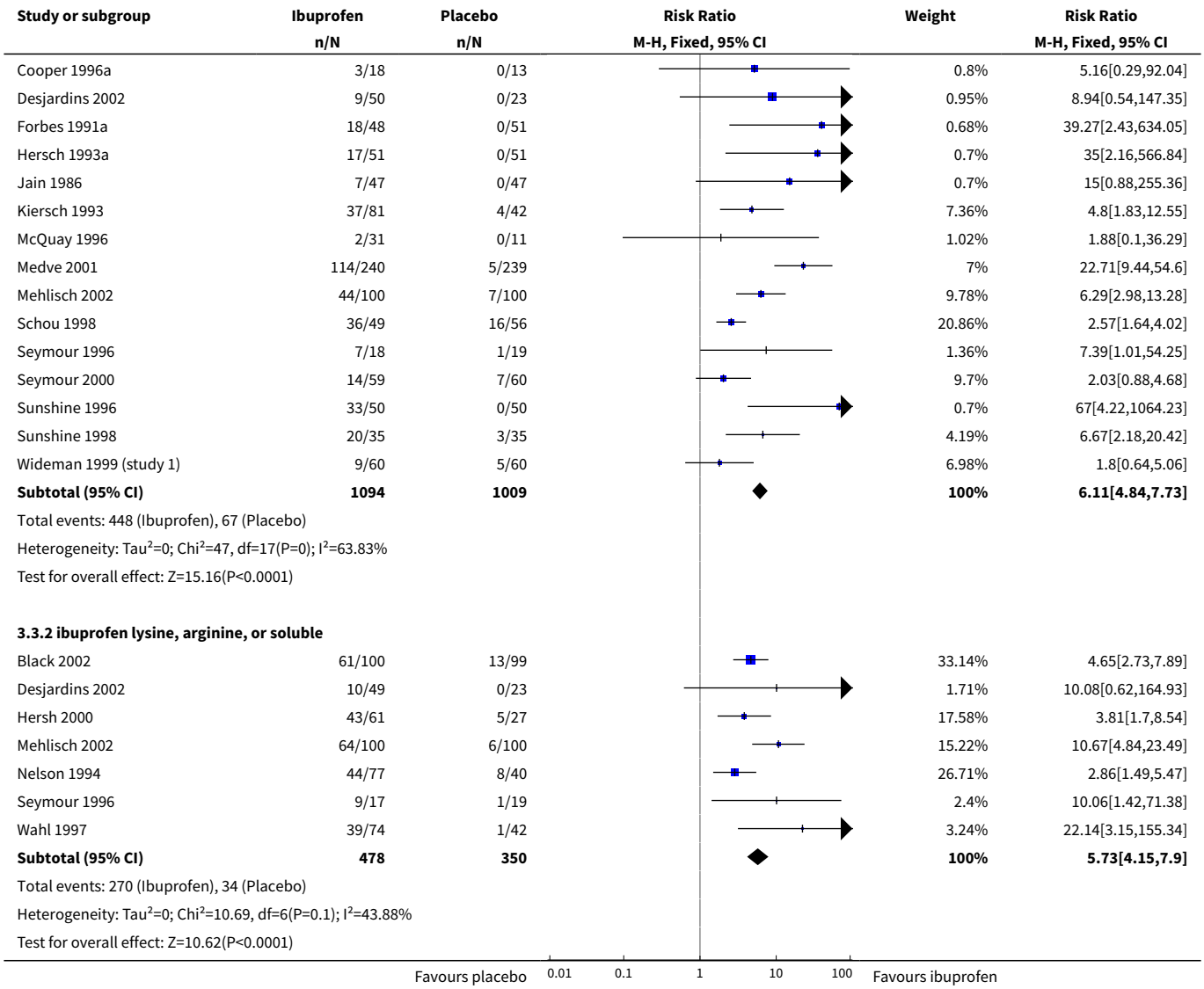
Favours placebo — Favours Ibuprofen

Analysis 3.2. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 2 Participants with at least 50% pain relief over 4 to 6 hours: type of surgery.

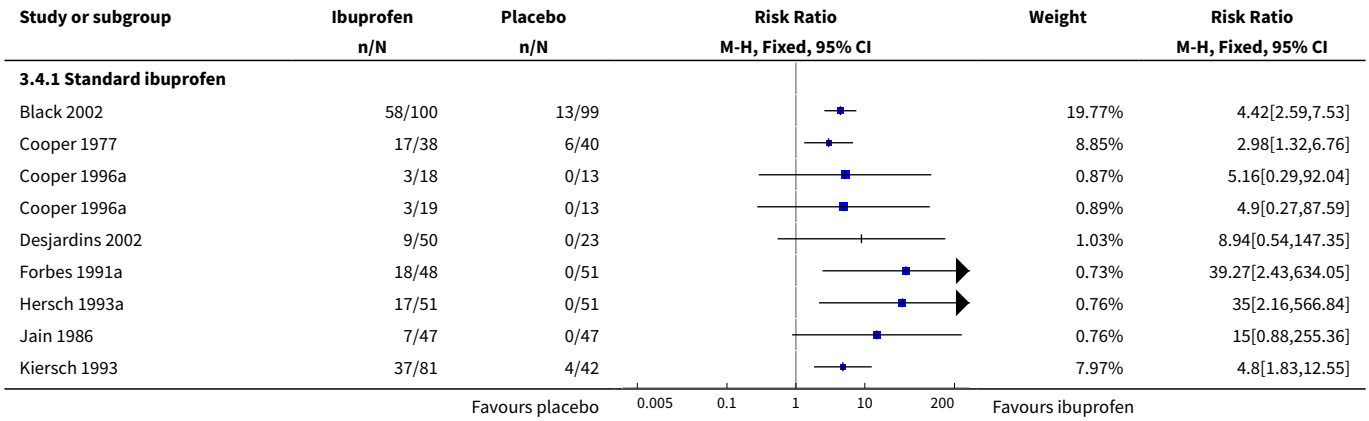
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Dental surgery					
Black 2002	61/100	13/50		14.51%	2.35[1.43,3.84]
Black 2002	58/100	13/49		14.61%	2.19[1.33,3.59]
Cooper 1977	17/38	6/40		4.9%	2.98[1.32,6.76]
Cooper 1996a	3/18	0/13		0.48%	5.16[0.29,92.04]
Cooper 1996a	3/19	0/13		0.49%	4.9[0.27,87.59]
Desjardins 2002	9/50	0/11		0.68%	4.47[0.28,71.59]
Desjardins 2002	10/49	0/12		0.66%	5.46[0.34,87.19]
Forbes 1991a	18/48	0/51		0.41%	39.27[2.43,634.05]
Hersch 1993a	17/51	0/51		0.42%	35[2.16,566.84]
Hersh 2000	43/61	5/27		5.8%	3.81[1.7,8.54]
Jain 1986	7/47	0/47		0.42%	15[0.88,255.36]
Kiersch 1993	37/81	4/42		4.41%	4.8[1.83,12.55]
McQuay 1996	2/31	0/11		0.61%	1.88[0.1,36.29]
Medve 2001	114/240	5/239		4.2%	22.71[9.44,54.6]
Mehlisch 2002	44/100	7/50		7.82%	3.14[1.53,6.47]
Mehlisch 2002	64/100	6/50		6.7%	5.33[2.48,11.46]
Nelson 1994	44/77	8/40		8.82%	2.86[1.49,5.47]
Schou 1998	36/49	16/56		12.5%	2.57[1.64,4.02]
Seymour 1996	7/18	1/9		1.12%	3.5[0.5,24.27]
Seymour 1996	9/17	1/10		1.05%	5.29[0.78,35.85]
Seymour 2000	14/59	7/60		5.81%	2.03[0.88,4.68]
Sunshine 1998	20/35	3/35		2.51%	6.67[2.18,20.42]
Wahl 1997	39/74	1/42		1.07%	22.14[3.15,155.34]
Subtotal (95% CI)	**1462**	**1008**		**100%**	**4.48[3.71,5.41]**
Total events: 676 (Ibuprofen), 96 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=49.96, df=22(P=0); I^2=55.96%					
Test for overall effect: Z=15.62(P<0.0001)					
3.2.2 Other surgery					
Sunshine 1996	33/50	0/50		9.09%	67[4.22,1064.23]
Wideman 1999 (study 1)	9/60	5/60		90.91%	1.8[0.64,5.06]
Subtotal (95% CI)	**110**	**110**		**100%**	**7.73[3.24,18.41]**
Total events: 42 (Ibuprofen), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.99, df=1(P=0); I^2=89.99%					
Test for overall effect: Z=4.62(P<0.0001)					

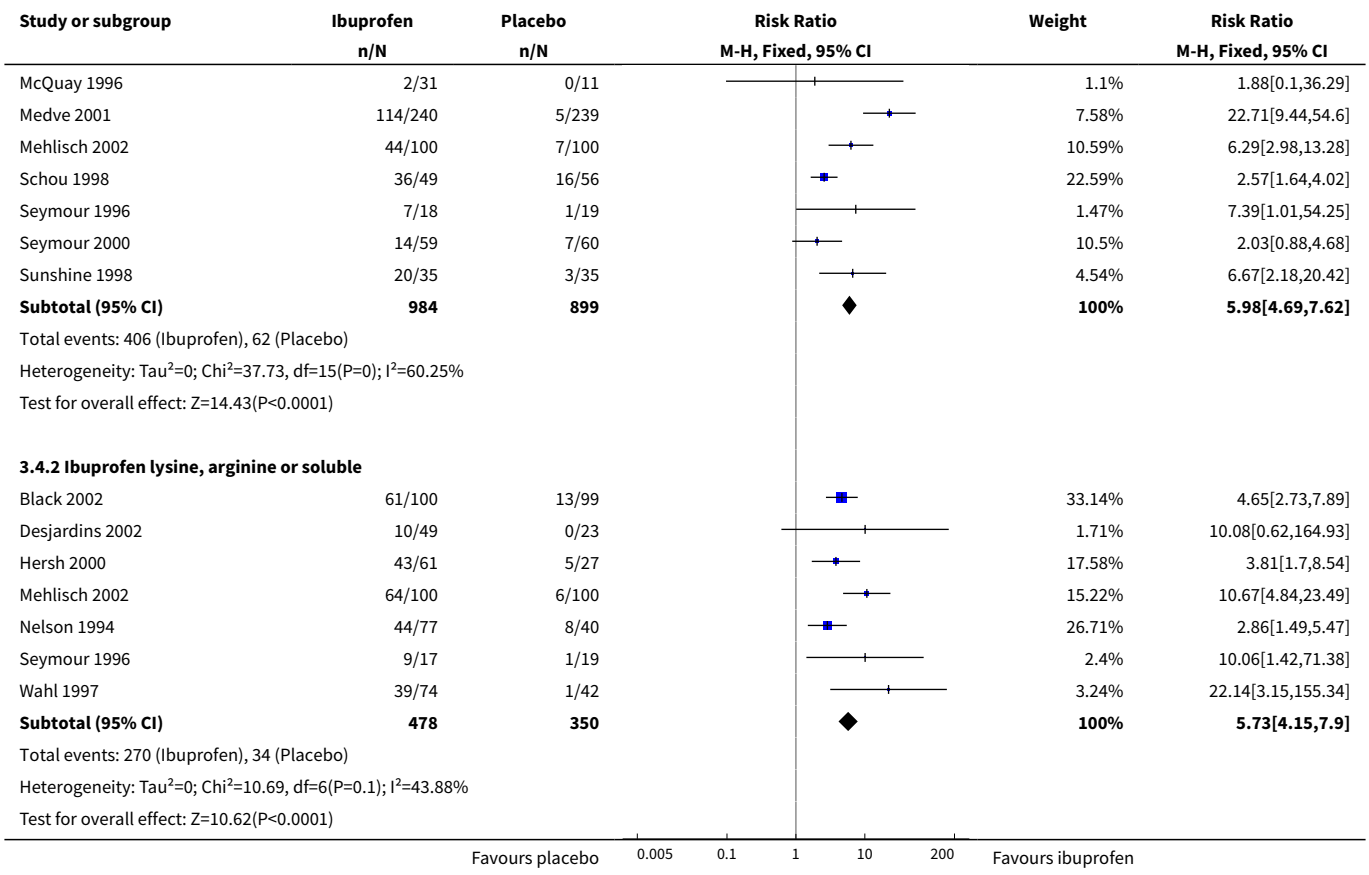
Analysis 3.3. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 3 Participants with at least 50% pain relief over 4 to 6 hours, all surgery: formulation.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Standard ibuprofen					
Black 2002	58/100	13/99		18.25%	4.42[2.59,7.53]
Cooper 1977	17/38	6/40		8.17%	2.98[1.32,6.76]
Cooper 1996a	3/19	0/13		0.82%	4.9[0.27,87.59]

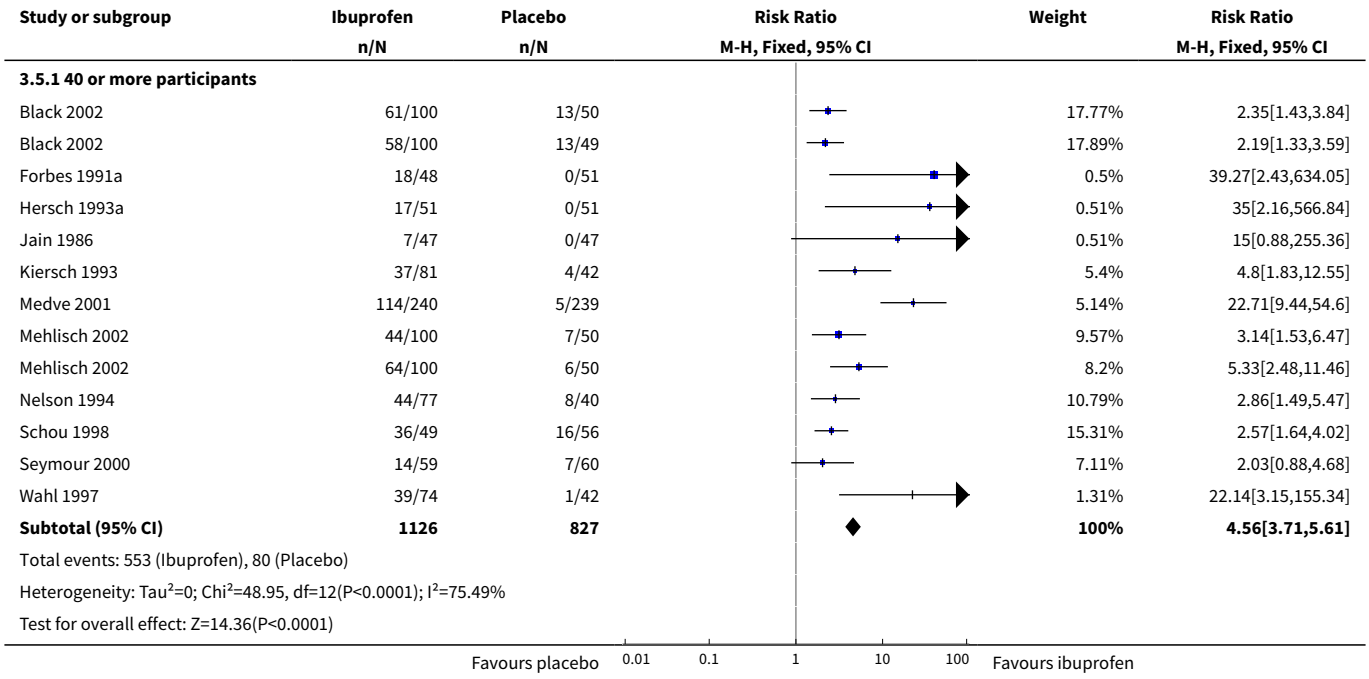


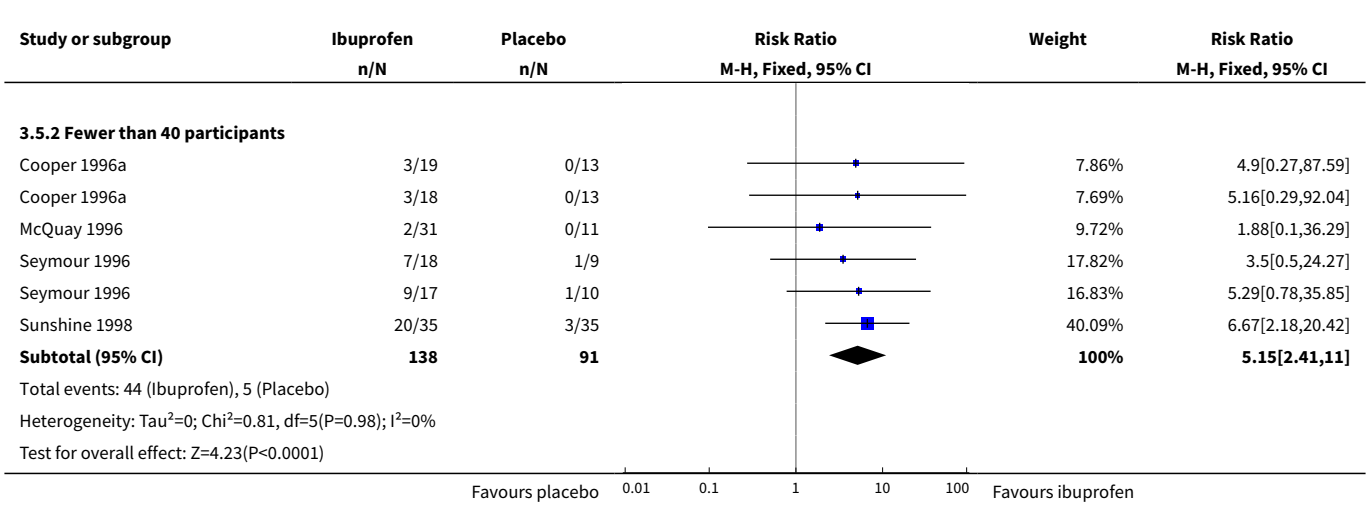
Analysis 3.4. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 4 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: formulation.





Analysis 3.5. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 5 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: study size.

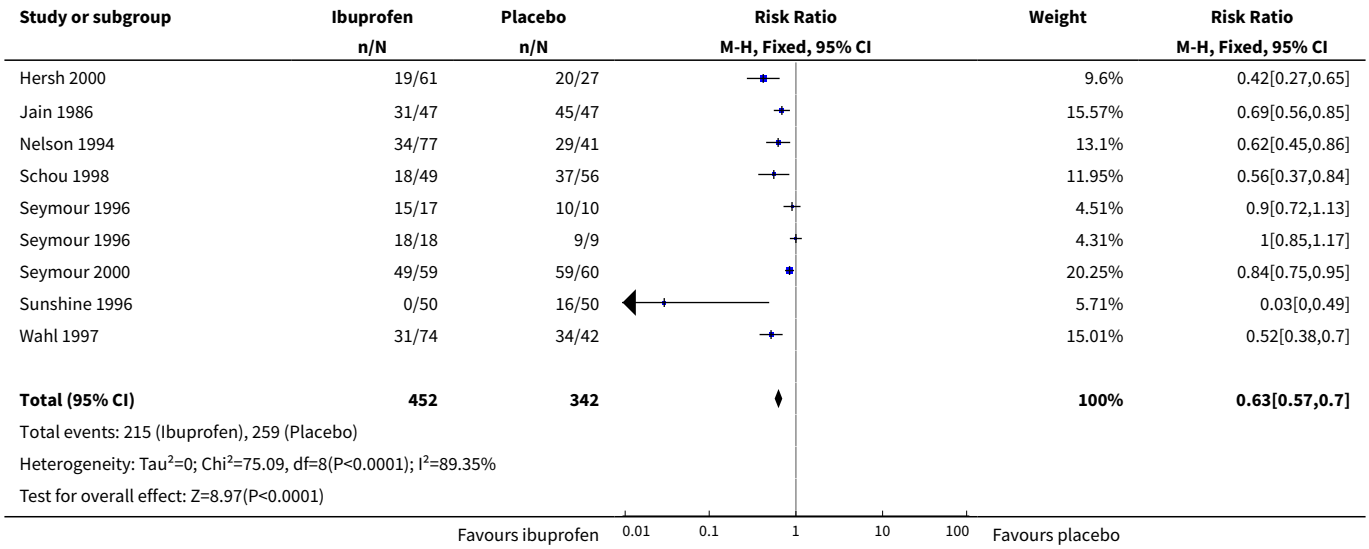




Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.2 Fewer than 40 participants					
Cooper 1996a	3/19	0/13		7.86%	4.9[0.27,87.59]
Cooper 1996a	3/18	0/13		7.69%	5.16[0.29,92.04]
McQuay 1996	2/31	0/11		9.72%	1.88[0.1,36.29]
Seymour 1996	7/18	1/9		17.82%	3.5[0.5,24.27]
Seymour 1996	9/17	1/10		16.83%	5.29[0.78,35.85]
Sunshine 1998	20/35	3/35		40.09%	6.67[2.18,20.42]
Subtotal (95% CI)	**138**	**91**		**100%**	**5.15[2.41,11]**
Total events: 44 (Ibuprofen), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=5(P=0.98); I^2=0%					
Test for overall effect: Z=4.23(P<0.0001)					

Favours placebo 0.01 0.1 1 10 100 Favours ibuprofen

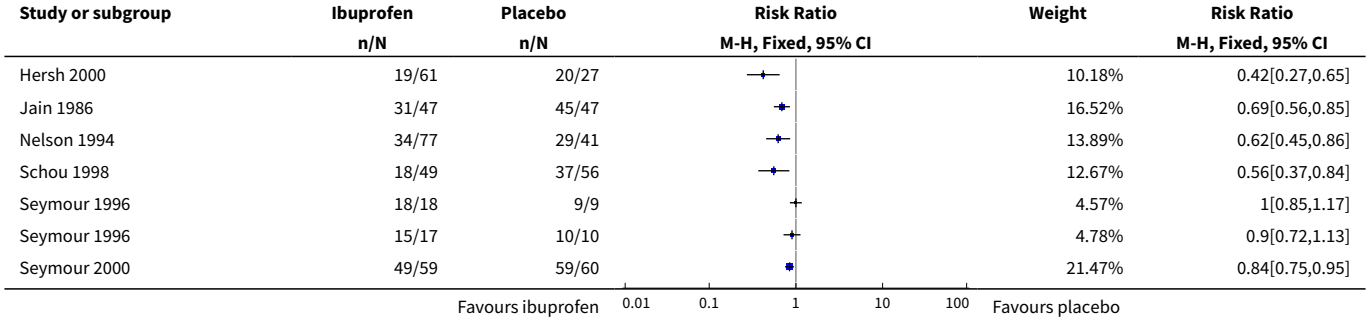
Analysis 3.6. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 6 Participants using rescue medication over 6 hours.



Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hersh 2000	19/61	20/27		9.6%	0.42[0.27,0.65]
Jain 1986	31/47	45/47		15.57%	0.69[0.56,0.85]
Nelson 1994	34/77	29/41		13.1%	0.62[0.45,0.86]
Schou 1998	18/49	37/56		11.95%	0.56[0.37,0.84]
Seymour 1996	15/17	10/10		4.51%	0.9[0.72,1.13]
Seymour 1996	18/18	9/9		4.31%	1[0.85,1.17]
Seymour 2000	49/59	59/60		20.25%	0.84[0.75,0.95]
Sunshine 1996	0/50	16/50		5.71%	0.03[0,0.49]
Wahl 1997	31/74	34/42		15.01%	0.52[0.38,0.7]
Total (95% CI)	**452**	**342**		**100%**	**0.63[0.57,0.7]**
Total events: 215 (Ibuprofen), 259 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=75.09, df=8(P<0.0001); I^2=89.35%					
Test for overall effect: Z=8.97(P<0.0001)					

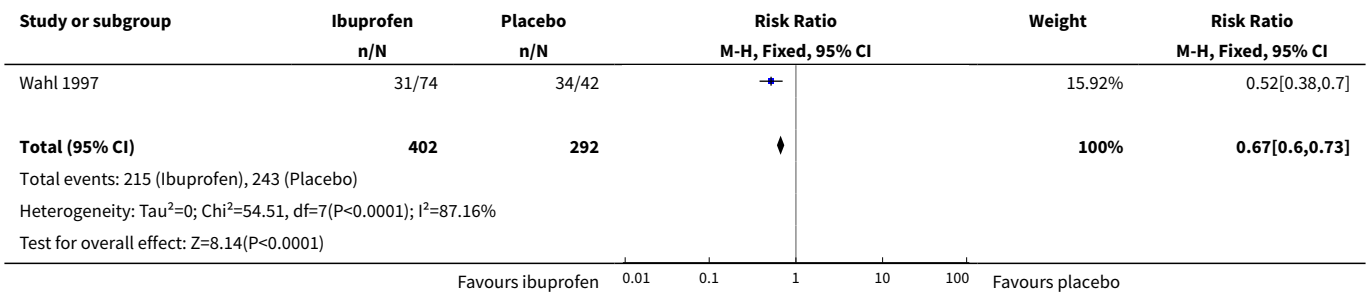
Favours ibuprofen 0.01 0.1 1 10 100 Favours placebo

Analysis 3.7. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 7 Participants using rescue medication over 6 hours, dental surgery.

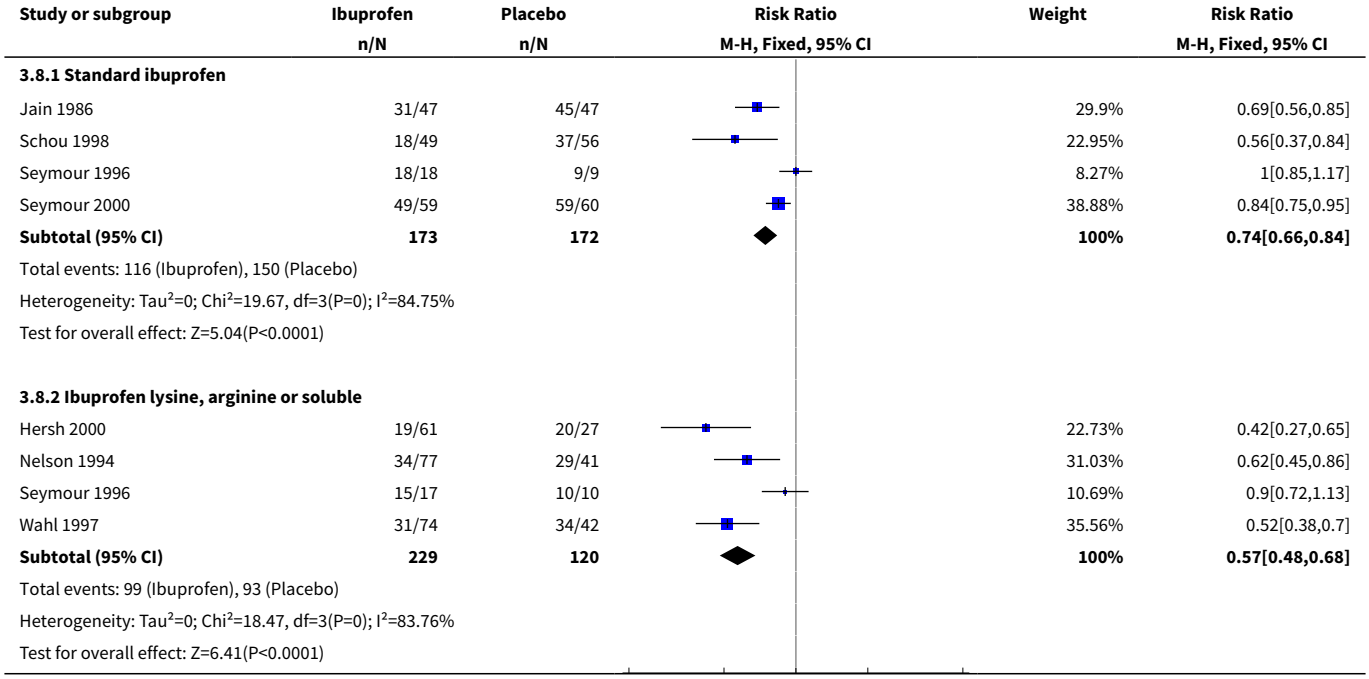


Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hersh 2000	19/61	20/27		10.18%	0.42[0.27,0.65]
Jain 1986	31/47	45/47		16.52%	0.69[0.56,0.85]
Nelson 1994	34/77	29/41		13.89%	0.62[0.45,0.86]
Schou 1998	18/49	37/56		12.67%	0.56[0.37,0.84]
Seymour 1996	18/18	9/9		4.57%	1[0.85,1.17]
Seymour 1996	15/17	10/10		4.78%	0.9[0.72,1.13]
Seymour 2000	49/59	59/60		21.47%	0.84[0.75,0.95]

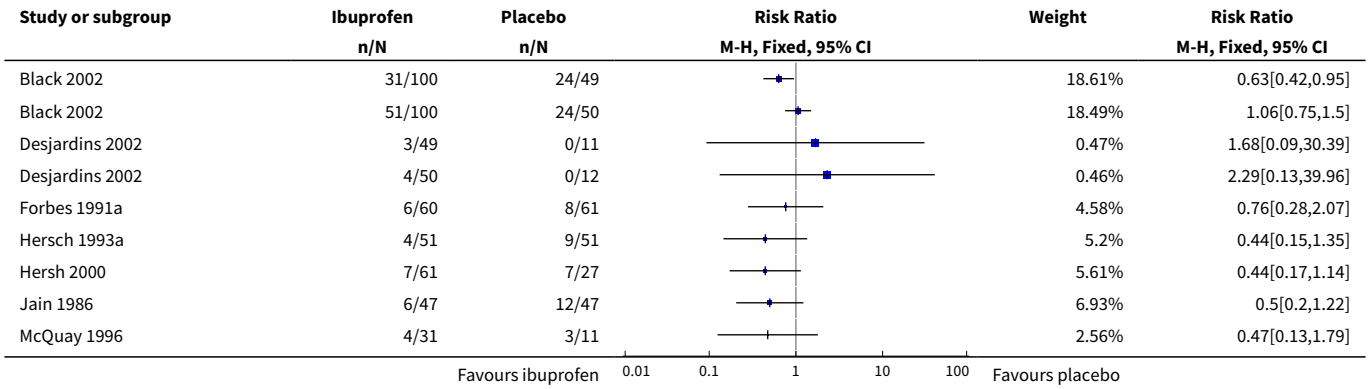
Favours ibuprofen 0.01 0.1 1 10 100 Favours placebo

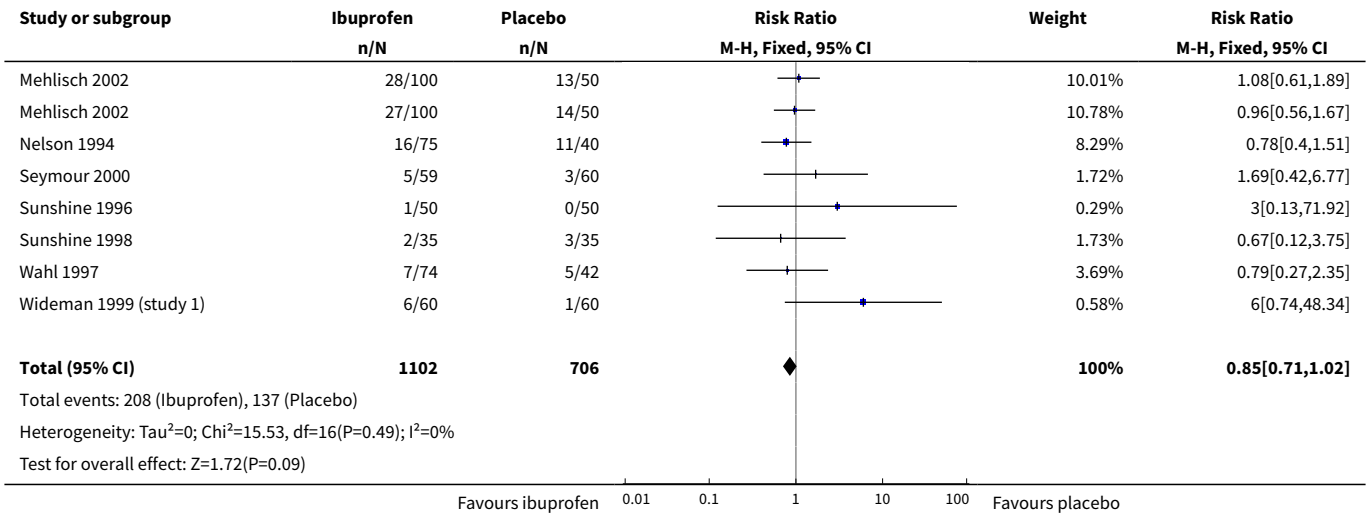


Analysis 3.8. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 8 Participants using rescue medication over 6 hours, dental surgery: formulation.



Analysis 3.9. Comparison 3 Ibuprofen 200 mg versus placebo, Outcome 9 Participants with any adverse event.





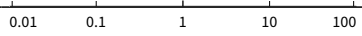
Comparison 4. Ibuprofen 400 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	57	6475	Risk Ratio (M-H, Fixed, 95% CI)	3.94 [3.58, 4.35]
2 Participants with at least 50% pain relief over 4 to 6 hours: type of surgery	57		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Dental surgery	45	5428	Risk Ratio (M-H, Fixed, 95% CI)	4.63 [4.13, 5.20]
2.2 Other surgery	12	1047	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.81, 2.62]
3 Participants with at least 50% pain relief over 4 to 6 hours, all surgery: formulation	57		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Standard ibuprofen	51	5604	Risk Ratio (M-H, Fixed, 95% CI)	4.64 [4.14, 5.18]
3.2 Ibuprofen lysine, arginine or soluble	12	1124	Risk Ratio (M-H, Fixed, 95% CI)	3.70 [3.00, 4.56]
4 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: formulation	45		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Standard ibuprofen	42	4772	Risk Ratio (M-H, Fixed, 95% CI)	5.17 [4.56, 5.87]
4.2 Ibuprofen lysine, arginine or soluble	9	959	Risk Ratio (M-H, Fixed, 95% CI)	6.55 [4.85, 8.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: study size	29		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 40 or more participants	15	3086	Risk Ratio (M-H, Fixed, 95% CI)	4.44 [3.80, 5.19]
5.2 Fewer than 40 participants	14	856	Risk Ratio (M-H, Fixed, 95% CI)	4.06 [3.21, 5.14]
6 Participants using rescue medication over 6 hours	28	2983	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.51, 0.57]
7 Participants using rescue medication over 6 hours, dental surgery	22	2554	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.48, 0.55]
8 Participants using rescue medication over 6 hours, dental surgery: formulation	21		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Standard ibuprofen	18	1857	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.51, 0.59]
8.2 Ibuprofen lysine, arginine or soluble	6	449	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.35, 0.50]
9 Participants with any adverse event	36	4865	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.04]

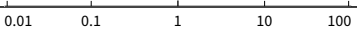
Analysis 4.1. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahlstrom 1993	19/32	2/30		0.5%	8.91[2.26,35.02]
Arnold 1990	2/15	0/14		0.12%	4.69[0.24,89.88]
Bakshi 1994	57/80	31/82		7.35%	1.88[1.38,2.57]
Black 2002	71/99	13/50		4.15%	2.76[1.7,4.47]
Black 2002	71/100	13/49		4.19%	2.68[1.65,4.34]
Cheung 2007	40/57	5/57		1.2%	8[3.41,18.79]
Cooper 1977	20/40	6/40		1.44%	3.33[1.5,7.42]
Cooper 1982	22/38	5/46		1.09%	5.33[2.23,12.72]
Cooper 1988a	19/37	6/43		1.33%	3.68[1.64,8.24]
Cooper 1989	37/61	9/64		2.11%	4.31[2.28,8.17]
De Miguel Rivero 1997	24/36	15/34		3.7%	1.51[0.97,2.35]
Desjardins 2002	16/49	0/12		0.19%	8.58[0.55,133.75]
Desjardins 2002	15/52	0/11		0.2%	7.02[0.45,109.31]
Dionne 1998	26/50	2/25		0.64%	6.5[1.68,25.22]
Edwards 2002	145/339	11/339		2.64%	13.18[7.28,23.88]
Ehrich 1999	14/20	1/32		0.18%	22.4[3.19,157.49]
Forbes 1984	21/28	3/28		0.72%	7[2.35,20.83]



Favours placebo — Favours ibuprofen

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1990	15/32	0/34		0.12%	32.88[2.05,527.71]
Forbes 1991b	18/37	3/39		0.7%	6.32[2.03,19.71]
Forbes 1992	21/38	0/38		0.12%	43[2.7,685.19]
Frame 1989	26/42	0/38		0.13%	48.07[3.03,762.59]
Fricke 1993	40/81	2/39		0.65%	9.63[2.45,37.81]
Gay 1996	26/41	7/39		1.72%	3.53[1.74,7.19]
Heidrich 1985	15/40	5/40		1.2%	3[1.2,7.47]
Hersch 1993a	11/49	0/51		0.12%	23.92[1.45,395.2]
Hersch 1993b	9/12	6/16		1.23%	2[0.98,4.08]
Hersh 2000	47/59	5/27		1.65%	4.3[1.93,9.59]
Hill 2001	22/49	5/50		1.19%	4.49[1.85,10.91]
Jain 1986	9/49	0/47		0.12%	18.24[1.09,304.82]
Jain 1988	33/49	17/48		4.12%	1.9[1.24,2.92]
Johnson 1997	15/48	9/48		2.16%	1.67[0.81,3.43]
Laska 1986	39/39	14/37		3.57%	2.59[1.72,3.89]
Laveneziana 1996	29/42	24/41		5.83%	1.18[0.85,1.64]
Malmstrom 1999	33/46	4/45		0.97%	8.07[3.11,20.93]
Malmstrom 2002	24/45	0/45		0.12%	49[3.07,781.94]
Malmstrom 2004	32/48	4/49		0.95%	8.17[3.13,21.33]
McQuay 1996	6/30	0/11		0.17%	5.03[0.31,82.6]
Mehlisch 1990	124/306	5/85		1.88%	6.89[2.91,16.3]
Mehlisch 1995	67/98	1/40		0.34%	27.35[3.93,190.3]
Mehlisch 2002	57/100	6/50		1.92%	4.75[2.2,10.26]
Mehlisch 2002	62/100	7/50		2.24%	4.43[2.19,8.95]
Morrison 1999	20/51	6/50		1.45%	3.27[1.43,7.46]
Nørholt 1998	22/26	8/31		1.75%	3.28[1.77,6.09]
Olson 2001	57/67	5/39		1.52%	6.64[2.91,15.14]
Pagnoni 1996	13/30	5/32		1.16%	2.77[1.12,6.84]
Schachtel 1989	27/36	13/38		3.04%	2.19[1.36,3.54]
Schou 1998	41/49	16/56		3.58%	2.93[1.9,4.51]
Schwartz 2007	5/15	0/16		0.12%	11.69[0.7,194.79]
Seymour 1991 (study 1)	22/32	5/16		1.6%	2.2[1.03,4.72]
Seymour 1991 (study 1)	20/31	5/16		1.58%	2.06[0.95,4.47]
Seymour 1991 (study 2)	20/30	3/15		0.96%	3.33[1.17,9.46]
Seymour 1991 (study 2)	8/30	4/15		1.28%	1[0.36,2.79]
Seymour 1996	11/15	1/9		0.3%	6.6[1.01,42.95]
Seymour 1996	11/16	1/10		0.3%	6.88[1.04,45.44]
Seymour 1998	27/76	3/70		0.75%	8.29[2.63,26.12]
Seymour 1999	19/41	7/39		1.72%	2.58[1.22,5.45]
Singla 2005	77/175	14/60		5%	1.89[1.16,3.07]
Sunshine 1983	21/30	3/30		0.72%	7[2.33,21]
Sunshine 1987	16/38	11/40		2.57%	1.53[0.82,2.86]
Sunshine 1997	17/40	1/39		0.24%	16.58[2.32,118.61]
Van Dyke 2004	112/186	9/62		3.24%	4.15[2.24,7.67]
Wideman 1999 (study 2)	21/50	3/51		0.71%	7.14[2.27,22.44]
Zelenakas 2004	27/51	6/50		1.45%	4.41[1.99,9.76]
Total (95% CI)	**3728**	**2747**		**100%**	**3.94[3.58,4.35]**
Total events: 2013 (Ibuprofen), 375 (Placebo)					
Heterogeneity: Tau²=0; Chi²=221.5, df=62(P<0.0001); I²=72.01%					
Test for overall effect: Z=27.58(P<0.0001)					

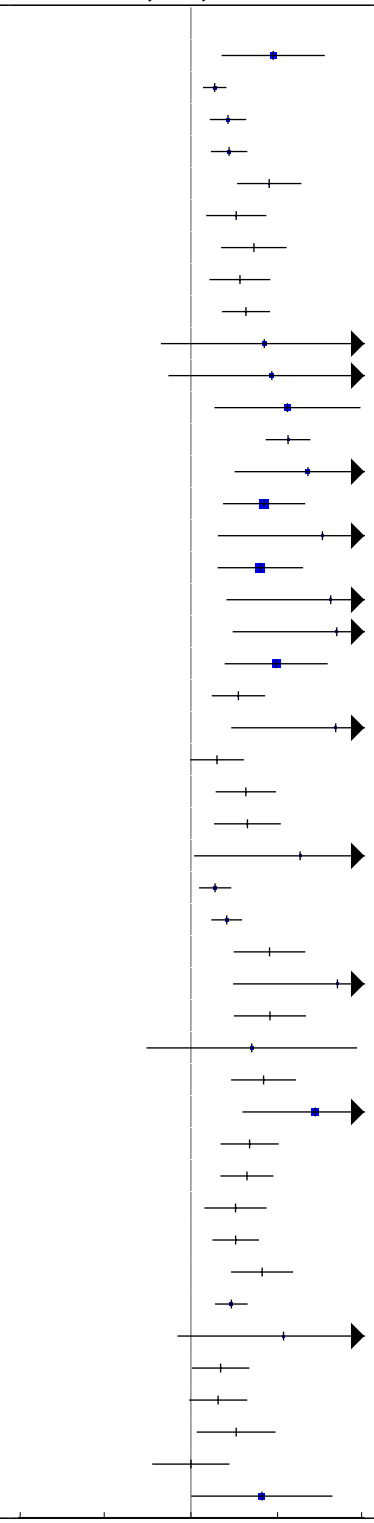


Favours placebo

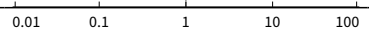
Favours ibuprofen

Analysis 4.2. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 2 Participants with at least 50% pain relief over 4 to 6 hours: type of surgery.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Dental surgery					
Ahlstrom 1993	19/32	2/30		0.68%	8.91[2.26,35.02]
Bakshi 1994	57/80	31/82		10.03%	1.88[1.38,2.57]
Black 2002	71/100	13/49		5.72%	2.68[1.65,4.34]
Black 2002	71/99	13/50		5.66%	2.76[1.7,4.47]
Cheung 2007	40/57	5/57		1.64%	8[3.41,18.79]
Cooper 1977	20/40	6/40		1.97%	3.33[1.5,7.42]
Cooper 1982	22/38	5/46		1.48%	5.33[2.23,12.72]
Cooper 1988a	19/37	6/43		1.82%	3.68[1.64,8.24]
Cooper 1989	37/61	9/64		2.88%	4.31[2.28,8.17]
Desjardins 2002	15/52	0/11		0.27%	7.02[0.45,109.31]
Desjardins 2002	16/49	0/12		0.26%	8.58[0.55,133.75]
Dionne 1998	26/50	1/25		0.44%	13[1.87,90.35]
Edwards 2002	145/339	11/339		3.61%	13.18[7.28,23.88]
Ehrich 1999	14/20	1/32		0.25%	22.4[3.19,157.49]
Forbes 1984	21/28	3/28		0.98%	7[2.35,20.83]
Forbes 1990	15/32	0/34		0.16%	32.88[2.05,527.71]
Forbes 1991b	18/37	3/39		0.96%	6.32[2.03,19.71]
Forbes 1992	20/38	0/38		0.16%	41[2.57,654.35]
Frame 1989	26/42	0/38		0.17%	48.07[3.03,762.59]
Fricke 1993	40/81	2/39		0.88%	9.63[2.45,37.81]
Gay 1996	26/41	7/39		2.35%	3.53[1.74,7.19]
Hersch 1993a	22/49	0/51		0.16%	46.8[2.92,750.92]
Hersch 1993b	9/12	6/16		1.69%	2[0.98,4.08]
Hersh 2000	47/59	5/27		2.25%	4.3[1.93,9.59]
Hill 2001	22/49	5/50		1.62%	4.49[1.85,10.91]
Jain 1986	9/49	0/47		0.17%	18.24[1.09,304.82]
Jain 1988	33/49	17/48		5.63%	1.9[1.24,2.92]
Laska 1986	39/39	14/37		4.87%	2.59[1.72,3.89]
Malmstrom 1999	33/46	4/45		1.33%	8.07[3.11,20.93]
Malmstrom 2002	24/45	0/45		0.16%	49[3.07,781.94]
Malmstrom 2004	32/48	4/49		1.3%	8.17[3.13,21.33]
McQuay 1996	6/30	0/11		0.24%	5.03[0.31,82.6]
Mehlisch 1990	124/306	5/85		2.56%	6.89[2.91,16.3]
Mehlisch 1995	67/98	1/40		0.47%	27.35[3.93,190.3]
Mehlisch 2002	57/100	6/50		2.62%	4.75[2.2,10.26]
Mehlisch 2002	62/100	7/50		3.06%	4.43[2.19,8.95]
Morrison 1999	20/51	6/50		1.99%	3.27[1.43,7.46]
Nørholt 1998	22/26	8/31		2.39%	3.28[1.77,6.09]
Olson 2001	57/67	5/39		2.07%	6.64[2.91,15.14]
Schou 1998	41/49	16/56		4.89%	2.93[1.9,4.51]
Schwartz 2007	5/15	0/16		0.16%	11.69[0.7,194.79]
Seymour 1991 (study 1)	22/32	5/16		2.18%	2.2[1.03,4.72]
Seymour 1991 (study 1)	20/31	5/16		2.16%	2.06[0.95,4.47]
Seymour 1991 (study 2)	20/30	3/15		1.31%	3.33[1.17,9.46]
Seymour 1991 (study 2)	8/30	4/15		1.75%	1[0.36,2.79]
Seymour 1996	11/15	1/9		0.41%	6.6[1.01,42.95]

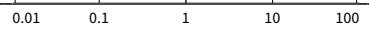


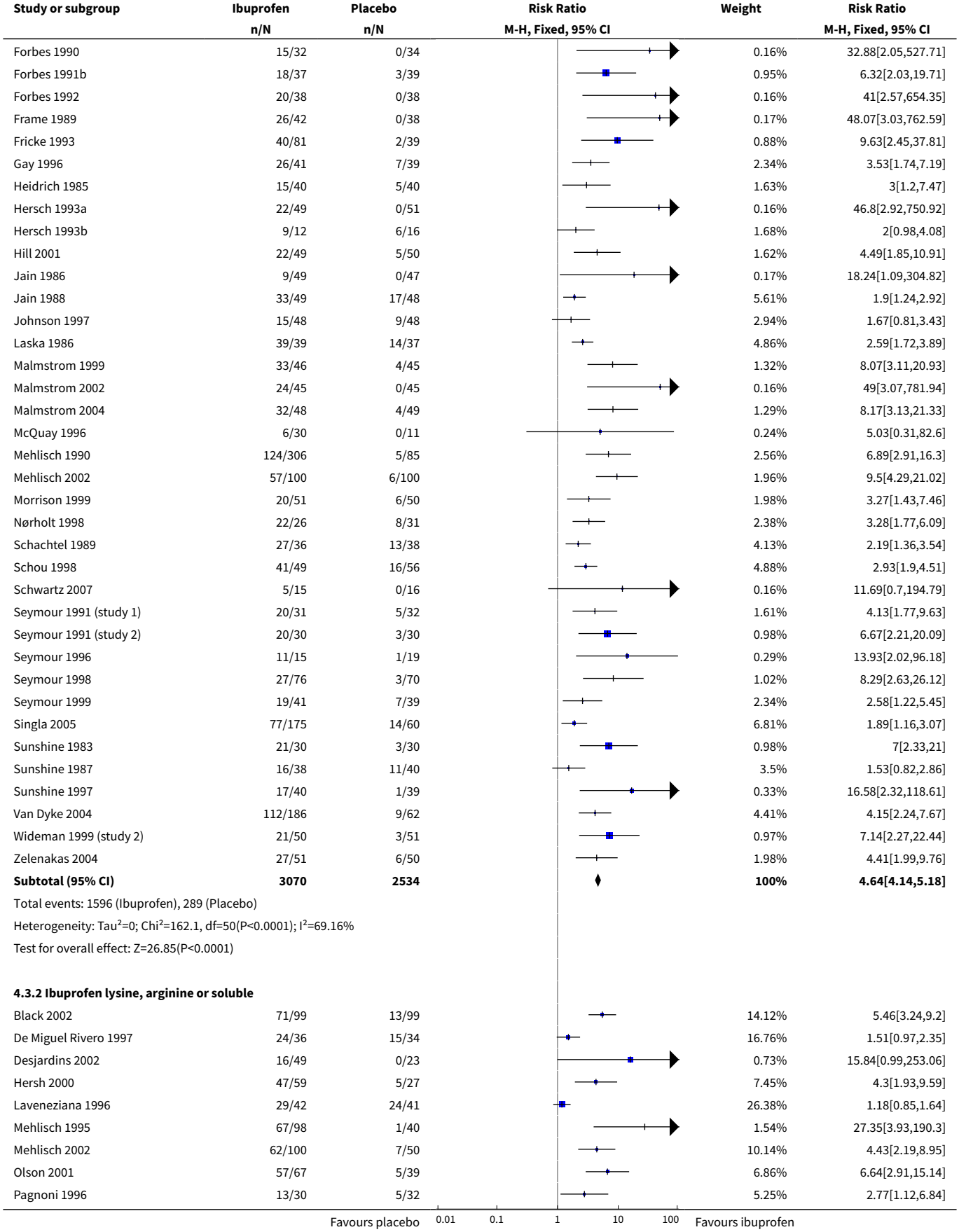
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Seymour 1996	11/16	1/10		0.4%	6.88[1.04,45.44]
Seymour 1998	27/76	3/70		1.02%	8.29[2.63,26.12]
Seymour 1999	19/41	7/39		2.35%	2.58[1.22,5.45]
Van Dyke 2004	112/186	9/62		4.42%	4.15[2.24,7.67]
Zelenakas 2004	27/51	6/50		1.99%	4.41[1.99,9.76]
Subtotal (95% CI)	**3148**	**2280**		**100%**	**4.63[4.13,5.2]**
Total events: 1746 (Ibuprofen), 271 (Placebo)					
Heterogeneity: Tau²=0; Chi²=141.36, df=50(P<0.0001); I²=64.63%					
Test for overall effect: Z=26.27(P<0.0001)					
4.2.2 Other surgery					
Arnold 1990	2/15	0/14		0.47%	4.69[0.24,89.88]
De Miguel Rivero 1997	24/36	15/34		13.99%	1.51[0.97,2.35]
Heidrich 1985	15/40	5/40		4.53%	3[1.2,7.47]
Johnson 1997	15/48	9/48		8.16%	1.67[0.81,3.43]
Laveneziana 1996	29/42	24/41		22.03%	1.18[0.85,1.64]
Pagnoni 1996	13/30	5/32		4.39%	2.77[1.12,6.84]
Schachtel 1989	27/36	13/38		11.47%	2.19[1.36,3.54]
Singla 2005	77/175	14/60		18.91%	1.89[1.16,3.07]
Sunshine 1983	21/30	3/30		2.72%	7[2.33,21]
Sunshine 1987	16/38	11/40		9.72%	1.53[0.82,2.86]
Sunshine 1997	17/40	1/39		0.92%	16.58[2.32,118.61]
Wideman 1999 (study 2)	21/50	3/51		2.69%	7.14[2.27,22.44]
Subtotal (95% CI)	**580**	**467**		**100%**	**2.18[1.81,2.62]**
Total events: 277 (Ibuprofen), 103 (Placebo)					
Heterogeneity: Tau²=0; Chi²=31.72, df=11(P=0); I²=65.32%					
Test for overall effect: Z=8.23(P<0.0001)					



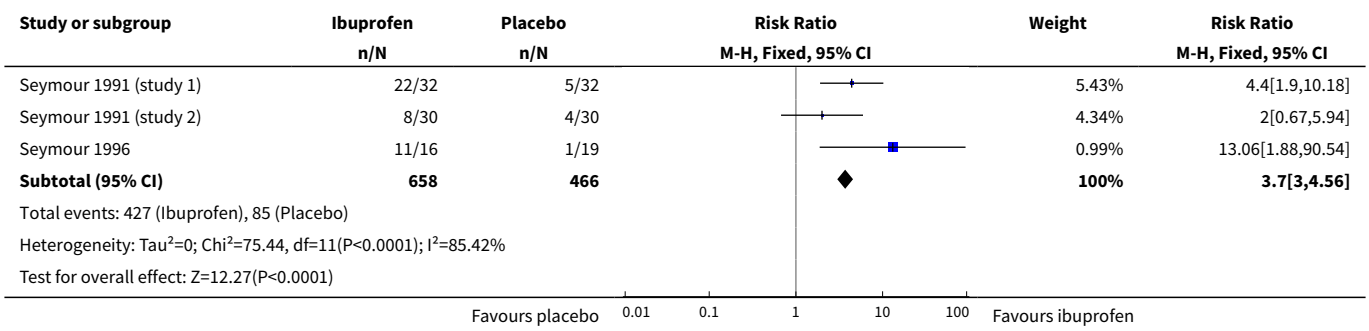
Analysis 4.3. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 3 Participants with at least 50% pain relief over 4 to 6 hours, all surgery: formulation.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Standard ibuprofen					
Ahlstrom 1993	19/32	2/30		0.67%	8.91[2.26,35.02]
Arnold 1990	2/15	0/14		0.17%	4.69[0.24,89.88]
Bakshi 1994	57/80	31/82		10%	1.88[1.38,2.57]
Black 2002	71/100	13/99		4.27%	5.41[3.21,9.11]
Cheung 2007	40/57	5/57		1.63%	8[3.41,18.79]
Cooper 1977	20/40	6/40		1.96%	3.33[1.5,7.42]
Cooper 1982	22/38	5/46		1.48%	5.33[2.23,12.72]
Cooper 1988a	19/37	6/43		1.81%	3.68[1.64,8.24]
Cooper 1989	37/61	9/64		2.87%	4.31[2.28,8.17]
Desjardins 2002	15/52	0/23		0.22%	14.04[0.88,225.05]
Dionne 1998	26/50	1/25		0.44%	13[1.87,90.35]
Edwards 2002	145/339	11/339		3.59%	13.18[7.28,23.88]
Ehrich 1999	14/20	1/32		0.25%	22.4[3.19,157.49]
Forbes 1984	21/28	3/28		0.98%	7[2.35,20.83]



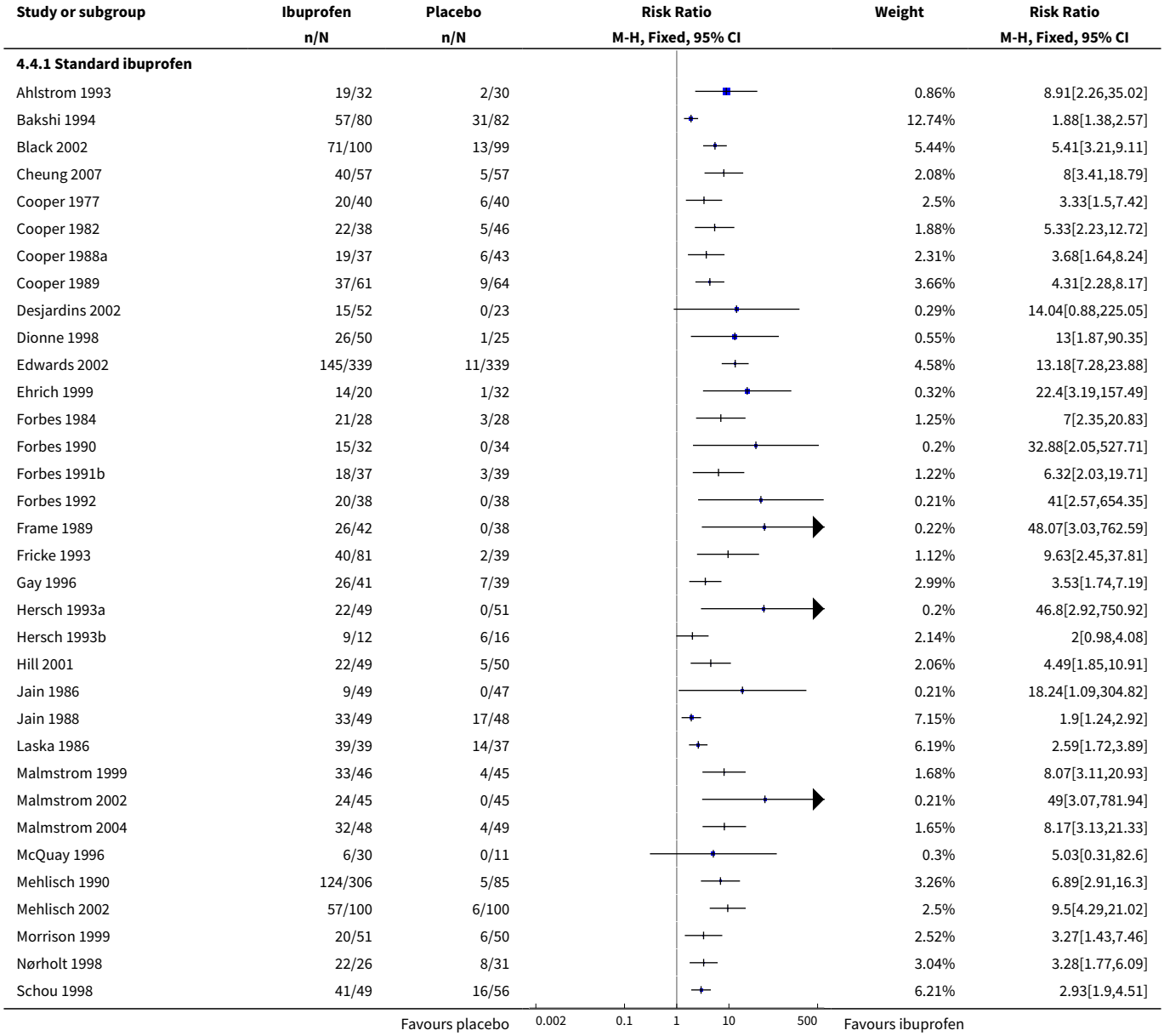


Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1990	15/32	0/34		0.16%	32.88[2.05,527.71]
Forbes 1991b	18/37	3/39		0.95%	6.32[2.03,19.71]
Forbes 1992	20/38	0/38		0.16%	41[2.57,654.35]
Frame 1989	26/42	0/38		0.17%	48.07[3.03,762.59]
Fricke 1993	40/81	2/39		0.88%	9.63[2.45,37.81]
Gay 1996	26/41	7/39		2.34%	3.53[1.74,7.19]
Heidrich 1985	15/40	5/40		1.63%	3[1.2,7.47]
Hersch 1993a	22/49	0/51		0.16%	46.8[2.92,750.92]
Hersch 1993b	9/12	6/16		1.68%	2[0.98,4.08]
Hill 2001	22/49	5/50		1.62%	4.49[1.85,10.91]
Jain 1986	9/49	0/47		0.17%	18.24[1.09,304.82]
Jain 1988	33/49	17/48		5.61%	1.9[1.24,2.92]
Johnson 1997	15/48	9/48		2.94%	1.67[0.81,3.43]
Laska 1986	39/39	14/37		4.86%	2.59[1.72,3.89]
Malmstrom 1999	33/46	4/45		1.32%	8.07[3.11,20.93]
Malmstrom 2002	24/45	0/45		0.16%	49[3.07,781.94]
Malmstrom 2004	32/48	4/49		1.29%	8.17[3.13,21.33]
McQuay 1996	6/30	0/11		0.24%	5.03[0.31,82.6]
Mehlisch 1990	124/306	5/85		2.56%	6.89[2.91,16.3]
Mehlisch 2002	57/100	6/100		1.96%	9.5[4.29,21.02]
Morrison 1999	20/51	6/50		1.98%	3.27[1.43,7.46]
Nørholt 1998	22/26	8/31		2.38%	3.28[1.77,6.09]
Schachtel 1989	27/36	13/38		4.13%	2.19[1.36,3.54]
Schou 1998	41/49	16/56		4.88%	2.93[1.9,4.51]
Schwartz 2007	5/15	0/16		0.16%	11.69[0.7,194.79]
Seymour 1991 (study 1)	20/31	5/32		1.61%	4.13[1.77,9.63]
Seymour 1991 (study 2)	20/30	3/30		0.98%	6.67[2.21,20.09]
Seymour 1996	11/15	1/19		0.29%	13.93[2.02,96.18]
Seymour 1998	27/76	3/70		1.02%	8.29[2.63,26.12]
Seymour 1999	19/41	7/39		2.34%	2.58[1.22,5.45]
Singla 2005	77/175	14/60		6.81%	1.89[1.16,3.07]
Sunshine 1983	21/30	3/30		0.98%	7[2.33,21]
Sunshine 1987	16/38	11/40		3.5%	1.53[0.82,2.86]
Sunshine 1997	17/40	1/39		0.33%	16.58[2.32,118.61]
Van Dyke 2004	112/186	9/62		4.41%	4.15[2.24,7.67]
Wideman 1999 (study 2)	21/50	3/51		0.97%	7.14[2.27,22.44]
Zelenakas 2004	27/51	6/50		1.98%	4.41[1.99,9.76]
Subtotal (95% CI)	**3070**	**2534**		**100%**	**4.64[4.14,5.18]**
Total events: 1596 (Ibuprofen), 289 (Placebo)					
Heterogeneity: Tau²=0; Chi²=162.1, df=50(P<0.0001); I²=69.16%					
Test for overall effect: Z=26.85(P<0.0001)					
4.3.2 Ibuprofen lysine, arginine or soluble					
Black 2002	71/99	13/99		14.12%	5.46[3.24,9.2]
De Miguel Rivero 1997	24/36	15/34		16.76%	1.51[0.97,2.35]
Desjardins 2002	16/49	0/23		0.73%	15.84[0.99,253.06]
Hersh 2000	47/59	5/27		7.45%	4.3[1.93,9.59]
Laveneziana 1996	29/42	24/41		26.38%	1.18[0.85,1.64]
Mehlisch 1995	67/98	1/40		1.54%	27.35[3.93,190.3]
Mehlisch 2002	62/100	7/50		10.14%	4.43[2.19,8.95]
Olson 2001	57/67	5/39		6.86%	6.64[2.91,15.14]
Pagnoni 1996	13/30	5/32		5.25%	2.77[1.12,6.84]



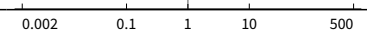
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Seymour 1991 (study 1)	22/32	5/32		5.43%	4.4[1.9,10.18]
Seymour 1991 (study 2)	8/30	4/30		4.34%	2[0.67,5.94]
Seymour 1996	11/16	1/19		0.99%	13.06[1.88,90.54]
Subtotal (95% CI)	**658**	**466**		**100%**	**3.7[3,4.56]**
Total events: 427 (Ibuprofen), 85 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=75.44, df=11(P<0.0001); I^2=85.42%					
Test for overall effect: Z=12.27(P<0.0001)					

Analysis 4.4. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 4 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: formulation.



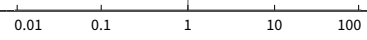
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Standard ibuprofen					
Ahlstrom 1993	19/32	2/30		0.86%	8.91[2.26,35.02]
Bakshi 1994	57/80	31/82		12.74%	1.88[1.38,2.57]
Black 2002	71/100	13/99		5.44%	5.41[3.21,9.11]
Cheung 2007	40/57	5/57		2.08%	8[3.41,18.79]
Cooper 1977	20/40	6/40		2.5%	3.33[1.5,7.42]
Cooper 1982	22/38	5/46		1.88%	5.33[2.23,12.72]
Cooper 1988a	19/37	6/43		2.31%	3.68[1.64,8.24]
Cooper 1989	37/61	9/64		3.66%	4.31[2.28,8.17]
Desjardins 2002	15/52	0/23		0.29%	14.04[0.88,225.05]
Dionne 1998	26/50	1/25		0.55%	13[1.87,90.35]
Edwards 2002	145/339	11/339		4.58%	13.18[7.28,23.88]
Ehrich 1999	14/20	1/32		0.32%	22.4[3.19,157.49]
Forbes 1984	21/28	3/28		1.25%	7[2.35,20.83]
Forbes 1990	15/32	0/34		0.2%	32.88[2.05,527.71]
Forbes 1991b	18/37	3/39		1.22%	6.32[2.03,19.71]
Forbes 1992	20/38	0/38		0.21%	41[2.57,654.35]
Frame 1989	26/42	0/38		0.22%	48.07[3.03,762.59]
Fricke 1993	40/81	2/39		1.12%	9.63[2.45,37.81]
Gay 1996	26/41	7/39		2.99%	3.53[1.74,7.19]
Hersch 1993a	22/49	0/51		0.2%	46.8[2.92,750.92]
Hersch 1993b	9/12	6/16		2.14%	2[0.98,4.08]
Hill 2001	22/49	5/50		2.06%	4.49[1.85,10.91]
Jain 1986	9/49	0/47		0.21%	18.24[1.09,304.82]
Jain 1988	33/49	17/48		7.15%	1.9[1.24,2.92]
Laska 1986	39/39	14/37		6.19%	2.59[1.72,3.89]
Malmstrom 1999	33/46	4/45		1.68%	8.07[3.11,20.93]
Malmstrom 2002	24/45	0/45		0.21%	49[3.07,781.94]
Malmstrom 2004	32/48	4/49		1.65%	8.17[3.13,21.33]
McQuay 1996	6/30	0/11		0.3%	5.03[0.31,82.6]
Mehlisch 1990	124/306	5/85		3.26%	6.89[2.91,16.3]
Mehlisch 2002	57/100	6/100		2.5%	9.5[4.29,21.02]
Morrison 1999	20/51	6/50		2.52%	3.27[1.43,7.46]
Nørholt 1998	22/26	8/31		3.04%	3.28[1.77,6.09]
Schou 1998	41/49	16/56		6.21%	2.93[1.9,4.51]

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schwartz 2007	5/15	0/16		0.2%	11.69[0.7,194.79]
Seymour 1991 (study 1)	20/31	5/32		2.05%	4.13[1.77,9.63]
Seymour 1991 (study 2)	20/30	3/30		1.25%	6.67[2.21,20.09]
Seymour 1996	11/15	1/19		0.37%	13.93[2.02,96.18]
Seymour 1998	27/76	3/70		1.3%	8.29[2.63,26.12]
Seymour 1999	19/41	7/39		2.99%	2.58[1.22,5.45]
Van Dyke 2004	112/186	9/62		5.62%	4.15[2.24,7.67]
Zelenakas 2004	27/51	6/50		2.52%	4.41[1.99,9.76]
Subtotal (95% CI)	**2598**	**2174**		**100%**	**5.17[4.56,5.87]**
Total events: 1385 (Ibuprofen), 230 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=131.66, df=41(P<0.0001); I^2=68.86%					
Test for overall effect: Z=25.61(P<0.0001)					
4.4.2 Ibuprofen lysine, arginine or soluble					
Black 2002	71/99	13/99		28.77%	5.46[3.24,9.2]
Desjardins 2002	16/49	0/23		1.5%	15.84[0.99,253.06]
Hersh 2000	47/59	5/27		15.18%	4.3[1.93,9.59]
Mehlisch 1995	67/98	1/40		3.14%	27.35[3.93,190.3]
Mehlisch 2002	62/100	7/100		15.49%	8.86[4.27,18.39]
Olson 2001	57/67	5/39		13.99%	6.64[2.91,15.14]
Seymour 1991 (study 1)	22/32	5/32		11.06%	4.4[1.9,10.18]
Seymour 1991 (study 2)	8/30	4/30		8.85%	2[0.67,5.94]
Seymour 1996	11/16	1/19		2.02%	13.06[1.88,90.54]
Subtotal (95% CI)	**550**	**409**		**100%**	**6.55[4.85,8.85]**
Total events: 361 (Ibuprofen), 41 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.57, df=8(P=0.23); I^2=24.31%					
Test for overall effect: Z=12.23(P<0.0001)					



Analysis 4.5. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 5 Participants with at least 50% pain relief over 4 to 6 hours, dental surgery: study size.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 40 or more participants					
Bakshi 1994	57/80	31/82		17.87%	1.88[1.38,2.57]
Black 2002	71/99	13/50		10.08%	2.76[1.7,4.47]
Black 2002	71/100	13/49		10.18%	2.68[1.65,4.34]
Cheung 2007	40/57	5/57		2.92%	8[3.41,18.79]
Cooper 1977	20/40	6/40		3.5%	3.33[1.5,7.42]
Cooper 1989	37/61	9/64		5.13%	4.31[2.28,8.17]
Edwards 2002	145/339	11/339		6.42%	13.18[7.28,23.88]
Hill 2001	22/49	5/50		2.89%	4.49[1.85,10.91]
Mehlisch 1990	124/306	5/85		4.57%	6.89[2.91,16.3]
Mehlisch 1995	67/98	1/40		0.83%	27.35[3.93,190.3]
Mehlisch 2002	57/100	6/50		4.67%	4.75[2.2,10.26]
Mehlisch 2002	62/100	7/50		5.45%	4.43[2.19,8.95]
Morrison 1999	20/51	6/50		3.54%	3.27[1.43,7.46]
Schou 1998	41/49	16/56		8.72%	2.93[1.9,4.51]

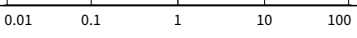


Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Seymour 1998	27/76	3/70		1.82%	8.29[2.63,26.12]
Van Dyke 2004	112/186	9/62		7.88%	4.15[2.24,7.67]
Zelenakas 2004	27/51	6/50		3.54%	4.41[1.99,9.76]
Subtotal (95% CI)	**1842**	**1244**		**100%**	**4.44[3.8,5.19]**
Total events: 1000 (Ibuprofen), 152 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=62.16, df=16(P<0.0001); I^2=74.26%					
Test for overall effect: Z=18.81(P<0.0001)					
4.5.2 Fewer than 40 participants					
Ahlstrom 1993	19/32	2/30		3.26%	8.91[2.26,35.02]
Ehrich 1999	14/20	1/32		1.21%	22.4[3.19,157.49]
Forbes 1984	21/28	3/28		4.74%	7[2.35,20.83]
Forbes 1990	15/32	0/34		0.77%	32.88[2.05,527.71]
Forbes 1991b	18/37	3/39		4.61%	6.32[2.03,19.71]
Forbes 1992	20/38	0/38		0.79%	41[2.57,654.35]
Hersch 1993b	9/12	6/16		8.12%	2[0.98,4.08]
Laska 1986	39/39	14/37		23.48%	2.59[1.72,3.89]
McQuay 1996	6/30	0/11		1.14%	5.03[0.31,82.6]
Nørholt 1998	22/26	8/31		11.52%	3.28[1.77,6.09]
Schwartz 2007	5/15	0/16		0.77%	11.69[0.7,194.79]
Seymour 1991 (study 1)	22/32	5/16		10.53%	2.2[1.03,4.72]
Seymour 1991 (study 1)	20/31	5/16		10.41%	2.06[0.95,4.47]
Seymour 1991 (study 2)	8/30	4/15		8.42%	1[0.36,2.79]
Seymour 1991 (study 2)	20/30	3/15		6.32%	3.33[1.17,9.46]
Seymour 1996	11/16	1/10		1.94%	6.88[1.04,45.44]
Seymour 1996	11/15	1/9		1.97%	6.6[1.01,42.95]
Subtotal (95% CI)	**463**	**393**		**100%**	**4.06[3.21,5.14]**
Total events: 280 (Ibuprofen), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=33.42, df=16(P=0.01); I^2=52.12%					
Test for overall effect: Z=11.64(P<0.0001)					

Analysis 4.6. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 6 Participants using rescue medication over 6 hours.

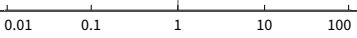
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahlstrom 1993	10/32	23/30		2.18%	0.41[0.24,0.71]
Arnold 1990	10/15	12/14		1.14%	0.78[0.51,1.18]
Bakshi 1994	22/80	53/82		4.82%	0.43[0.29,0.63]
Cooper 1988a	24/37	34/43		2.89%	0.82[0.62,1.09]
Cooper 1989	32/61	56/64		5.03%	0.6[0.46,0.77]
Forbes 1990	19/32	33/34		2.94%	0.61[0.46,0.82]
Forbes 1991b	16/37	37/39		3.31%	0.46[0.31,0.66]
Forbes 1992	14/38	35/38		3.22%	0.4[0.26,0.61]
Gay 1996	11/41	26/39		2.45%	0.4[0.23,0.7]
Heidrich 1985	23/40	36/40		3.31%	0.64[0.48,0.85]
Hersh 2000	14/59	20/27		2.52%	0.32[0.19,0.53]
Hill 2001	30/49	41/50		3.73%	0.75[0.58,0.97]

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Jain 1986	29/49	45/47		4.23%	0.62[0.49,0.79]
Jain 1988	10/49	24/48		2.23%	0.41[0.22,0.76]
Johnson 1997	38/48	43/48		3.96%	0.88[0.74,1.05]
Laveneziana 1996	15/42	17/41		1.58%	0.86[0.5,1.49]
Mehlisch 1990	125/306	64/85		9.22%	0.54[0.45,0.65]
Mehlisch 1995	25/98	35/40		4.57%	0.29[0.2,0.42]
Olson 2001	14/67	31/39		3.61%	0.26[0.16,0.43]
Pagnoni 1996	13/30	21/32		1.87%	0.66[0.41,1.07]
Schou 1998	8/49	37/56		3.18%	0.25[0.13,0.48]
Seymour 1991 (study 1)	14/32	11/16		1.35%	0.64[0.38,1.06]
Seymour 1991 (study 1)	12/31	11/16		1.34%	0.56[0.32,0.98]
Seymour 1991 (study 2)	18/30	14/15		1.72%	0.64[0.47,0.89]
Seymour 1991 (study 2)	22/30	14/15		1.72%	0.79[0.61,1.01]
Seymour 1996	13/16	10/10		1.17%	0.83[0.63,1.09]
Seymour 1996	10/15	9/9		1.08%	0.69[0.47,1.01]
Seymour 1998	42/76	60/70		5.75%	0.64[0.52,0.81]
Seymour 1999	23/41	39/39		3.72%	0.57[0.43,0.74]
Sunshine 1997	10/40	32/39		2.98%	0.3[0.17,0.53]
Van Dyke 2004	71/186	52/62		7.18%	0.46[0.37,0.56]
Total (95% CI)	**1756**	**1227**		**100%**	**0.54[0.51,0.57]**
Total events: 737 (Ibuprofen), 975 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=121.71, df=30(P<0.0001); I^2=75.35%					
Test for overall effect: Z=19.76(P<0.0001)					



Analysis 4.7. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 7 Participants using rescue medication over 6 hours, dental surgery.

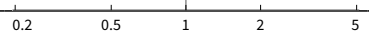
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahlstrom 1993	10/32	23/30		2.57%	0.41[0.24,0.71]
Bakshi 1994	22/80	53/82		5.66%	0.43[0.29,0.63]
Cooper 1988a	24/37	34/43		3.4%	0.82[0.62,1.09]
Cooper 1989	32/61	56/64		5.91%	0.6[0.46,0.77]
Forbes 1990	19/32	33/34		3.46%	0.61[0.46,0.82]
Forbes 1991b	16/37	37/39		3.89%	0.46[0.31,0.66]
Forbes 1992	14/38	35/38		3.78%	0.4[0.26,0.61]
Gay 1996	11/41	26/39		2.88%	0.4[0.23,0.7]
Hersh 2000	14/59	20/27		2.96%	0.32[0.19,0.53]
Hill 2001	30/49	41/50		4.38%	0.75[0.58,0.97]
Jain 1986	29/49	45/47		4.96%	0.62[0.49,0.79]
Jain 1988	10/49	24/48		2.62%	0.41[0.22,0.76]
Mehlisch 1990	125/306	64/85		10.82%	0.54[0.45,0.65]
Mehlisch 1995	25/98	35/40		5.37%	0.29[0.2,0.42]
Olson 2001	14/67	31/39		4.23%	0.26[0.16,0.43]
Schou 1998	8/49	37/56		3.73%	0.25[0.13,0.48]
Seymour 1991 (study 1)	12/31	11/16		1.57%	0.56[0.32,0.98]
Seymour 1991 (study 1)	14/32	11/16		1.58%	0.64[0.38,1.06]



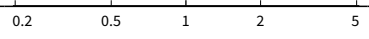
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Seymour 1991 (study 2)	18/30	14/15		2.02%	0.64[0.47,0.89]
Seymour 1991 (study 2)	22/30	14/15		2.02%	0.79[0.61,1.01]
Seymour 1996	10/15	9/9		1.26%	0.69[0.47,1.01]
Seymour 1996	13/16	10/10		1.38%	0.83[0.63,1.09]
Seymour 1998	42/76	60/70		6.75%	0.64[0.52,0.81]
Seymour 1999	23/41	39/39		4.37%	0.57[0.43,0.74]
Van Dyke 2004	71/186	52/62		8.43%	0.46[0.37,0.56]
Total (95% CI)	**1541**	**1013**		**100%**	**0.52[0.48,0.55]**
Total events: 628 (Ibuprofen), 814 (Placebo)					
Heterogeneity: Tau²=0; Chi²=85.56, df=24(P<0.0001); I²=71.95%					
Test for overall effect: Z=19.22(P<0.0001)					

Analysis 4.8. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 8 Participants using rescue medication over 6 hours, dental surgery: formulation.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 Standard ibuprofen					
Ahlstrom 1993	10/32	23/30		3.47%	0.41[0.24,0.71]
Bakshi 1994	22/80	53/82		7.64%	0.43[0.29,0.63]
Cooper 1988a	24/37	34/43		4.59%	0.82[0.62,1.09]
Cooper 1989	32/61	56/64		7.98%	0.6[0.46,0.77]
Forbes 1990	19/32	33/34		4.67%	0.61[0.46,0.82]
Forbes 1991b	16/37	37/39		5.26%	0.46[0.31,0.66]
Forbes 1992	14/38	35/38		5.11%	0.4[0.26,0.61]
Gay 1996	11/41	26/39		3.89%	0.4[0.23,0.7]
Hill 2001	30/49	41/50		5.92%	0.75[0.58,0.97]
Jain 1986	29/49	45/47		6.7%	0.62[0.49,0.79]
Jain 1988	10/49	24/48		3.54%	0.41[0.22,0.76]
Mehlisch 1990	125/306	64/85		14.62%	0.54[0.45,0.65]
Schou 1998	8/49	37/56		5.04%	0.25[0.13,0.48]
Seymour 1991 (study 1)	12/31	11/16		2.12%	0.56[0.32,0.98]
Seymour 1991 (study 2)	18/30	14/15		2.72%	0.64[0.47,0.89]
Seymour 1996	10/15	9/9		1.71%	0.69[0.47,1.01]
Seymour 1998	42/76	60/70		9.12%	0.64[0.52,0.81]
Seymour 1999	23/41	39/39		5.91%	0.57[0.43,0.74]
Subtotal (95% CI)	**1053**	**804**		**100%**	**0.55[0.51,0.59]**
Total events: 455 (Ibuprofen), 641 (Placebo)					
Heterogeneity: Tau²=0; Chi²=33.5, df=17(P=0.01); I²=49.25%					
Test for overall effect: Z=15.16(P<0.0001)					
4.8.2 Ibuprofen lysine, arginine or soluble					
Hersh 2000	14/59	20/27		16.9%	0.32[0.19,0.53]
Mehlisch 1995	25/98	35/40		30.61%	0.29[0.2,0.42]
Olson 2001	14/67	31/39		24.13%	0.26[0.16,0.43]
Seymour 1991 (study 1)	14/32	11/16		9.03%	0.64[0.38,1.06]
Seymour 1991 (study 2)	22/30	14/15		11.49%	0.79[0.61,1.01]

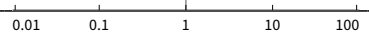


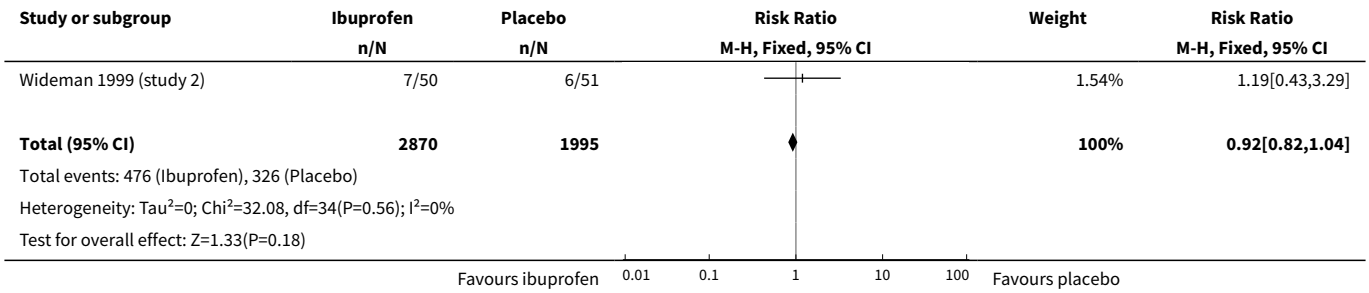
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Seymour 1996	13/16	10/10		7.85%	0.83[0.63,1.09]
Subtotal (95% CI)	**302**	**147**		**100%**	**0.42[0.35,0.5]**
Total events: 102 (Ibuprofen), 121 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=58.22, df=5(P<0.0001); I^2=91.41%					
Test for overall effect: Z=10.06(P<0.0001)					



Analysis 4.9. Comparison 4 Ibuprofen 400 mg versus placebo, Outcome 9 Participants with any adverse event.

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahlstrom 1993	3/32	2/30		0.54%	1.41[0.25,7.84]
Arnold 1990	6/15	3/14		0.81%	1.87[0.57,6.07]
Bakshi 1994	6/80	5/82		1.28%	1.23[0.39,3.87]
Black 2002	41/100	24/49		8.37%	0.84[0.58,1.21]
Black 2002	36/99	24/50		8.28%	0.76[0.51,1.12]
Cheung 2007	35/57	39/57		10.13%	0.9[0.68,1.18]
Cooper 1982	11/38	5/46		1.17%	2.66[1.01,7]
Cooper 1988a	10/40	7/45		1.71%	1.61[0.68,3.82]
Cooper 1989	5/63	7/64		1.8%	0.73[0.24,2.17]
De Miguel Rivero 1997	1/36	1/34		0.27%	0.94[0.06,14.51]
Desjardins 2002	4/52	0/11		0.21%	2.04[0.12,35.36]
Desjardins 2002	7/49	0/12		0.21%	3.9[0.24,63.94]
Edwards 2002	41/339	58/337		15.11%	0.7[0.49,1.02]
Forbes 1990	8/43	0/38		0.14%	15.07[0.9,252.65]
Forbes 1991b	7/43	3/47		0.74%	2.55[0.7,9.24]
Forbes 1992	4/45	2/46		0.51%	2.04[0.39,10.61]
Frame 1989	4/42	3/36		0.84%	1.14[0.27,4.77]
Gay 1996	3/41	4/41		1.04%	0.75[0.18,3.14]
Hersch 1993a	6/49	9/51		2.29%	0.69[0.27,1.8]
Hersh 2000	4/59	7/27		2.49%	0.26[0.08,0.82]
Hill 2001	6/49	8/50		2.06%	0.77[0.29,2.04]
Jain 1986	10/49	12/47		3.18%	0.8[0.38,1.67]
Jain 1988	2/49	1/48		0.26%	1.96[0.18,20.9]
Laska 1986	0/39	3/37		0.93%	0.14[0.01,2.54]
McQuay 1996	2/30	1/11		0.38%	0.73[0.07,7.31]
Mehlisch 1990	31/306	12/85		4.88%	0.72[0.39,1.34]
Mehlisch 1995	12/98	4/40		1.48%	1.22[0.42,3.57]
Mehlisch 2002	26/100	14/50		4.85%	0.93[0.53,1.62]
Mehlisch 2002	27/100	13/50		4.5%	1.04[0.59,1.83]
Olson 2001	7/67	2/39		0.66%	2.04[0.45,9.33]
Pagnoni 1996	0/30	0/32			Not estimable
Schachtel 1989	0/36	0/38			Not estimable
Seymour 1998	5/76	3/68		0.82%	1.49[0.37,6.01]
Singla 2005	74/175	33/60		12.76%	0.77[0.58,1.02]
Sunshine 1983	0/30	0/30			Not estimable
Sunshine 1987	0/38	0/40			Not estimable
Sunshine 1997	5/40	4/40		1.04%	1.25[0.36,4.32]
Van Dyke 2004	20/186	7/62		2.73%	0.95[0.42,2.14]

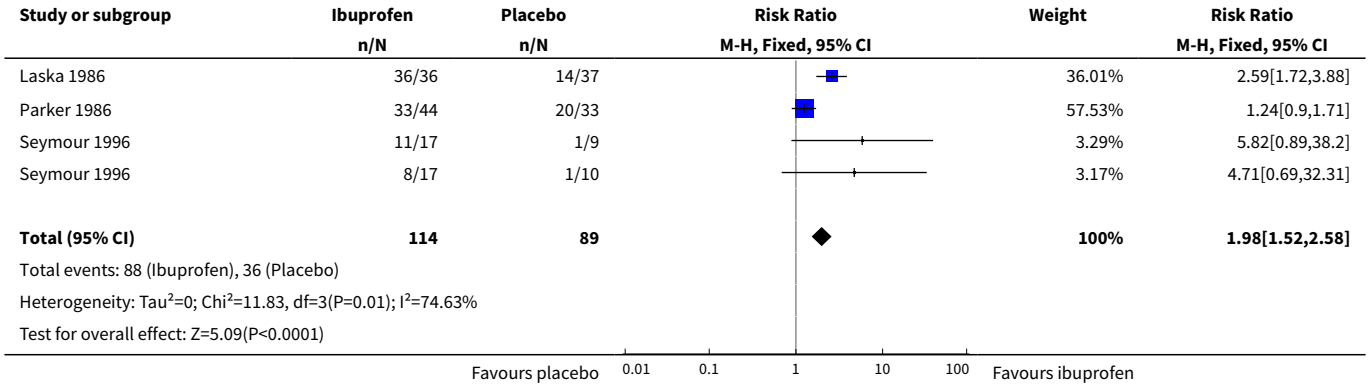




Comparison 5. Ibuprofen 600 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	3	203	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.52, 2.58]

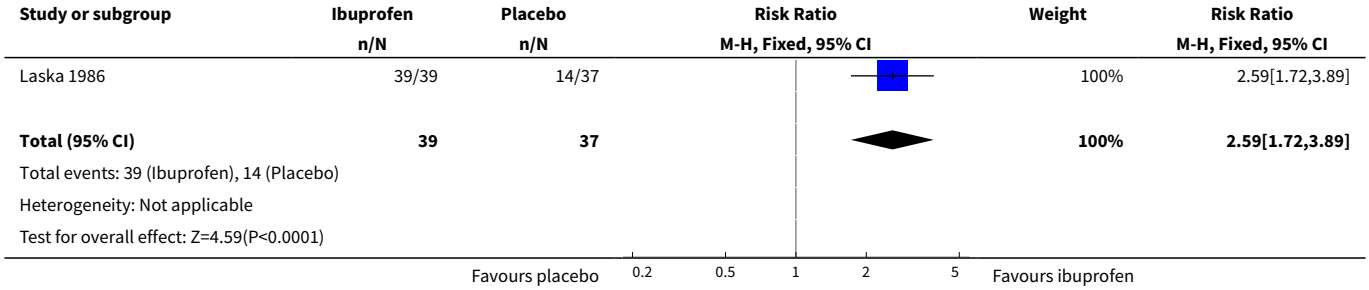
Analysis 5.1. Comparison 5 Ibuprofen 600 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.



Comparison 6. Ibuprofen 800 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	1	76	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.72, 3.89]

Analysis 6.1. Comparison 6 Ibuprofen 800 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.



ADDITIONAL TABLES

Table 1. Summary of outcomes: analgesia and use of rescue medication

		Analgesia			Rescue medication	
Study ID	**Treatment**	**PI or PR**	**Number with 50% PR**	**PGE: v good or excellent**	**Median time to use (h)**	**% using**
Ahlstrom 1993	(1) Ibuprofen 400 mg, n = 32 (3) Placebo n = 30	SPID 6: (1) 188 mm (3) 32 mm	(1) 19/32 (3) 2/30	at 6 h: (1) 75% (3) 17%	No data	at 6 h: (1) 31 (3) 77
Arnold 1990	(1) Ibuprofen 400 mg, n = 15 (2) Ketoprofen 25 mg, n = 14 (3) Ketoprofen 100 mg, n = 16 (4) Placebo, n = 14	TOTPAR 6: (1) 4.2 (4) 1.5	(1) 2/15 (4) 0/14	No usable data	Mean: (1) 3.9 (4) 2.4	at 6 h: (1) 67 (4) 83
Bakshi 1994	(1) Ibuprofen 400 mg, n = 80 (2) Diclofenac (dispersible) 50 mg, n = 83 (3) Placebo, n = 82	TOTPAR 6: (1) 14.9 (3) 8.9	(1) 57/80 (3) 31/82	No usable data	Mean: (1) 5.3 (3) 3.4	at 6 h: (1) 28 (3) 65
Black 2002	(1) Ibuprofen 200 mg, n = 100 (2) Ibuprofen 400 mg, n = 100 (3) Ibuprofen arginate 200 mg, n = 100 (4) Ibuprofen arginate 400 mg, n = 99 (5) Placebo, n = 99	TOTPAR 6: (1) 12.6 (2) 14.9 (3) 13.1 (4) 15.0 (5) 6.9	(1) 58/100 (2) 71/100 (3) 61/100 (4) 71/99 (5) 26/99	No usable data	(1) 4.2 (2) 5.2 (3) 4.0 (4) 4.5 (5) 1.3	No data
Cheung 2007	(1) Ibuprofen 440 mg, n = 57 (2) Celecoxib 400 mg, n = 57	TOTPAR 6: (1) 14.9	(1) 40/57 (3) 5/57	No data	(1) 11 (3) 1.9	at 24 h: (1) 72

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(3) Placebo, n = 57	(3) 3.7				(3) 86
Cooper 1977	(1) Ibuprofen 200 mg n = 38 (2) Ibuprofen 400 mg, n = 40 (3) Aspirin 325 mg, n = 37 (4) Aspirin 650 mg, n = 37 (5) Placebo, n= 40	TOTPAR 4: (1) 7.32 (2) 6.27 (5) 3.32	(1) 17/38 (2) 20/40 (5) 6/40	No data	No data	No data
Cooper 1982	(1) Ibuprofen 400 mg, n =38 (2) Ibuprofen 400 mg + Codeine 60 mg, n = 41 (3) Aspirin 650 mg, n = 38 (4) Aspirin 650 mg + codeine 60 mg, n = 45 (5) Codeine 60 mg, n = 41 (6) Placebo, n = 46	TOTPAR 4: (1) 8.4 (6) 2.7	(1) 22/38 (2) 27/41 (6) 5/46	No usable data	Mean: (1) 3.8 (6) 2.4	No data
Cooper 1988a	(1) Ibuprofen 400 mg, n = 37 (2) Ketoprofen 100 mg, n = 39 (3) Ketoprofen 25 mg, n = 42 (4) Placebo, n = 43	TOTPAR 6: (1) 11.3 (4) 4.7	(1) 19/37 (4) 6/43	at 6 h: (1) 12/37 (4) 2/43	(1) 4.0 (4) 3.0	at 6 h: (1) 65 (4) 79
Cooper 1989	(1) Ibuprofen 400 mg, n = 61 (2) Paracetamol 1000 mg, n = 59 (3) Placebo, n = 64	TOTPAR 6: (1) 13.1 (3) 4.7	(1) 37/61 (3) 9/64	at 6 h: (1) 32/61 (3) 4/64	(1) 5.5 (3) 2.3 Mean: (1) 4.5 (3) 3.3	at 6 h: (1) 52 (3) 78
Cooper 1996a	(1) Ibuprofen 200 mg, n = 19 (2) Misoprostal 200 mg, n = 18 (3) Ibuprofen 200 mg + misoprostal 200 mg, n = 20 (4) Placebo, n = 13	TOTPAR 6: (1) 5.3 (3) 5.1 (4) 1.2	(1) 3/19 (3) 3/18 (4) 0/33	No usable data	Mean: (1) 3.0 (3) 2.8 (4) 1.8	No data
De Miguel Rivero 1997	(1) Ibuprofen arginine 400 mg, n = 36 (2) Magnesic dipyrone, 2 g (IM), n = 33 (3) Placebo, n = 34	VAS SPID 5: (1) 187 mm (3) 120 mm	(1) 24/36 (3) 15/34	at 5 h: (1) 20/36 (3) 7/34	Mean: (1) 3.5 (3) 1.8	at 5 h: (1) 14 (3) 12
Desjardins 2002	(1) Ibuprofen 200 mg, n = 50 (2) Ibuprofen 400 mg, n = 52 (3) Ibuprofen arginine 200 mg, n = 49 (4) Ibuprofen arginine 400 mg, n = 50	TOTPAR 6: (1) 5.4 (2) 7.3 (3) 5.8	(1) 9/50 (2) 15/52 (3) 10/49 (4) 16/49	No data	(1) 2.6 (2) 4.0 (3) 3.0 (4) 4.0	No data

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(5) Placebo, n = 24	(4) 7.9 (5) 1.7	(5) 0/23		(5) 1.5	
Dionne 1998	(1) S(+)-Ibuprofen 200 mg, n = 51 (2) S(+)-Ibuprofen 400 mg, n = 50 (3) Ibuprofen (racemic) 400 mg, n = 50 (4) Placebo, n = 25	TOTPAR 6: (1) 13.0 (2) 14.9 (3) 11.5 (4) 3.5	(1) 31/51 (2) 35/40 (3) 26/50 (4) 2/25	No data	(1) 5.8 (2) 6.1 (3) 5.4 (4) 1.8	No data
Ehrich 1999	(1) Ibuprofen 400 mg, n = 20 (2) Rofecoxib 50 mg, n = 32 (3) Rofecoxib 500 mg, n = 20 (4) Placebo, n = 32	TOTPAR 6: (1) 15.1 (4) 2.7	(1) 14/20 (4) 1/32	No usable data	(1) >6 (4) 1.6	No usable data
Forbes 1984	(1) Ibuprofen 400 mg, n = 28 (2) Fendosal 200 mg, n = 29 (3) Aspirin 650 mg, n = 24 (4) Placebo n = 28	TOTPAR 6: (1) 15.8 (4) 3.8	(1) 21/28 (4) 3/28	No usable data	(1) 8.3 (4) 2.7 Mean: (1) 8.5 (4) 4.5	at 12 h: (1) 75 (4) 89
Forbes 1990	(1) Ibuprofen 400 mg, n = 32 (2) Ketorolac 10 mg, n = 31 (3) Ketorolac 20 mg, n = 35 (4) Paracetamol 600 mg, n = 36 (5) Paracetamol 600 mg + codeine 60 mg, n = 38 (6) Placebo, n = 34	TOTPAR 6: (1) 10.5 (6) 1.9	(1) 15/32 (6) 0/34	No usable data	(1) 4.7 (6) 1.9 Mean: (1) 4.6 (6) 2.9	at 6 h: (1) 58 (6) 97
Forbes 1991a	(1) Ibuprofen 50 mg, n = 57 (2) Ibuprofen 100 mg, n = 49 (3) Ibuprofen 200 mg, n = 48 (4) Ibuprofen 100 mg + Caffeine 100 mg, n = 49 (5) Ibuprofen 200 mg + Caffeine 100 mg, n = 44 (6) Placebo n = 51	TOTPAR 6: (1) 7.0 (2) 7.0 (3) 8.7 (4) 9.3 (5) 12.6 (6) 2.2	(1) 16/57 (2) 13/49 (3) 18/48 (4) 19/49 (5) 26/44 (6) 0/51	No usable data	Mean: 1) 4.9 (2) 4.8 (3) 5.1 (4) 5.4 (5) 6.1 (6) 3.0	at 8 h: (1) 79 (2) 78 (3) 79 (4) 69 (5) 57 (6) 94
Forbes 1991b	(1) Ibuprofen 400 mg, n = 37 (2) Bromfenac 5 mg, n = 39 (3) Bromfenac 10 mg, n = 43	TOTPAR 6: (1) 11.0 (6) 2.5	(1) 18/37 (6) 3/39	No usable data	(1) 6.9 (6) 1.8 Mean:	at 6 h: (1) 42 (6) 96

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(4) Bromfenac 25 mg, n = 42 (5) Aspirin 650 mg, n = 41 (6) Placebo, n = 39				(1) 5.7 (6) 2.8	at 8 h: (1) 57 (6) 97
Forbes 1992	(1) Ibuprofen 400 mg, n = 38 (2) Bromfenac 10 mg, n = 43 (3) Bromfenac 25 mg, n = 41 (4) Bromfenac 50 mg, n = 42 (5) Bromfenac 100 mg, n = 40 (6) Aspirin 650 mg, n = 38 (7) Placebo, n = 38	TOTPAR 6: (1) 11.8 (7) 2.1	(1) 20/38 (7) 0/38	No usable data	(1) 7.3 (7) 1.8 Mean: (1) 6.3 (7) 2.7	at 6 h: (1) 38 (7) 92 at 8 h: 1) 58 (7) 97
Frame 1989	(1) Ibuprofen 400 mg, n = 42 (2) Dihydrocodeine 30 mg, n = 43 (3) Placebo, n = 38	TOTPAR 5: (1) 11.1 (3) 1.9	(1) 26/42 (3) 0/38	No data	No usable data	at 5 h: (1) 40 (3) 89
Fricke 1993	(1) Ibuprofen 400 mg, n = 81 (2) Naproxen Na 440 mg, n = 81 (3) Placebo, n = 39	TOTPAR 6: (1) 10.9 (3) 2.9	(1) 40/81 (3) 2/39	No usable data	(1) 6.0 (3) 1.1	at 12 h: (1) 78 (3) No data
Gay 1996	(1) Ibuprofen 400 mg, n = 41 (2) DKP.TRIS 5 mg, n = 41 (3) DKP.TRIS 10 mg, n = 42 (4) DKP.TRIS 20 mg, n = 41 (5) Placebo, n = 39	TOTPAR 6: (1) 13.6 (5) 5.2	(1) 26/41 (5) 7/39	No usable data	Mean: (1) 5.04 (5) 3.65	at 6 h: (1) 27 (5) 67
Heidrich 1985	(1) Ibuprofen 400 mg, n = 40 (2) Paracetamol 300 + codeine 30 mg, n = 40 (3) Placebo, n = 40	VAS TOTPAR 6: (1) 234 mm (3) 104 mm	(1) 15/40 (3) 5/40	No data	No data	No data
Hersch 1993a	(1) Ibuprofen 200 mg, n = 51 (2) Ibuprofen 400 mg, n = 49 (3) Meclofenamate 100 mg, n = 52 (4) Meclofenamate 50 mg, n = 51 (5) Placebo, n = 51	TOTPAR 6: (1) 10.3 (2) 8.0 (5) 1.7	(1) 17/51 (2) 22/49 (5) 0/51	at 8 h: (1) 24/51 (2) 14/49 (5) 6/51	Mean: (1) 3.1 (2) 4.2 (5) 1.5	at 8 h: (1) 94 (2) 94 (5) 98
Hersch 1993b	(1) Ibuprofen 400 mg, n = 12 (2) Codeine 60 mg, n = 16 (3) Placebo, n = 16	TOTPAR 6: (1) 15.7 (3) 9.0	(1) 9/12 (3) 6/16	No usable data	Mean: (1) 5.0 (3) 4.0	No data

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

Hersh 2000	(1) Ibuprofen liquigel 200 mg, n = 61 (2) Ibuprofen liquigel 400 mg, n = 59 (3) Paracetamol 1000 mg, n = 63 (4) Placebo, n = 27	TOTPAR 6: (1) 14.7 (2) 16.6 (4) 5.2	(1) 43/61 (2) 47/59 (4) 5/27	at 6 h: (1) 38/61 (2) 41/59 (4) 4/27	(1) > 6 (2) > 6 (4) 1.6	at 6 h: (1) 31 (2) 23 (4) 75
Hill 2001	(1) Ibuprofen 400 mg, n = 49 (2) Pregabalin 50 mg, n = 49 (3) Pregabalin 300 mg, n = 50 (4) Placebo, n = 50	TOTPAR 6: (1) 10.1 (4) 3.8	(1) 22/49 (4) 5/50	No usable data	(1) 4.1 (4) 2.0	at 6 h: (1) 61 (4) 81
Jain 1986	(1) Ibuprofen 100 mg, n = 39 (2) Ibuprofen 200 mg, n = 47 (3) Ibuprofen 400 mg, n = 49 (4) Aspirin 650 mg, n = 45 (5) Placebo, n = 47	SPID 6: (1) 1.5 (2) 2.3 (3) 3.0 (5) -1.7	(1) 3/39 (2) 7/47 (3) 9/49 (5) 0/47	No usable data	Mean: (1) 3.9 (2) 4.2 (3) 4.0 (5) 2.1	at 6 h: (1) 74 (2) 67 (3) 59 (5) 96
Jain 1988	(1) Ibuprofen 400 mg, n = 49 (2) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (3) Placebo, n = 48	TOTPAR 6: (1) 14.4 (2) 13.9 (3) 8.6	(1) 33/49 (2) 33/50 (3) 17/48	No usable data	No data	at 6 h: (1) 20 (2) 24 (3) 49
Johnson 1997	(1) Ibuprofen 400 mg, n = 48 (2) Paracetamol 650 mg + oxycodone 10 mg, n = 47 (3) Bromfenac 100 mg, n = 48 (4) Bromfenac 50 mg, n = 47 (5) Placebo, n = 48	TOTPAR 6: (1) 7.7 (5) 5.5	(1) 15/48 (5) 9/48	No usable data	(1) 3.4 (5) 2.7	at 6 h: (1) 79 (5) 89
Kiersch 1993	(1) Ibuprofen 200 mg, n = 81 (2) Naproxen Na 220 mg, n = 80 (3) Placebo, n = 42	TOTPAR 6: (1) 10.3 (3) 3.7	(1) 37/81 (3) 4/42	at 12 h: (1) 34/81 (3) 4/42	(1) 8.0 (3) 2.0	at 12 h: (1) 63 (3) 90
Laska 1986	(1) Ibuprofen 400 mg, n = 39 (2) Ibuprofen 600 mg, n = 36 (3) Ibuprofen 800 mg, n = 39 (4) Aluminium ibuprofen 400 mg, n = 39 (5) Placebo, n = 37	SPID 6: (1) 13.9 (2) 14.1 (3) 13.4 (5) 5.3	(1) 39/39 (2) 36/36 (3) 39/39 (5) 14/37	No data	No data	No usable data
Laveneziana 1996	(1) Ibuprofen arginine soluble 400 mg, n = 42	VAS SPID 6: (1) 233 mm	(1) 29/42 (3) 24/41	No usable data	(1) 1.2 (3) 1.2	at 6 h: (1) 36

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(2) Ketorolac 30 mg, n = 41 (3) Placebo, n = 41	(3) 204 mm				(3) 41
Malmstrom 1999	(1) Ibuprofen 400 mg, n = 46 (2) Rofecoxib 50 mg, n = 90 (3) Celecoxib 200 mg, n = 91 (4) Placebo, n = 45	TOTPAR 6: (1) 15.2 (4) 3.7	(1) 33/46 (4) 4/45	No usable data	(1) 8.9 (4) 1.5	at 24 h: (1) 76 (4) 91
Malmstrom 2002	(1) Ibuprofen 400 mg, n = 45 (2) Rofecoxib 50 mg, n = 151 (3) Celecoxib 400 mg, n = 151 (4) Celecoxib 200 mg, n = 90 (5) Placebo, n = 45	TOTPAR 6: (1) 11.7 (5) 1.0	(1) 24/45 (5) 0/45	No usable data	(1) 10.0 (5) 1.6	at 24 h: (1) 87 (5) 98
Malmstrom 2004	(1) Ibuprofen 400 mg, n = 48 (2) Etoricoxib 60 mg, n = 75 (3) Etoricoxib 120 mg, n = 76 (4) Etoricoxib 180 mg, n = 74 (5) Etoricoxib 240 mg, n = 76 (6) Placebo, n = 49	TOTPAR 6: (1) 14.1 (6) 3.4	(1) 32/48 (6) 4/49	No usable data	(1) 10.1 (6) 2.1	at 24 h: (1) 81 (6) 82
McQuay 1996	(1) Ibuprofen 200 mg, n = 31 (2) Ibuprofen 400 mg, n = 30 (3) Ibuprofen 200 mg + caffeine 50 mg, n = 30 (4) Ibuprofen 200 mg + caffeine 100 mg, n = 30 (5) Ibuprofen 200 mg + caffeine 200 mg, n = 29 (6) Placebo, n = 11	TOTPAR 6: (1) 3.0 (2) 7.0 (3) 10.3 (4) 9.5 (5) 5.5 (6) 0	(1) 2/31 (2) 6/30 (3) 8/30 (4) 14/30 (5) 12/29 (6) 0/11	No usable data	No data	No data
Medve 2001	(1) Ibuprofen 200 mg, n = 240 (2) Tramadol 37.5 mg, n = 238 (3) Paracetamol 325 mg, n = 240 (4) Tramadol 37.5 mg + paracetamol 325 mg, n = 240 (5) Placebo, n = 239		Data taken from IPMA: (1) 114/240 (5) 5/239	No usable data	(1) 5.4 (5) 2.0	No data
Mehlisch 1990	(1) Ibuprofen 400 mg, n = 306 (2) Paracetamol 1000 mg, n = 306	SPID 6: (1) 5.8	(1) 124/306 (3) 5/85	No data	No data	at 6 h: (1) 41

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(3) Placebo, n = 85	(3) 1.2				(3) 75
Mehlisch 1995	(1) Ibuprofen lysine 400 mg, n = 98 (2) Paracetamol 1000 mg, n = 101 (3) Placebo, n = 40	TOTPAR 6: (1) 14.4 (3) 2.6	(1) 67/98 (3) 1/40	at 6 h: (1) 65/98 (3) 1/40	(1) > 6 (3) 1.4	at 6 h: (1) 26 (3) 88
Mehlisch 2002	(1) Ibuprofen 200 mg, n = 100 (2) Ibuprofen 400 mg, n = 100 (3) Ibuprofen arginine 200 mg, n = 100 (4) Ibuprofen arginine 400 mg, n = 100 (5) Placebo, n = 100	TOTPAR 6: (1) 10.0 (2) 12.4 (3) 13.6 (4) 13.3 (5) 4.5	(1) 44/100 (2) 57/100 (3) 64/100 (4) 62/100 (5) 13/100		(1) 3.8 (2) 4.2 (3) 4.5 (4) 4.4 (5) 2.3	at 4 h: (1) 32 (2) 47 (3) 27 (4) 33 (5) No data
Morrison 1999	(1) Ibuprofen 400 mg, n = 51 (2) Rofecoxib 50 mg, n = 50 (3) Placebo, n = 50	TOTPAR 6: (1) 9.3 (3) 4.2	(1) 20/51 (3) 6/50	No usable data	(1) 6.1 (3) 2.4	at 24 h: (1) 82 (3) 92
Nelson 1994	(1) Ibuprofen lysine 200 mg, n = 77 (2) Aspirin 500 mg, n = 65 (3) Placebo, n = 40	TOTPAR 6: (1) 12.3 (3) 5.6	(1) 44/77 (3) 8/40	at 6 h: (1) 39/77 (3) 6/40	(1) >6 (3) 2.9	at 6 h: (1) 44 (3) 70
Nørholt 1998	(1) Ibuprofen 400 mg, n = 26 (2) Placebo, n = 31	TOTPAR 4: (1) 11.7 (2) 4.5	(1) 22/26 (2) 8/31	No data	No data	at 4 h: (1) 15 (2) 71
Olson 2001	(1) Ibuprofen liquigel 400 mg, n = 67 (2) Ketoprofen 25 mg, n = 67 (3) Paracetamol 1000 mg, n = 66 (4) Placebo, n = 39	TOTPAR 6: (1) 17.4 (4) 4.3	(1) 57/67 (4) 5/39	at 6 h: (1) 52/67 (4) 4/49	(1) > 6 (4) 1.3	at 6 h: (1) 21 (4) 79
Pagnoni 1996	(1) Ibuprofen arginine soluble 400 mg, n = 30 (2) Ketorolac (IM) 30 mg, n = 30 (3) Placebo, n = 32	VAS SPID 6: (1) 279 (3) 114	(1) 13/30 (3) 5/32	at 6 h: (1) 5/30 (3) 0/32	(1) 2.1 (3) 1.9	at 6 h: (1) 43 (3) 66
Parker 1986	(1) Ibuprofen syrup 600 mg, n = 44 (2) Aspirin syrup 600 mg, n = 33 (3) Placebo, n = 33	TOTPAR 4: (1) 10.4 (3) 8.8	(1) 33/44 (3) 20/33	No data	No data	No data
Schachtel 1989	(1) Ibuprofen 400 mg, n = 36 (2) Paracetamol 1000 mg, n = 37 (3) Placebo, n = 38	TOTPAR 4: (1) 10.4 (3) 5.5	(1) 27/36 (3) 13/38	No data	No data	at 4 h: (1) 22 (3) 58

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

Schou 1998	(1) Ibuprofen 50 mg, n = 51 (2) Ibuprofen 100 mg, n = 53 (3) Ibuprofen 200 mg, n = 49 (4) Ibuprofen 400 mg, n = 49 (5) Placebo, n = 56	TOTPAR 6: (1) 11.8 (2) 11.2 (3) 15.5 (4) 17.2 (5) 7.3	(1) 27/51 (2) 27/53 (3) 36/49 (4) 41/49 (5) 16/56	No data	(1) 5.5 (2) >6 (3) >6 (4) >6 (5) 3.7	Up to 6 h: (1) 54 (2) 48 (3) 36 (4) 16 (5) 66
Schwartz 2007	(1) Ibuprofen 400 mg, n = 15 (2) MK-0703 12.5 mg, n = 31 (3) MK-0703 50 mg, n = 28 (4) MK-0703 100 mg, n = 31 (5) Placebo, n = 16	No data	Not available	at 8 h: (1) 5/15 (5) 0/16	(1) 7.1 (5) 1.6	at 8 h: (1) 80 (5) 100
Seymour 1991 (study 1)	(1) Ibuprofen tablets 400 mg, n = 31 (2) Ibuprofen liquid in gelatin capsules 400 mg, n = 32 (3) Placebo n = 32	VAS SPID 6: (1) 243 mm (2) 233 mm (3) 120 mm	(1) 20/31 (2) 22/32 (3) 10/32	No usable data	Mean: (1) 3.6 (2) 3.5 (3) 2.1	at 6 h: (1) 39 (2) 44 (3) 69
Seymour 1991 (study 2)	(1) Ibuprofen tablets 400 mg, n = 30 (2) Ibuprofen soluble 400 mg, n = 32 (3) Placebo, n = 30	VAS SPID 6: (1) 214 mm (2) 228 mm (3) 86 mm	(1) 20/30 (2) 8/30 (3) 7/30	No usable data	Mean: (1) 3.24 (2) 3.15 (3) 1.40	at 6 h: (1) 60 (2) 72 (3) 93
Seymour 1996	(1) Ibuprofen tablets 200 mg, n = 18 (2) Ibuprofen soluble 200 mg, n = 17 (3) Ibuprofen tablets 400 mg, n = 15 (4) Ibuprofen soluble 400 mg, n = 16 (5) Ibuprofen tablets 600 mg, n = 17 (6) Ibuprofen soluble 600 mg, n = 17 (7) Placebo, n = 19	VAS SPID 6: (1) 230 mm (2) 148 mm (3) 258 mm (4) 238 mm (5) 140 mm (6) 198 mm (7) 44 mm	(1) 7/18 (2) 9/17 (3) 11/15 (4) 11/16 (5) 11/17 (6) 8/17 (7) 2/19	No usable data	(1) 3.0 (2) 1.6 (3) 2.8 (4) 2.1 (5) 2.0 (6) 1.5 (7) 0.8	at 6 h: (1) 88 (2) 88 (3) 67 (4) 81 (5) 100 (6) 88 (7) 100
Seymour 1998	(1) Ibuprofen 400 mg, n = 76 (2) Aceclofenac 150 mg, n = 71 (3) Placebo, n = 70	VAS TOTPAR 4: (1) 151 mm (3) 46 mm	(1) 27/76 (3) 3/70	No usable data	(1) 3.5 (3) 1.6	at 6 h: (1) 55 (3) 86
Seymour 1999	(1) Ibuprofen 400 mg, n = 41 (2) WAG 994 1 mg, n = 42	TOTPAR 6: (1) 10.4	(1) 19/41 (3) 7/39	No usable data	(1) 5.2 (3) 2.0	at 6 h: (1) 56

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(3) Placebo, n = 39	(3) 5.1				(3) 100
Seymour 2000	(1) Ibuprofen 200 mg, n = 59 (2) Buffered ketoprofen 12.5 mg, n = 61 (3) Placebo, n = 60	TOTPAR 6: (1) 6.4 (3) 4.1	(1) 14/59 (3) 7/60	No usable data	(1) 2.0 (3) 1.9	at 6 h: (1) 83 (3) 98
Singla 2005	(1) Ibuprofen 400 mg, n = 175 (2) Ibuprofen 400 mg + oxycodone 5 mg, n = 169 (3) Oxycodone 5 mg, n = 52 (4) Placebo, n = 60	TOTPAR 6: (1) 10.0 (4) 6.4	(1) 77/175 (4) 14/60	No usable data	(1) 4.0 (4) 2.3	at 6 h: (1) 71 (4) No data
Sunshine 1983	(1) Ibuprofen 400 mg, n = 30 (2) Aspirin 600 mg, n = 30 (3) Zomepirac 100 mg, n = 30 (4) Placebo, n = 30	SPID 4: (1) 6.0 (4) 1.0	(1) 21/30 (4) 3/30	No data	No data	at 4 h: (1) 0 (4) 17
Sunshine 1987	(1) Ibuprofen 400 mg, n = 38 (2) Ibuprofen 200 mg + codeine 30 mg, n = 40 (3) Ibuprofen 400 mg + codeine 60 mg, n = 40 (4) Codeine 60 mg, n = 37 (5) Placebo, n = 40	SPID 4: (1) 4.8 (5) 3.4	(1) 16/38 11/40	No usable data	No usable data	at 4 h: (1) 13 (5) 50
Sunshine 1996	(1) Ibuprofen 50 mg, n = 51 (2) Ibuprofen 100 mg, n = 51 (3) Ibuprofen 200 mg, n = 50 (4) Ibuprofen 100 mg + caffeine 100 mg, n = 50 (5) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (6) Placebo, n = 50	TOTPAR 6: (1) 4.7 (2) 8.2 (3) 13.9 (4) 10.9 (5) 14.9 (6) 2.2	(1) 7/51 (2) 17/51 (3) 33/50 (4) 24/50 (5) 36/50 (6) 0/50	No usable data	No data	at 6 h: (1) 4 (2) 0 (3) 0 (4) 0 (5) 2 (6) 32
Sunshine 1997	(1) Ibuprofen 400 mg, n = 40 (2) Ibuprofen 400 mg + hydrocodone 15 mg, n = 40 (3) Placebo, n = 39	TOTPAR 6: (1) 9.7 (3) 2.7	(1) 17/40 (3) 1/39	No usable data	No usable data	at 6 h: (1) 25 (3) 82
Sunshine 1998	(1) Ibuprofen 200 mg, n = 35 (2) Ketoprofen 6.25 mg, n = 35 (3) Ketoprofen 12.5 mg, n = 35	TOTPAR 6: (1) 12.5 (5) 3.6	(1) 20/35 (5) 3/35	No usable data	No usable data	No usable data

Table 1. Summary of outcomes: analgesia and use of rescue medication *(Continued)*

	(4) Ketoprofen 25 mg, n = 35 (5) Placebo, n = 35					
Unpublished from Edwards 2002	(1) Ibuprofen 400 mg, n = 339 (2) Placebo, n = 339	Individual patient meta-analysis	(1) 145/339 (2) 11/339	No usable data	No usable data	at 8 h: (1) 43/339 (2) 121/337
Van Dyke 2004	(1) Ibuprofen 400 mg, n = 186 (2) Ibuprofen 400 mg + oxycodone 5 mg, n = 187 (3) Oxycodone 5 mg, n = 63 (4) Placebo, n = 62	TOTPAR 6: (1) 12.9 (4) 4.8	(1) 112/186 (4) 9/62	No usable data	1) > 6 (4) 2.0	at 6 h: (1) 38 (4) 84
Wahl 1997	(1) Ibuprofen lysinate 342 mg (= 200 mg Ibu), n = 74 (2) Paracetamol 200 mg + aspirin 250 mg + caffeine 50 mg, n = 73 (3) Placebo, n = 42	TOTPAR 6: (1) 11.6 (3) 2.5	(1) 39/74 (3) 1/42	No usable data	No data	at 6 h: (1) 42 (3) 81
Wideman 1999 (study 1)	(1) Ibuprofen 200 mg, n = 60 (2) Ibuprofen 200 mg, + hydrocodone 7.5 mg, n = 59 (3) Hydrocodone 7.5 mg, n = 61 (4) Placebo, n = 60	TOTPAR 6: (1) 4.9 (4) 3.5	(1) 9/60 (4) 5/60	No data	No data	No data
Wideman 1999 (study 2)	(1) Ibuprofen 400 mg, n = 50 (2) Ibuprofen 400 mg + hydrocodone 15 mg, n = 50 (3) Hydrocodone 15 mg, n = 50 (4) Placebo, n = 51	TOTPAR 6: (1) 9.7 (4) 3.0	(1) 21/50 (4) 3/51	No data	(1) 4.2 (4) 1.8	at 8 h: (1) 69 (4) 100
Zelenakas 2004	(1) Ibuprofen 400 mg, n = 51 (2) Lumiracoxib 100 mg, n = 51 (3) Lumiracoxib 400 mg, n = 50 (4) Placebo, n = 50	TOTPAR 6: (1) 11.6 (4) 4.2	(1) 27/51 (4) 6/50	No usable data	(1) ˜8 (4) ˜2	at 12 h: (1) 73 (4) 92

Table 2. Summary of outcomes: adverse events and withdrawals

		Adverse events		Withdrawals	
Study ID	**Treatment**	**Any**	**Serious**	**Adverse event**	**Other**

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

Ahlstrom 1993	(1) Ibuprofen 400 mg, n = 32 (2) Diclofenac (drinkable) 50 mg, n = 35 (3) Placebo n = 30	at 6 h: (1) 3/32 (3) 2/30	None	None	30 excluded for various protocol violations
Arnold 1990	(1) Ibuprofen 400 mg, n = 15 (2) Ketoprofen 25 mg, n = 14 (3) Ketoprofen 100 mg, n = 16 (4) Placebo, n = 14	at 6 h: (1) 6/15 (4) 3/14	None	None	No data
Bakshi 1994	(1) Ibuprofen 400 mg, n = 80 (2) Diclofenac (dispersible) 50 mg, n = 83 (3) Placebo, n = 82	at 6 h: (1) 6/80 (3) 5/82	None	None	12 exclusions: 9 with insufficient baseline pain, 2 remedicated early, 1 completed diary incorrectly
Black 2002	(1) Ibuprofen 200 mg, n = 100 (2) Ibuprofen 400 mg, n = 100 (3) Ibuprofen arginate 200 mg, n = 100 (4) Ibuprofen arginate 400 mg, n = 99 (5) Placebo, n = 99	at 6 h: (1) 31/100 (2) 41/100 (3) 51/100 (4) 36/99 (5) 48/99	(3) 1/100 (dysphagia and pharyngitis after 60 min assessment)	(3) 1/100	4 exclusions from efficacy analysis: 2 from Ibu Arg groups vomited soon after taking drug, 1 ibu arg 200 mg and 1 placebo took prohibited medication
Cheung 2007	(1) Ibuprofen 440 mg, n = 57 (2) Celecoxib 400 mg, n = 57 (3) Placebo, n = 57	at 24 h: (1) 35/57 (3) 39/57	None	(3) 3/57 (vomiting and anxiety)	(3) 1/57 (withdrew consent)
Cooper 1977	(1) Ibuprofen 200 mg n = 38 (2) Ibuprofen 400 mg, n = 40 (3) Aspirin 325 mg, n = 37 (4) Aspirin 650 mg, n = 37 (5) Placebo, n = 40	No data	None	None	Exclusions: 17 provided uninterpretable data, 12 took confounding medication, 10 were lost to follow up, 9 did not need medication, 5 fell asleep
Cooper 1982	(1) Ibuprofen 400 mg, n =38 (2) Ibuprofen 400 mg + Codeine 60 mg, n = 41 (3) Aspirin 650 mg, n = 38 (4) Aspirin 650 mg + codeine 60 mg, n = 45 (5) Codeine 60 mg, n = 41 (6) Placebo, n = 46	at 4 h: (1) 11/38 (6) 5/46	None	None	Exclusions: 30 were lost to follow up, 15 did not need medication, 11 remedicated early, 6 missed more the 1 evaluation, 3 medicated with slight pain, 1 did not take all the medication, 1 medicated over 24 hrs after surgery

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

Cooper 1988a	(1) Ibuprofen 400 mg, n = 37 (2) Ketoprofen 100 mg, n = 39 (3) Ketoprofen 25 mg, n = 42 (4) Placebo, n = 43	at 6 h: (1) 10/40 (4) 7/45	None reported	None reported	Exclusions: 20 did not need medication, 13 were lost to follow up, 7 had various protocol violations
Cooper 1989	(1) Ibuprofen 400 mg, n = 61 (2) Paracetamol 1000 mg, n = 59 (3) Placebo, n = 64	at 6 h: (1) 5/63 (3) 7/64	None	None	Exclusions: 2 were lost to follow up, 2 did not need medication, 4 missed more than 1 evaluation, 1 had insufficient baseline pain, 1 failed to complete the diary at the appropriate time
Cooper 1996a	(1) Ibuprofen 200 mg, n = 19 (2) Misoprostal 200 mg, n = 18 (3) Ibuprofen 200 mg + misoprostal 200 mg, n = 20 (4) Placebo, n = 13	No usable data All transient and mild	None reported	No data	No data
De Miguel Rivero 1997	(1) Ibuprofen arginine 400 mg, n = 36 (2) Magnesic dipyrone, 2 g (IM), n = 33 (3) Placebo, n = 34	at 5 h: (1) 1/36 (3) 1/34	None	None	Exclusions: 3 did not need medication
Desjardins 2002	(1) Ibuprofen 200 mg, n = 50 (2) Ibuprofen 400 mg, n = 52 (3) Ibuprofen arginine 200 mg, n = 49 (4) Ibuprofen arginine 400 mg, n = 50 (5) Placebo, n = 24	at 6 h: (1) 4/50 (2) 4/52 (3) 3/49 (4) 7/50 (5) 1/24	None	None	Exclusions from efficacy analysis: 1 (placebo) for protocol violation, 1 (placebo) for vomiting after receiving study drug and 1 (Ibu arg 400) for having a seizure 11 hours post-dose
Dionne 1998	(1) S(+)-Ibuprofen 200 mg, n = 51 (2) S(+)-Ibuprofen 400 mg, n = 50 (3) Ibuprofen (racemic) 400 mg, n = 50 (4) Placebo, n = 25	No usable data	None reported	None	Exclusions: 4 had neither partial or bony impaction, 1 remedicated early
Ehrich 1999	(1) Ibuprofen 400 mg, n = 20 (2) Rofecoxib 50 mg, n = 32 (3) Rofecoxib 500 mg, n = 20 (4) Placebo, n = 32	No usable data Any events mild and transient	None	No data	No data Exclusions: 2 remedicated early

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

Forbes 1984	(1) Ibuprofen 400 mg, n = 28 (2) Fendosal 200 mg, n = 29 (3) Aspirin 650 mg, n = 24 (4) Placebo n = 28	at 12 h: (1) 5/29 (4) 3/30 All transitory and did not require treatment	None	None	Exclusions: 2 remedicated early, 2 remedicated with some pain relief, 2 took rescue medication not test drug
Forbes 1990	(1) Ibuprofen 400 mg, n = 32 (2) Ketorolac 10 mg, n = 31 (3) Ketorolac 20 mg, n = 35 (4) Paracetamol 600 mg, n = 36 (5) Paracetamol 600 mg + codeine 60 mg, n = 38 (6) Placebo, n = 34	at 6 h: (1) 8/43 (6) 0/38 All transitory and did not require treatment	None	None	Exclusions; 3 were lost to follow up, 1 lost report card, 27 remedicated early or while still experiencing some pain relief from study medication, 7 failed to follow instructions, 3 did not complete the forms
Forbes 1991a	(1) Ibuprofen 50 mg, n = 57 (2) Ibuprofen 100 mg, n = 49 (3) Ibuprofen 200 mg, n = 48 (4) Ibuprofen 100 mg + Caffeine 100 mg, n = 49 (5) Ibuprofen 200 mg + Caffeine 100 mg, n = 44 (6) Placebo n = 51	at 8 h: (1) 10/63 (2) 5/62 (3) 6/60 (4) 12/58 (5) 8/58 (6) 8/61 All transitory and did not require treatment	None	None	Exclusions from efficacy analysis: 33 did not need medication, 14 remedicated early, 1 ate caffeine containing food, 2 medicated for a headache, 1 rated only one side of mouth, 1 form completed by relative, 3 lacked consistency, 22 evaluated at incorrect time, 3 incomplete forms
Forbes 1991b	(1) Ibuprofen 400 mg, n = 37 (2) Bromfenac 5 mg, n = 39 (3) Bromfenac 10 mg, n = 43 (4) Bromfenac 25 mg, n = 42 (5) Aspirin 650 mg, n = 41 (6) Placebo, n = 39	at 8 h: (1) 7/43 (6) 3/47 All transitory and did not require treatment	None	None	Exclusions: 7 were lost to follow up, 12 did not need medication, 24 remedicated early or while still experiencing some pain relief from study medication, 2 lacked consistency, 1 did not complete the form, 1 took only part of the med
Forbes 1992	(1) Ibuprofen 400 mg, n = 38 (2) Bromfenac 10 mg, n = 43 (3) Bromfenac 25 mg, n = 41 (4) Bromfenac 50 mg, n = 42 (5) Bromfenac 100 mg, n = 40	at 8 h: (1) 4/45 (7) 2/46 All transitory and did not	None	None	Exclusions; 3 did not return form, 14 did not need medication, 28 remedicated early or while still experiencing some pain relief from study medication, 2 lacked consistency, 2

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

	(6) Aspirin 650 mg, n = 38 (7) Placebo, n = 38	require treatment			did not complete form, 2 took only part of medication, 5 took back up medication, 2 evaluated at incorrect time
Frame 1989	(1) Ibuprofen 400 mg, n = 42 (2) Dihydrocodeine 30 mg, n = 43 (3) Placebo, n = 38	at 5 h: (1) 4/42 (3) 3/38	None reported	(3) 1/38 (postoperative bleed)	Exclusions: 9 did not take the medication, 7 were lost to follow up, 1 was asleep so did not complete the forms, 1 had postoperative complications so did not complete the form
Fricke 1993	(1) Ibuprofen 400 mg, n = 81 (2) Naproxen Na 440 mg, n = 81 (3) Placebo, n = 39	at 12 h: (1) 8/81 (3) 1/39	None	(1) 1/81 (soreness and swelling at 8 hrs)	Exclusions: 5 did not need medication, 1 took study medication twice - excluded from efficacy analysis
Gay 1996	(1) Ibuprofen 400 mg, n = 41 (2) DKP.TRIS 5 mg, n = 41 (3) DKP.TRIS 10 mg, n = 42 (4) DKP.TRIS 20 mg, n = 41 (5) Placebo, n = 39	at 6 h: (1) 3/41 (5) 4/41	None	None	Exclusion from efficacy analysis: 2 remedicated early
Heidrich 1985	(1) Ibuprofen 400 mg, n = 40 (2) Paracetamol 300 + codeine 30 mg, n = 40 (3) Placebo, n = 40	No usable data Overall occurrence ±15%, no difference between groups	None reported	None	No data
Hersch 1993a	(1) Ibuprofen 200 mg, n = 51 (2) Ibuprofen 400 mg, n = 49 (3) Meclofenamate 100 mg, n = 52 (4) Meclofenamate 50 mg, n = 51 (5) Placebo, n = 51	at 8 h: (1) 6/49 (2) 4/51 (5) 9/51 All transitory and did not require treatment	None reported	None	No data
Hersch 1993b	(1) Ibuprofen 400 mg, n = 12 (2) Codeine 60 mg, n = 16 (3) Placebo, n = 16	No data	None reported	None reported	Exclusions: 19 lost to follow up, 11 did not need medication, 3 excluded for various protocol violations
Hersh 2000	(1) Ibuprofen liquigel 200 mg, n = 61	at 6 h: (1) 7/61	None	None	None

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

	(2) Ibuprofen liquigel 400 mg, n = 59 (3) Paracetamol 1000 mg, n = 63 (4) Placebo, n = 27	(2) 4/59 (4) 7/27			
Hill 2001	(1) Ibuprofen 400 mg, n = 49 (2) Pregabalin 50 mg, n = 49 (3) Pregabalin 300 mg, n = 50 (4) Placebo, n = 50	at 12 h: (1) 6/49 (4) 8/50	None	None	None
Jain 1986	(1) Ibuprofen 400 mg, n = 49 (2) Ibuprofen 200 mg, n = 47 (3) Ibuprofen 100 mg, n = 39 (4) Aspirin 650 mg, n = 45 (5) Placebo, n = 47	at 6 h: (1) 10/49 (2) 6/47 (3) 13/39 (5) 12/47	None reported	None reported	None
Jain 1988	(1) Ibuprofen 400 mg, n = 49 (2) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (3) Placebo, n = 48	at 6 h: (1) 2/49 (2) 5/50 (3) 1/48	None reported	None reported	Exclusions: 11 remedicated early, 2 received confounding agents, 1 was under 18 yrs old
Johnson 1997	(1) Ibuprofen 400 mg, n = 48 (2) Paracetamol 650 mg + oxycodone 10 mg, n = 47 (3) Bromfenac 100 mg, n = 48 (4) Bromfenac 50 mg, n = 47 (5) Placebo, n = 48	No usable data CNS AEs at 8 h: (1) 5/48 (5) 2/48	None reported	None reported	Exclusions: 2 had invalid data
Kiersch 1993	(1) Ibuprofen 200 mg, n = 81 (2) Naproxen Na 220 mg, n = 80 (3) Placebo, n = 42	at 12 h: (1) 16/81 (3) 5/43	None	(1) 1/81	Exclusions: 2 had protocol violations
Laska 1986	(1) Ibuprofen 400 mg, n = 39 (2) Ibuprofen 600 mg, n = 36 (3) Ibuprofen 800 mg, n = 39 (4) Aluminium ibuprofen 400 mg, n = 39 (5) Placebo, n = 37	at 6 h: (1) 0/39 (2) 1/36 (3) 0/39 (4) 1/39 (5) 3/37	None reported	None	Exclusions: 4 remedicated early, 1 vomited within 5 mins of taking the study medication. 4 with moderate pain dropped to keep populations homogeneous (author letter)
Laveneziana 1996	(1) Ibuprofen arginine soluble 400 mg, n = 42	None	None	None	Exclusions: 1 had insufficient pain

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

	(2) Ketorolac 30 mg, n = 41 (3) Placebo, n = 41				
Malmstrom 1999	(1) Ibuprofen 400 mg, n = 46 (2) Rofecoxib 50 mg, n = 90 (3) Celecoxib 200 mg, n = 91 (4) Placebo, n = 45	No usable data	None reported	(4) 1/45 (excessive bleeding)	None 4 patients lost to follow up at post-study visit
Malmstrom 2002	(1) Ibuprofen 400 mg, n = 45 (2) Rofecoxib 50 mg, n = 151 (3) Celecoxib 400 mg, n = 151 (4) Celecoxib 200 mg, n = 90 (5) Placebo, n = 45	at 24 h: (1) 8/45 (5) 12/45	None	None	None
Malmstrom 2004	(1) Ibuprofen 400 mg, n = 48 (2) Etoricoxib 60 mg, n = 75 (3) Etoricoxib 120 mg, n = 76 (4) Etoricoxib 180 mg, n = 74 (5) Etoricoxib 240 mg, n = 76 (6) Placebo, n = 49	Up to 14 days: (1) 17/48 (6) 24/49	None	(1) 1/48 (vomiting)	None
McQuay 1996	(1) Ibuprofen 200 mg, n = 31 (2) Ibuprofen 400 mg, n = 30 (3) Ibuprofen 200 mg + caffeine 50 mg, n = 30 (4) Ibuprofen 200 mg + caffeine 100 mg, n = 30 (5) Ibuprofen 200 mg + caffeine 200 mg, n = 29 (6)Placebo, n = 11	at 8 h: (1) 4/31 (2) 1/30 (3) 2/30 (4) 0/29 (5) 2/30 (6) 1/11	None reported	None	Exclusions: 3 with protocol violations
Medve 2001	(1) Ibuprofen 200 mg, n = 240 (2) Tramadol 37.5 mg, n = 238 (3) Paracetamol 325 mg, n = 240 (4) Tramadol 37.5 mg + paracetamol 325 mg, n = 240 (5) Placebo, n = 239	No usable data Generally transient and mild to moderate in severity	None reported	No data	No details for 3 exclusions
Mehlisch 1990	(1) Ibuprofen 400 mg, n = 306 (2) Paracetamol 1000 mg, n = 306 (3) Placebo, n = 85	at 6 h: (1) 31/306 (3) 12/85	None reported	None	Exclusions: 4 were lost to follow up, 4 entered in the trial twice (1st entry only was analysed for efficacy but both

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

					were included in safety analysis) and 1 excluded for failing to meet inclusion criteria
Mehlisch 1995	(1) Ibuprofen lysine 400 mg, n = 98 (2) Paracetamol 1000 mg, n = 101 (3) Placebo, n = 40	at 6 h: (1) 12/98 (3) 4/40	None	None	Exclusions: 1 failed to complete diary
Mehlisch 2002	(1) Ibuprofen 200 mg, n = 100 (2) Ibuprofen 400 mg, n = 100 (3) Ibuprofen arginine 200 mg, n = 100 (4) Ibuprofen arginine 400 mg, n = 100 (5) Placebo, n = 100	at 6 h: (1) 28/100 (2) 27/100 (3) 27/100 (4) 26/100 (5) 27/100	None	None	Exclusions: 3 from efficacy analysis for protocol violation
Morrison 1999	(1) Ibuprofen 400 mg, n = 51 (2) Rofecoxib 50 mg, n = 50 (3) Placebo, n = 50	at 24 h: (1) 13/51 (3) 17/50	None	None	None
Nelson 1994	(1) Ibuprofen lysine 200 mg, n = 77 (2) Aspirin 500 mg, n = 65 (3) Placebo, n = 40	at 6 h: (1) 16/75 (3) 11/40	None	None	Exclusions: 2 remedicated early, 1 did not record baseline pain intensity
Nørholt 1998	(1) Ibuprofen 400 mg, n = 26 (2) Placebo, n = 31	No data	No data	None	None
Olson 2001	(1) Ibuprofen liquigel 400 mg, n = 67 (2) Ketoprofen 25 mg, n = 67 (3) Paracetamol 1000 mg, n = 66 (4) Placebo, n = 39	at 6 h: (1) 7/67 (4) 2/39	None	None	None
Pagnoni 1996	(1) Ibuprofen arginine soluble 400 mg, n = 30 (2) Ketorolac (IM) 30 mg, n = 30 (3) Placebo, n = 32	None	None	None	None
Parker 1986	(1) Ibuprofen syrup 600 mg, n = 44 (2) Aspirin syrup 600 mg, n = 33 (3) Placebo, n = 33	No usable data	None reported	(3) 1/33 (probably in multiple dose phase)	Exclusions: 29 for which there is no further data
Schachtel 1989	(1) Ibuprofen 400 mg, n = 36	at 4 h:	None	None	Exclusions: 4 remedicated early

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

	(2) Paracetamol 1000 mg, n = 37 (3) Placebo, n = 38	None			
Schou 1998	(1) Ibuprofen 50 mg, n = 51 (2) Ibuprofen 100 mg, n = 53 (3) Ibuprofen 200 mg, n = 49 (4) Ibuprofen 400 mg, n = 49 (5) Placebo, n = 56	No usable data 18 patients reported mild transient AEs - no details of groups	None	None	Exclusions: 46 due to insufficient baseline pain, 3 withdrew (reasons not related to AE), 5 failed to attend follow-up, 5 lost self-report measure, 3 took study prohibited additional analgesia, 3 did not require surgery, 2 remedicated early, 1 had concomitant surgical removal of maxillary third molar
Schwartz 2007	(1) Ibuprofen 400 mg, n = 15 (2) MK-0703 12.5 mg, n = 31 (3) MK-0703 50 mg, n = 28 (4) MK-0703 100 mg, n = 31 (5) Placebo, n = 16	No usable data 38 patients in total reported AEs, no details of groups	None	None	None
Seymour 1991 (study 1)	(1) Ibuprofen tablets 400 mg, n = 31 (2) Ibuprofen liquid in gelatin capsules 400 mg, n = 32 (3) Placebo n = 32	at 6 h: (1) 0/31 (2) 0/32 (3) 1/32	None	None	No data
Seymour 1991 (study 2)	(1) Ibuprofen tablets 400 mg, n = 30 (2) Ibuprofen soluble 400 mg, n = 32 (3) Placebo, n = 30	at 6 h: None	None	None	No data
Seymour 1996	(1) Ibuprofen tablets 200 mg, n = 18 (2) Ibuprofen soluble 200 mg, n = 17 (3) Ibuprofen tablets 400 mg, n = 15 (4) Ibuprofen soluble 400 mg, n = 16 (5) Ibuprofen tablets 600 mg, n = 17 (6) Ibuprofen soluble 600 mg, n = 17 (7) Placebo, n = 19	No data	No data	No usable data 4 reported adverse effects, 3 had received ibuprofen (did not clarify which dose) and 1 had taken placebo	25 had inadequate baseline pain intensity

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

Seymour 1998	(1) Ibuprofen 400 mg, n = 76 (2) Aceclofenac 150 mg, n = 71 (3) Placebo, n = 70	at 6 h: (1) 5/76 (3) 3/68	None reported	None reported	Exclusions: 2 patients in group 2 and 2 patients in group 3 not accounted for
Seymour 1999	(1) Ibuprofen 400 mg, n = 41 (2) WAG 994 1 mg, n = 42 (3) Placebo, n = 39	No data	None	No data	No data
Seymour 2000	(1) Ibuprofen 200 mg, n = 59 (2) Buffered ketoprofen 12.5 mg, n = 61 (3) Placebo, n = 50	at 6 h: (1) 5/59 (3) 3/60	None	None	Exclusions: 2 remedicated early, one in Ibuprofen group and one in placebo group
Singla 2005	(1) Ibuprofen 400 mg, n = 175 (2) Ibuprofen 400 mg + oxycodone 5 mg, n = 169 (3) Oxycodone 5 mg, n = 52 (4) Placebo, n = 60	at 6 h: (1) 74/175 (4) 33/60	None	(1) 1/175 (4) 0/60	1 patient in Ibu group excluded due to protocol violation
Sunshine 1983	(1) Ibuprofen 400 mg, n = 30 (2) Aspirin 600 mg, n = 30 (3) Zomepirac 100 mg, n = 30 (4) Placebo, n = 30	None	None	None	None
Sunshine 1987	(1) Ibuprofen 400 mg, n = 38 (2) Ibuprofen 200 mg + codeine 30 mg, n = 40 (3) Ibuprofen 400 mg + codeine 60 mg, n = 40 (4) Codeine 60 mg, n = 37 (5) Placebo, n = 40	at 4 h: (1) 0/38 (5) 0/40	None	None	Exclusions: 1 had not complied with the washout period, 4 did not complete the evaluations
Sunshine 1996	(1) Ibuprofen 50 mg, n = 51 (2) Ibuprofen 100 mg, n = 51 (3) Ibuprofen 200 mg, n = 50 (4) Ibuprofen 100 mg + caffeine 100 mg, n = 50 (5) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (6) Placebo, n = 50	at 6 h: (1) 1/51 (2) 4/51 (3) 1/50 (4) 2/50 (5) 4/50 (6) 0/50	None	None	Exclusions: 3 for protocol violations
Sunshine 1997	(1) Ibuprofen 400 mg, n = 40	at 6 h:	None	None	Exclusions: One from placebo group refused

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

	(2) Ibuprofen 400 mg + hydrocodone 15 mg, n = 40 (3) Placebo, n = 39	(1) 5/40 (3) 4/40			to cooperate and was excluded from the study
Sunshine 1998	(1) Ibuprofen 200 mg, n = 35 (2) Ketoprofen 6.25 mg, n = 35 (3) Ketoprofen 12.5 mg, n = 35 (4) Ketoprofen 25 mg, n = 35 (5) Placebo, n = 35	Up to 6 h: (1) 2/35 (5) 3/35	None	None	Exclusions: 2 remedicated early, 1 vomited study drug, 1 withdrew consent
Unpubl 2002 (Edwards 2002)	(1) Ibuprofen 400 mg, n = 339 (2) Placebo, n = 339	at 6 h: (1) 41/339 (2) 58/337	None	No usable data	Total withdrawals not due to lack of efficacy (1) 2/339 (2) 3/337
Van Dyke 2004	(1) Ibuprofen 400 mg, n = 186 (2) Ibuprofen 400 mg + oxycodone 5 mg, n = 187 (3) Oxycodone 5 mg, n = 63 (4) Placebo, n = 62	at 6 h: (1) 20/186 (4) 7/62	None	None	Exclusions: 1 had inadequate baseline pain (1) 1/186 no reason given
Wahl 1997	(1) Ibuprofen lysinate 342 mg (= 200 mg Ibu), n = 74 (2) Paracetamol 200 mg + aspirin 250 mg + caffeine 50 mg, n = 73 (3) Placebo, n = 42	at 6 h: (1) 7/74 (3) 5/42	None	None	Exclusions: 12 withdrew consent, 13 did not require analgesia after surgery, 6 failed to complete their study lists, and 1 may not have taken study medication correctly
Wideman 1999 (study 1)	(1) Ibuprofen 200 mg, n = 60 (2) Ibuprofen 200 mg, + hydrocodone 7.5 mg, n = 59 (3) Hydrocodone 7.5 mg, n = 61 (4) Placebo, n = 60	at 8 h: (1) 6/60 (4) 1/60	None	None	None
Wideman 1999 (study 2)	(1) Ibuprofen 400 mg, n = 50 (2) Ibuprofen 400 mg + hydrocodone 15 mg, n = 50 (3) Hydrocodone 15 mg, n = 50 (4) Placebo, n = 51	at 8 h: (1) 7/50 (4) 6/51	None	None	None
Zelenakas 2004	(1) Ibuprofen 400 mg, n = 51 (2) Lumiracoxib 100 mg, n = 51 (3) Lumiracoxib 400 mg, n = 50	at 12 h: (1) 5/51 (4) 10/50	(1) 0/51 (4) 1/50 (deep vein thrombosis)	(1) 1/51 (postoperative bleed)	(1) 1/51 (? withdrew consent)

Table 2. Summary of outcomes: adverse events and withdrawals *(Continued)*

(4) Placebo, n = 50

APPENDICES

Appendix 1. Search strategy for MEDLINE via Ovid

1. Ibuprofen.sh
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid).ti,ab,kw.
3. OR/1-2
4. Pain, postoperative.sh
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi $) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")).ti,ab,kw.
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $")).ti,ab,kw.
11. OR/4-10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. OR/12-19
21. humans.sh.
22. 20 AND 21
23. 3 AND 11 AND 22

Appendix 2. Search strategy for EMBASE via Ovid

1. Ibuprofen.sh
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid).ti,ab,kw.
3. OR/1-2
4. Postoperative pain.sh
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi $) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")).ti,ab,kw.
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $")).ti,ab,kw.
11. OR/4-10
12. clinical trials.sh
13. controlled clinical trials.sh
14. randomized controlled trial.sh
15. double-blind procedure.sh
16. (clin$ adj25 trial$).ab
17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab
18. placebo$.ab
19. random$.ab
20. OR/12-19
21. 3 AND 11 AND 20

Appendix 3. Search strategy for Cochrane CENTRAL

1. MESH descriptor Ibuprofen
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid).ti,ab,kw.
3. OR/1-2
4. MESH descriptor Pain, Postoperative
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi $) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")):ti,ab,kw.
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)):ti,ab,kw.
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")):ti,ab,kw.
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $")):ti,ab,kw.
11. OR/4-10
12. Clinical trials:pt.
13. Controlled Clinical Trial:pt.
14. Randomized Controlled Trial.pt.
15. MESH descriptor Double-Blind Method
16. (clin$ adj25 trial$):ti,ab,kw.
17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)):ti,ab,kw.
18. placebo$:ti,ab,kw.
19. random$:ti,ab,kw.
20. OR/12-19
21. 3 AND 11 AND 20

Appendix 4. Glossary

Categorical rating scale:

The commonest is the five category scale (none, slight, moderate, good or lots, and complete). For analysis numbers are given to the verbal categories (for pain intensity, none = 0, mild = 1, moderate = 2 and severe = 3, and for relief none = 0, slight = 1, moderate = 2, good or lots = 3 and complete = 4). Data from different subjects is then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means). The validity of converting categories into numerical scores was checked by comparison with concurrent visual analogue scale measurements. Good correlation was found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

VAS:

Visual analogue scale: lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain", seem to overcome this limitation. Patients mark the line at the point which corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the patient's mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. More concentration and coordination are needed, which can be difficult post-operatively or with neurological disorders.

TOTPAR:

Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the composite trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

SPID:

Summed pain intensity difference (SPID) is calculated as the sum of the differences between the pain scores over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the trapezoidal rule.

VAS TOTPAR and VAS SPID are visual analogue versions of TOTPAR and SPID.

See "Measuring pain" in Bandolier's Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13 (Moore 2003).

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
7 July 2017	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 1998

Date	Event	Description
25 April 2012	Review declared as stable	Although new studies on Ibuprofen may be published, they are unlikely to impact on the results of this review and so the authors suggest there should be no need to update this review for at least five years.
8 February 2011	Amended	Contact details updated.
6 October 2010	Amended	Contact details updated.
11 May 2009	New citation required and conclusions have changed	Information from 37 new studies with 5595 participants was added, giving a total of 72 studies and 9186 participants. NNTs for at least 50% pain relief over 4 to 6 hours were not significantly changed. Additional information on the proportion of participants requiring rescue medication, and median or mean time to use of rescue medication, are provided, with higher doses giving slightly better results. Pain model and ibuprofen formulation may both affect the result, with dental impaction models and soluble ibuprofen salts producing better efficacy estimates. A dose response was demonstrated in dental pain.
11 May 2009	New search has been performed	The original review published in 1999 was updated and an additional updated search was run prior to publication from January 2009 to May 2009 which found four new studies; two were subsequently excluded, and two are awaiting classification.
23 May 2008	Amended	Converted to new review format.
25 January 2002	Amended	New studies found but not yet included or excluded

CONTRIBUTIONS OF AUTHORS

CD and SD carried out searches, identified studies for inclusion, and carried out data extraction and analysis. SD entered the data into RevMan. RAM was involved with analysis and writing. HJM acted as arbitrator and was involved with writing. SD will be responsible for conducting the next update of this review.

DECLARATIONS OF INTEREST

RAM and HJM have consulted for various pharmaceutical companies. RAM and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. RAM, HJM and SD have received research support from charities,

government and industry sources at various times. Support for this review came from Oxford Pain Research, the NHS Cochrane Collaboration Programme Grant Scheme, and NIHR Biomedical Research Centre Programme.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research funds, UK.

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.
- NIHR Biomedical Research Centre Programme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no major differences between the protocol and review.

NOTES

We performed a restricted search in June 2017. We are aware of some additional relevant studies, but given the existing wealth of information, the large numbers of studies and participants, the stability of the efficacy estimate over time, and the fact that due attention has been given to issues over formulation, it is unlikely that any update will change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage] [adverse effects]; Ibuprofen [*administration & dosage] [adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans