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[Intervention Review]

Single dose oral aspirin for acute postoperative pain in adults

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ABSTRACT

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews on 'Single dose oral aspirin for acute pain'. Aspirin has been known for many years to be an effective analgesic for many different pain conditions. Although its use as an analgesic is now limited in developed countries, it is widely available, inexpensive, and remains commonly used throughout the world.

Objectives

To assess the analgesic efficacy and associated adverse events of single dose oral aspirin in acute postoperative pain.

Search methods

For the earlier review, we identified randomised trials by searching CENTRAL (*The Cochrane Library*) (1998, Issue 1), MEDLINE (1966 to March 1998), EMBASE (1980 to January 1998), and the Oxford Pain Relief Database (1950 to 1994). We updated searches of CENTRAL, MEDLINE, and EMBASE to January 2012.

Selection criteria

Single oral dose, randomised, double-blind, placebo-controlled trials of aspirin for relief of established moderate to severe postoperative pain in adults.

Data collection and analysis

We assessed studies for methodological quality and two review authors extracted the data independently. We used summed total pain relief (TOTPAR) over four to six hours to calculate the number of participants achieving at least 50% pain relief. We used these derived results to calculate, with 95% confidence intervals, the relative benefit compared to placebo, and the number needed to treat (NNT) for one participant to experience at least 50% pain relief over four to six hours. We sought numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, as additional measures of efficacy. We collected information on adverse events and withdrawals.

Main results

We included 68 studies in which aspirin was used at doses from 300 mg to 1200 mg, but the vast majority of participants received either 600/650 mg (2409 participants, 64 studies) or 990/1000 mg (380 participants, eight studies). There was only one new study.

Studies were overwhelmingly of adequate or good methodological quality. NNTs for at least 50% pain relief over four to six hours were 4.2 (3.9 to 4.8), 3.8 (3.0 to 5.1), and 2.7 (2.0 to 3.8) for 600/650 mg, 900/1000 mg, and 1200 mg respectively, compared with placebo. Type of pain model had no significant impact on the results. Lower doses were not significantly different from placebo. These results do not differ from those of the earlier review.

Fewer participants required rescue medication with aspirin than with placebo over four to eight hours postdose, but by 12 hours there was no difference. The number of participants experiencing adverse events was not significantly different from placebo for 600/650 mg aspirin, but for 900/1000 mg the number needed to treat to harm was 7.5 (4.8 to 17). The most commonly reported events were dizziness, drowsiness, gastric irritation, nausea, and vomiting, nearly all of which were of mild to moderate severity.

Authors' conclusions

Aspirin is an effective analgesic for acute pain of moderate to severe intensity. High doses are more effective, but are associated with increased adverse events, including drowsiness and gastric irritation. The pain relief achieved with aspirin was very similar milligram for milligram to that seen with paracetamol. There was no change to the conclusions in this update.

PLAIN LANGUAGE SUMMARY

Single dose oral aspirin for acute postoperative pain in adults

Aspirin is commonly used throughout the world as an over the counter (OTC) analgesic medication used to treat various painful conditions and to reduce fever. This review assessed both the pain-relieving effectiveness and the adverse effects of a single dose of aspirin in acute postoperative pain of moderate to severe intensity. We included 67 studies, with 3111 participants given aspirin in comparisons with 2632 given placebo. Most of the information was for a 600 mg or 650 mg dose. The results confirm that in patients with moderate to severe postoperative pain, about 40% of those treated with aspirin 600/650 mg will experience good levels of pain relief, compared with about 15% treated with placebo. This level of pain relief is comparable to that experienced with the same dose of paracetamol. In these single dose studies there was no significant difference between aspirin 600/650 mg and placebo for the number of participants experiencing adverse events, but at 900/1000 mg, twice as many did so, with dizziness, drowsiness, gastric irritation, nausea, and vomiting being the most common events reported.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews on 'Single dose oral aspirin for acute pain' (Edwards 2000). The title now states that the review is limited to postoperative pain in adults.

Description of the condition

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 increase awareness of the range of analgesics that are potentially available, and 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. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in an overview (Moore 2011), and important individual reviews include ibuprofen (Derry 2009), paracetamol (Toms 2008), and etoricoxib (Clarke 2009).

Description of the intervention

Acute pain trials

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are 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 four to six 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 four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful. An example is the relative efficacy in the third molar extraction pain model (Barden 2004).

Aspirin

Aspirin (acetylsalicylic acid, (ASA)) is an analgesic and a non-steroidal anti-inflammatory drug (NSAID); it also has antipyretic (reducing fever) and anti-inflammatory effects. Aspirin has been known to be an effective analgesic for many years. Rheumatism has affected man since the great river cultures of the Middle East. Clay tablets from the Sumerian period described the use of willow leaves to treat it. The Egyptians were also aware of the pain-relieving effects of potions made from myrtle or willow leaves. Edward Stone, a vicar from Chipping Norton in Oxfordshire, is generally recognised as the man who gave the first scientific description of the effects of willow bark. In 1763 he wrote a letter to the Earl of Macclesfield, then President of the Royal Society in London, in which he described treating patients suffering from ague (fever) with 20 grains (approximately a 1000 mg) of powdered willow bark in a dram of water every four hours. Today aspirin is commonly used throughout the world for many different pain conditions.

When used as an analgesic for adults, aspirin is given orally at a dose of 300 to 1000 mg every four to six hours, with a maximum of 4000 mg daily. In some countries/the UK it is contraindicated in children under 16 years (due to its association with Reye's syndrome), except in certain conditions, such as Kawasaki disease. Much lower doses (typically 75 mg or 81 mg daily) are used for antiplatelet effects to prevent cardiovascular events.

Aspirin use is associated with a high incidence of gastrointestinal irritation and occult (hidden) blood loss, and occasional overt gastrointestinal bleeding, even with short-term use. Dispersible and enteric coated formulations have been developed to limit these gastrointestinal adverse effects. The availability of alternative drugs with better tolerability has reduced the use of aspirin for pain relief in many countries in recent years. In the UK in 2010 just over 4 million prescriptions for aspirin were written in primary care, mostly for 300 mg dispersible or enteric coated tablets (PCA 2011); in 2009 the number was almost 4.6 million, while in 2006 it was just over 6 million. In other parts of the world, where newer alternatives are either not available or are too expensive, aspirin may still be the main analgesic in use.

How the intervention might work

Clinicians prescribe 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. Aspirin's main mechanism of action is irreversible inhibition of the enzyme cyclooxygenase 1 (COX-1) and modification of cyclooxygenase 2 (COX-2), which interferes with thromboxane and prostaglandin synthesis, and increases production of anti-inflammatory lipoxins. Other non-steroidal anti-inflammatory drugs cause reversible inhibition of the cyclooxygenases.

Why it is important to do this review

Aspirin is an inexpensive and effective analgesic available worldwide, and therefore an important drug for treating pain.

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral aspirin for acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Included studies were double-blind trials of single dose oral aspirin compared with placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. We included multiple dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first arm were presented separately.

We excluded the following:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported);
- studies of less than four hours duration or studies that fail to present data over four to six hours postdose.

For postpartum pain, we included studies if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; we excluded studies investigating pain due to uterine cramps alone.

Types of participants

We included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery. For studies using a visual analogue scale (VAS), we considered that pain intensity of greater than 30 mm equated to pain of at least moderate intensity (Collins 1997).

Types of interventions

Aspirin or matched placebo administered as a single oral dose for postoperative pain.

Types of outcome measures

Data collected included the following if available:

- participant characteristics;
- patient reported pain at baseline (physician, nurse, or carer reported pain was not included in the analysis);
- patient reported pain relief expressed at least hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both);
- patient global assessment of efficacy (PGE), using a standard categorical scale;
- time to use of rescue medication;
- number of participants using rescue medication;
- number of participants with one or more adverse events;
- number of participants with serious adverse events;
- number of withdrawals (all-cause, adverse events).

Search methods for identification of studies

Electronic searches

We searched the following databases for the original review:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (1998, Issue 1);
- MEDLINE (1966 to March 1998);
- EMBASE (1980 to January 1998);
- Oxford Pain Relief Database (1950 to 1994; [Jadad 1996a](#)).

We updated searches using the following electronic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (issue 1, 2012);
- MEDLINE via Ovid (25 January 2012);
- EMBASE via Ovid (25 January 2012).

See [Appendix 1](#) for the MEDLINE search strategy, [Appendix 2](#) for the EMBASE search strategy and [Appendix 3](#) for the CENTRAL search strategy.

Language

We did not limit the searches by language.

Searching other resources

We sought additional studies in reference lists of retrieved articles and reviews. We did not attempt to contact manufacturers since aspirin is so widely available in generic formulations.

Unpublished studies

We did not contact any manufacturing pharmaceutical company producing this drug for unpublished trial data.

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 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](#)) that considers randomisation, blinding, and study withdrawals and dropouts.

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 1 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 'Risk of bias in included studies' section below, and '[Characteristics of included studies](#)' table.

Data management

Two review authors extracted data and recorded them on a standard data extraction form. We entered data suitable for pooling into RevMan 5.1 ([RevMan 2011](#)).

Data analysis

For each study we converted the mean summed total pain relief (TOTPAR), summed pain intensity difference (SPID), VAS TOTPAR or VAS SPID ([Appendix 4](#)) values for active and placebo to %maxTOTPAR or %maxSPID by division into the calculated maximum value ([Cooper 1991](#)), and calculated the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations ([Moore 1996](#); [Moore 1997a](#); [Moore 1997b](#)). We then converted these proportions into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. We used this information on the number of participants with at least 50%maxTOTPAR for active and placebo to calculate relative benefit or relative risk, and number needed to treat to benefit (NNT).

We accepted the following pain measures for the calculation of TOTPAR or SPID:

- 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";
- VAS for pain relief;
- VAS for pain intensity.

If none of these measures were available, we used the number of participants reporting "very good or excellent" on a five-point categorical global scale with the wording "poor, fair, good, very good, excellent" for the number of participants achieving at least 50% pain relief ([Collins 2001](#)).

For each treatment group we extracted the number of participants reporting treatment-emergent adverse effects, and calculated relative benefit and risk estimates with 95% confidence intervals (CI) using a fixed-effect model ([Morris 1995](#)). We calculated NNT and number needed to treat to harm (NNH) and 95% CI using the pooled

number of events using the method devised by Cook and Sackett ([Cook 1995](#)). We assumed a statistically significant difference from control when the 95% CI of the relative risk (RR) or relative benefit (RB) did not include the number one. We examined homogeneity visually using L'Abbé plots ([L'Abbé 1987](#)).

We planned subgroup analyses to determine the effect of dose and presenting condition (pain model), and sensitivity analyses for high versus low (two or fewer versus three or more) quality trials. A minimum of two studies and 200 participants had to be available in any subgroup or sensitivity analysis ([Moore 1998](#)), which was restricted to the primary outcome (50% pain relief over four to six hours) and the dose with the greatest amount of data (600/650 mg).

RESULTS

Description of studies

Included studies

We identified 72 publications, reporting on 67 studies with 5743 participants, that satisfied our inclusion criteria. We included two studies that were not in the earlier review: [Gaston 1984](#) had been excluded because of non-standard labelling of the pain scale, but an adjustment could be made for this, and [Seymour 2003](#) was published after the earlier review. We identified three further studies, [Beaver 1983](#), [Cooper 1983](#), and [Lindenmuth 1989](#), as reporting on the same studies as [Forbes 1982](#), [Mardirossian 1985](#), and [Clark 1989](#) respectively, and these are now linked to the parent IDs.

Aspirin was used at doses from 300 mg to 1200 mg: 77 participants took a 300 mg dose (two studies), 135 took 500 mg (two studies), 2379 took 600 mg or 650 mg (63 studies), 380 took 900 mg or 1000 mg (eight studies), 140 took 1200 mg (five studies), and 2632 took placebo (68 studies). Three studies ([Holland 1988](#); [Seymour 1986](#); [Seymour 2003](#)) specified using a soluble formulation, and five ([Kempf 1987](#); [Markowitz 1985](#); [Parkhouse 1969](#); [Rowe 1985](#); [Seymour 1992](#)) specified using a buffered formulation. The remaining studies are assumed to have used a standard formulation tablet.

Most studies included one or more active comparators, so that a large number of other drugs were used: amfenac, aspirin plus caffeine, aspirin plus codeine, aspirin plus chlorphenasin, aspirin plus mefenamic acid, aspirin plus pentazocine, bicipadine, bromfenac, caffeine, carprofen, chlorphenasin, codeine, codeine plus ibuprofen, codeine plus paracetamol, codeine plus naproxen, diclofenac, diflunisal, dipyron, etodolac, fenbufen, fendosal, fluproquazone, fluradolone, flurbiprofen, FS205-397, ibuprofen, indoprofen, ketorolac, lornoxicam, meclofenamate, naproxen, oxaprozin, paracetamol, paracetamol plus phenyltoloxamine, piroxicam, propoxyphene, propiram fumarate, proquazone, suprofen, and zomepirac. There were insufficient data to compare a given dose of aspirin with a given dose of any active comparator.

Forty-eight studies treated participants with pain following dental surgery, 12 following episiotomy or other gynaecological surgery, three following orthopaedic surgery, one following urological surgery, and four included participants who had undergone a mixture of types of surgery, or the type of surgery was not specified.

Further details of included studies are in the '[Characteristics of included studies](#)' table.

Excluded studies

We excluded five studies that were included in the earlier review because they included participants with pain due to trauma (Herrmann 1980c; Herrmann 1980d), fracture (Kantor 1965; Wang 1979), or fracture and musculoskeletal pain (Okun 1979), which are outside the scope of this update.

In total we excluded 102 studies after reading the full report. Reasons for exclusion are in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

All included studies were randomised and double-blind. Twenty studies scored 5/5, 25 scored 4/5, 19 scored 3/5, and three scored

2/5 on the Oxford Quality Scale. Points were lost mostly for failure to describe the methods used to ensure randomisation and blinding adequately, but 14 studies failed to report adequately on withdrawals (Boraks 1987; Breivik 1984; Clark 1989; Coutinho 1976; Herbertson 1994; Herrmann 1980a; Herrmann 1980b; London 1983b; Mardirossian 1985; Nelson 1994b; Rowe 1985; Seymour 1986; Seymour 1992; Wang 1982). Details of scores in individual studies are in the 'Characteristics of included studies' table.

We also drew up a 'Risk of bias' table to consider randomisation, allocation, and blinding. We considered no studies at high risk of bias, but the majority did not adequately report the methods used for randomisation and allocation concealment. This may reflect older reporting of methods rather than actual poor study quality (Figure 1).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of interventions

Participants with at least 50% pain relief

Aspirin 300/325 mg versus placebo

There were insufficient data for analysis of aspirin 300/325 mg.

Aspirin 500 mg versus placebo

Two studies (213 participants) compared aspirin 500 mg with placebo (Nelson 1994a; Seymour 1992).

- The proportion of participants with $\geq 50\%$ pain relief with aspirin 500 mg was 34% (45/135, range 31% to 36%).
- The proportion of participants with $\geq 50\%$ pain relief with placebo was 26% (20/78, range 20% to 32%).

- The relative benefit of treatment compared with placebo was 1.3 (0.82 to 2.0), showing no significant benefit. We did not calculate the number needed to treat (NNT) (Analysis 1.1).

Aspirin 600/650 mg versus placebo

Sixty studies (4659 participants) compared aspirin 600 or 650 mg with placebo.

- The proportion of participants with $\geq 50\%$ pain relief with aspirin 600/650 mg was 39% (905/2339, range 12% to 90%).
- The proportion of participants with $\geq 50\%$ pain relief with placebo was 15% (352/2320, range 0% to 46%).
- The relative benefit of treatment compared with placebo was 2.5 (2.2 to 2.7), giving a NNT of 4.2 (3.9 to 4.8) (Analysis 2.1; Figure 2; Figure 3).

Figure 2. Forest plot of comparison: 2 Aspirin 600 or 650 mg versus placebo, outcome: 2.1 Participants with at least 50% pain relief.

Figure 2. (Continued)

London 1983a	12	40	7	40	1.9%	1.71 [0.75, 3.90]
London 1983b	22	41	14	39	4.0%	1.49 [0.90, 2.48]
McQuay 1987	6	30	1	30	0.3%	6.00 [0.77, 46.87]
Olsen 1997	27	50	15	52	4.1%	1.87 [1.14, 3.08]
Parkhouse 1969	85	169	29	85	10.7%	1.47 [1.06, 2.05]
Sunshine 1983b	14	29	0	31	0.1%	30.93 [1.93, 496.05]
Sunshine 1983c	14	30	0	30	0.1%	29.00 [1.81, 465.07]
Sunshine 1988	11	15	4	15	1.1%	2.75 [1.13, 6.72]
Wang 1982	10	25	2	25	0.6%	5.00 [1.22, 20.55]
Subtotal (95% CI)	649		562	33.7%		2.31 [1.93, 2.75]

Total events 308 112
Heterogeneity: $\text{Chi}^2 = 32.80$, $\text{df} = 16$ ($P = 0.008$); $I^2 = 51\%$
Test for overall effect: $Z = 9.25$ ($P < 0.00001$)

Total (95% CI) 2334 2310 100.0% 2.46 [2.22, 2.72]

Total events 905 352
Heterogeneity: $\text{Chi}^2 = 93.51$, $\text{df} = 59$ ($P = 0.003$); $I^2 = 37\%$
Test for overall effect: $Z = 17.04$ ($P < 0.00001$)
Test for subgroup differences: $\text{Chi}^2 = 0.71$, $\text{df} = 1$ ($P = 0.40$), $I^2 = 0\%$

Figure 3. L'Abbé plot showing $\geq 50\%$ pain relief for all studies using 600/650 mg aspirin versus placebo. Each circle represents a different study. Size of circle is proportional to size of study.

Subgroup analysis for pain model

For the 43 studies in dental pain only (3433 participants) the relative benefit (RB) was 2.5 (2.2 to 2.9), giving a NNT of 4.6 (4.1 to 5.3), while for the 17 studies in other types of surgery (1211 participants), the RB was 2.3 (1.9 to 2.8), giving a NNT of 3.6 (3.0 to 4.5). There was no significant difference between the different types of surgery in these studies (Analysis 2.1).

Sensitivity analysis for study quality

For the 57 studies scoring $\geq 3/5$ on the Oxford Quality Score (4373 participants), the RB was 2.4 (2.2 to 2.7), giving a NNT of 4.3 (3.8 to 4.8), while for the three studies scoring only 2/5 (257 participants), the RB was 2.9 (1.9 to 4.6), giving a NNT of 3.4 (2.5 to 5.4). There was no significant difference between studies scoring the minimum for inclusion in this review (2/5), and those with higher scores.

Aspirin 1000 mg versus placebo

Six studies (618 participants) compared aspirin 1000 mg with placebo ([Forbes 1990a](#); [Herrmann 1980a](#); [Herrmann 1980b](#); [Lehnert 1990](#); [Seymour 1992](#); [Seymour 2003](#)).

- The proportion of participants with $\geq 50\%$ pain relief with aspirin 1000 mg was 41% (138/340, range 24% to 64%).
- The proportion of participants with $\geq 50\%$ pain relief with placebo was 14% (40/278, range 0% to 32%).
- The relative benefit of treatment compared with placebo was 2.7 (2.0 to 3.7), giving a NNT of 4.2 (3.8 to 4.6) ([Analysis 3.1](#)).

Aspirin 1200 mg versus placebo

Three studies (249 participants) compared aspirin 1000 mg with placebo ([Holland 1988](#); [London 1983b](#); [Seymour 1986](#)).

- The proportion of participants with $\geq 50\%$ pain relief with aspirin 1200 mg was 61% (85/140, range 53% to 70%).
- The proportion of participants with $\geq 50\%$ pain relief with placebo was 23% (25/109, range 7% to 36%).
- The relative benefit of treatment compared with placebo was 2.9 (2.0 to 4.2), giving a NNT of 2.7 (2.0 to 3.8) ([Analysis 4.1](#)).

Summary of results A: Number of participants with $\geq 50\%$ pain relief over 6 hours

Dose	Studies	Participants	Aspirin (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
500 mg	2	213	33	26	1.3 (0.82 to 2.0)	not calculated
600/650 mg	60	4630	39	15	2.5 (2.2 to 2.7)	4.2 (3.9 to 4.8)
900/1000 mg	6	618	41	14	2.7 (2.0 to 3.7)	3.8 (3.0 to 5.1)
1200 mg	3	249	61	23	2.9 (2.0 to 4.2)	2.7 (2.0 to 3.8)

Results for the different doses are compatible with a dose response, with the 1200 mg dose being significantly superior to the 600/650 mg dose ($z = 2.416$, $P = 0.016$).

Participants using rescue medication at four to five hours

Aspirin 600/650 mg versus placebo

Eleven studies (982 participants) compared aspirin 600 or 650 mg with placebo ([Boraks 1987](#); [Calimlim 1977](#); [Frame 1986](#); [Jain 1985b](#); [Jain 1986a](#); [London 1983b](#); [Mehlich 1984](#); [Mehlich 1994](#); [Parkhouse 1969](#); [Sunshine 1983b](#); [Sunshine 1983c](#)).

- The proportion of participants using rescue medication at four or five hours with aspirin 600/650 mg was 27% (144/530, range 2% to 71%).
- The proportion of participants using rescue medication at four or five hours with placebo was 47% (211/452, range 5% to 89%).
- The relative benefit of treatment compared with placebo was 0.65 (0.56 to 0.76), giving a number needed to treat to prevent one event (NNTp) of 5.1 (3.9 to 7.4) ([Analysis 2.2](#)).

Aspirin 1000 mg versus placebo

Five studies (501 participants) compared aspirin 900/1000 mg with placebo ([Herrmann 1980a](#); [Herrmann 1980b](#); [London 1983b](#); [Seymour 1992](#); [Seymour 2003](#)).

- The proportion of participants using rescue medication at four or five hours with aspirin 900/1000 mg was 46% (121/264, range 3% to 81%).
- The proportion of participants using rescue medication at four or five hours with placebo was 67% (158/237, range 26% to 91%).

- The relative benefit of treatment compared with placebo was 0.64 (0.56 to 0.74), giving a NNTp of 4.8 (3.4 to 8.1) ([Analysis 3.2](#)).

There were insufficient data for analysis of other doses of aspirin for use of rescue medication at four or five hours.

Participants using rescue medication at six to eight hours

Aspirin 600/650 mg versus placebo

Twenty studies (1838 participants) compared aspirin 600 or 650 mg with placebo.

- The proportion of participants using rescue medication at six or eight hours with aspirin 600/650 mg was 55% (530/955, range 3% to 98%).
- The proportion of participants using rescue medication at six or eight hours with placebo was 75% (664/883, range 37% to 97%).
- The relative benefit of treatment compared with placebo was 0.77 (0.73 to 0.82), giving a NNTp of 5.1 (4.2 to 6.5) ([Analysis 2.3](#)).

Aspirin 1000 mg versus placebo

Two studies (233 participants) compared aspirin 1000 mg with placebo ([Forbes 1990a](#); [Lehnert 1990](#)).

- The proportion of participants using rescue medication at six or eight hours with aspirin 1000 mg was 67% (78/116, range 51% to 77%).
- The proportion of participants using rescue medication at six or eight hours with placebo was 83% (97/117, range 64% to 93%).
- The relative benefit of treatment compared with placebo was 0.82 (0.71 to 0.95), giving a NNTp of 6.4 (3.8 to 21) ([Analysis 3.3](#)).

There were insufficient data for analysis of other doses of aspirin for use of rescue medication at six or eight hours.

Participants using rescue medication at 12 hours

Aspirin 600/650 mg versus placebo

Four studies (291 participants) compared aspirin 600 or 650 mg with placebo (Clark 1989; Forbes 1982; Forbes 1983; Forbes 1984).

- The proportion of participants using rescue medication at 12 hours with aspirin 600/650 mg was 81% (117/145, range 65% to 97%).

- The proportion of participants using rescue medication at 12 hours with placebo was 86% (125/146, range 76% to 90%).
- The relative benefit of treatment compared with placebo was 0.95 (0.86 to 1.05). There was no significant difference between treatment groups for use of rescue medication by 12 hours (Analysis 2.4).

There were insufficient data for analysis of other doses of aspirin for use of rescue medication at 12 hours.

Summary of results B: Number of participants using rescue medication

Dose	Studies	Participants	Aspirin (%)	Placebo (%)	Relative benefit (95% CI)	NNTP (95% CI)
at 4 to 5 hours						
600/650 mg	11	1067	27	47	0.58 (0.50 to 0.67)	4.9 (3.9 to 6.8)
1000 mg	5	501	46	67	0.64 (0.56 to 0.74)	4.8 (3.4 to 8.1)
at 6 to 8 hours						
600/650 mg	20	1838	55	75	0.77 (0.73 to 0.82)	5.1 (4.2 to 6.5)
1000 mg	2	233	67	83	0.82 (0.71 to 0.95)	6.4 (3.8 to 21)
at 12 hours						
600/650 mg	4	291	81	86	0.95 (0.86 to 1.05)	not calculated

Time to use of rescue medication

Aspirin 600/650 mg versus placebo

Eighteen studies reported the mean time to use of rescue medication following 600 or 650 mg aspirin (Cooper 1982; Cooper 1983; Cooper 1986; Cooper 1988; Cooper 1991; Desjardins 1984; Forbes 1980; Forbes 1983; Forbes 1984; Forbes 1986; Forbes 1989; Forbes 1990a; Forbes 1990b; Forbes 1991; Forbes 1992; Jain 1986a; Mardrossian 1985; Mehlich 1990). The weighted mean of the mean time to use was 3.8 hours with aspirin 600/650 mg, and 3.0 hours with placebo.

A further 11 studies reported the median time to use of rescue medication following 600 or 650 mg aspirin (Clark 1989; Cooper 1992; Forbes 1982; Frame 1986; Herbertson 1994; McQuay 1987; Mehlich 1994; Nelson 1994b; Olsen 1997; Parkhouse 1969; Sunshine 1988). The weighted mean of the median time to use was 5.2 hours with aspirin 600/650 mg, and 3.4 hours with placebo.

Aspirin 900/1000 mg versus placebo

Only one study (Forbes 1990a; 146 participants) reported the mean time to use of rescue medication following 1000 mg aspirin, which was 3.9 hours with aspirin and 2.8 hours with placebo. Two studies reported the mean time to use of rescue medication

following 900 or 1000 mg aspirin (Seymour 1992; Seymour 2003; 203 participants). The weighted mean of the mean time to use was 1.9 hours with aspirin 900/1000 mg, and 1.2 hours with placebo.

There were insufficient data for analysis of other doses of aspirin for this outcome.

Participants with any adverse event

The most frequently reported effects were dizziness, drowsiness, gastric irritation, nausea, and vomiting. Nearly all effects were of mild or moderate severity and only one study (Herbertson 1994) reported any withdrawals (8/217) due to "medical problems". In this study one event was considered possibly related to study medication (nausea and vomiting with the active comparator, diclofenac), while the other seven were most likely due to the surgical procedure itself.

Aspirin 600/650 mg versus placebo

Forty-six studies (3633 participants) compared aspirin 600 or 650 mg with placebo.

- The proportion of participants experiencing any adverse event with aspirin 600/650 mg was 11% (205/1791, range 0% to 33%).

- The proportion of participants experiencing any adverse event with placebo was 9.5% (175/1842, range 0% to 38%).
- The relative harm of treatment compared with placebo was 1.2 (1.0 to 1.4). There was no difference between treatment groups, and we did not calculate the number needed to treat to harm (NNH) (Analysis 2.5).

Aspirin 900/1000 mg versus placebo

Four studies (404 participants) compared aspirin 900 or 1000 mg with placebo (Forbes 1990a; Holland 1988; Lehnert 1990; Seymour 2003).

- The proportion of participants experiencing any adverse event with aspirin 900/1000 mg was 26% (55/215, range 0% to 75%).
- The proportion of participants experiencing any adverse event with placebo was 12% (23/189, range 0% to 41%).
- The relative harm of treatment compared with placebo was 1.6 (1.1 to 2.3), giving a NNH of 7.5 (4.8 to 17) (Analysis 3.4).

There were insufficient data for analysis of other doses of aspirin for participants experiencing any adverse event.

DISCUSSION

Summary of main results

This updated review included essentially the same studies as the earlier review, adding one more recent study with 153 participants in comparisons of aspirin 900 mg with placebo and excluding five studies that were included in the earlier review because they included participants with pain due to trauma (Herrmann 1980c; Herrmann 1980d), fracture (Kantor 1965; Wang 1979), or fracture and musculoskeletal pain (Okun 1979), all outside the scope of this update. Results for the primary outcome of at least 50% total pain relief over four to six hours are unchanged for doses of 600/650 mg (number needed to treat (NNT) 4.2), 900/1000 mg (3.8), and 1200 mg (2.7), compared with placebo. There was no statistically significant difference between doses of 600/650 mg and 900/1000 mg, or between 900/1000 mg and 1200 mg, but 1200 mg was significantly better than 600/650 mg ($z = 2.416$, $P = 0.016$) for this outcome, based on limited numbers of participants at the higher dose; dose response for analgesics is consistently difficult to determine except in direct comparisons (McQuay 2007). Doses below 500 mg were not significantly better than placebo.

Indirect comparison with other common analgesics, evaluated in the same way, indicate that aspirin 600/650 mg has comparable efficacy for at least 50% pain relief over four to six hours, to celecoxib 200 mg (NNT 4.2 (3.4 to 5.6); Derry 2008), ibuprofen 100 mg (4.3 (3.2 to 6.4); Derry 2009), and paracetamol 600/650 mg (4.6 (3.9 to 5.5); Toms 2008). This 'mg for mg' equivalence between 600 mg of aspirin and 600 mg paracetamol was also seen in a randomised direct comparison in 1965 (Houde 1965).

This review also considered number of participants requiring rescue medication within defined time periods, and time to use of rescue medication, as additional measures of analgesic efficacy. The NNT to prevent remedication was about 5 over four to eight hours after dosing for both 600/650 mg and 900/1000 mg doses, and not significantly different from placebo by 12 hours for the 600/650 mg dose. In most studies, participants were asked to wait for two hours after taking study medication before using rescue

medication; the weighted mean of the median time to use of rescue medication was about five hours for 600/650 mg aspirin and three hours for placebo. The time to remedication with the 900/1000 mg dose was unexpectedly much shorter, at 1.9 hours for aspirin and 1.2 hours for placebo. The reason for much earlier remedication in these participants is unclear, but in one of the studies they could take rescue medication at any time, and in the other they were encouraged to wait for one hour.

There was no difference in the number of participants reporting any adverse event for aspirin 600/650 mg compared with placebo, but for 900/1200 mg significantly more aspirin than placebo treated participants experienced adverse events, with a number needed to treat to harm (NNH) of 7.5. Most events were mild or moderate in severity and transient (self limiting, did not require treatment), with only one study reporting any adverse event ("medical problems") withdrawals. Gastrointestinal events (e.g. gastric irritation) and central nervous system events (e.g. nausea) were more common with aspirin, but many of the events reported may be due to the anaesthetic and surgery, rather than the test drug.

Overall completeness and applicability of evidence

We carried out extensive bibliographic searches for published studies, and identified a large body of data. Studies followed standard methods and the great majority reported data for most of our prespecified outcomes. Single dose studies can tell us whether a drug is an effective analgesic, but do not tell us about the best dosing regimens, or how the drug performs or is tolerated in the longer term.

Adverse events were collected using various methods (spontaneous reporting, observed at clinic visits, 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 have been noted before (Edwards 1999a). The usefulness of single dose studies for assessing adverse events is questionable, but it is nonetheless reassuring that no serious adverse events were reported, and only one study reported withdrawals due to "medical problems". 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.

Quality of the evidence

Many of the studies were older, with only one published in the last 10 years, but 65/68 satisfied minimum criteria for adequate quality ($\geq 3/5$ on the Oxford Quality Scale), and 45/68 scored 4 or 5/5. All studies were randomised and double-blind, with points lost due to failure to report sufficient detail of the methods of randomisation and blinding, which may reflect older reporting of methods rather than actual poor study quality. The variability seen between individual studies (Figure 3) is that to be expected for their size (Moore 1998).

Potential biases in the review process

We identified a large amount of information in studies that satisfied out inclusion criteria, but four studies could not be obtained in full copy in the UK, and we excluded a number of studies either because they did not describe their methods in sufficient detail to determine eligibility, or because they used non-standard methods. It is also possible that there are data that we failed to identify, for example because they are unpublished. However, we think it unlikely that the amount of missing data is large enough to significantly affect the primary outcome, particularly for the 600/650 mg dose. An additional 4000 participants would have to have been involved in unpublished trials with zero treatment effects for the NNT for at least 50% pain relief to increase above 8, a level we consider to be the limit of clinical utility for this outcome ([Moore 2008](#)).

Agreements and disagreements with other studies or reviews

This review is in agreement with the earlier review ([Edwards 1999b](#); [Edwards 2000](#)) for the outcomes they have in common.

AUTHORS' CONCLUSIONS

Implications for practice

This updated review confirms that aspirin is an effective analgesic for acute postoperative pain of moderate to severe intensity. The 600/650 mg dose has comparable efficacy to the same dose of paracetamol, and a 1200 mg gives a better response. However, even in these single dose studies, adverse events such as gastric irritation and nausea were more common with aspirin than placebo at higher doses.

Implications for research

It is unlikely that further studies of this sort will be carried out for aspirin, and we have a sufficiently large body of evidence to be confident with the results for the 600/650 mg dose. In many parts of the world, use of aspirin as an analgesic is falling because of its known gastrointestinal effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bloomfield 1967

Methods	RCT, DB, single oral dose, parallel groups. Medication administered when pain was moderate or severe Assessed at 0, 1, 2, 3, 4, 5, 6 h
Participants	Episiotomy N = 100 (88 moderate/severe pain) Age 18 to 39 years
Interventions	Aspirin 600 mg, n = 17 Chlorphenesin 400 mg, n = 18

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

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Bloomfield 1967 (Continued)

	Chlorphenesin 800 mg, n = 17
	Chlorphenesin 400 mg + aspirin 600 mg, n = 18
	Placebo, n = 18
Outcomes	PI: standard 4-point scale
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" but method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical black capsules"

Boraks 1987

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 6 h
Participants	Dental extraction N = 159 Age ≥ 16 years
Interventions	Aspirin 650 mg, n = 41 Flurbiprofen 50 mg, n = 40 Dipyron 500 mg, n = 39 Placebo, n = 39 Rescue medication allowed after 1 h (LOCF)
Outcomes	PI: standard 4-point scale PR: 5-point scale Global assessment Use of rescue medication
Notes	Language: Portuguese Oxford Quality Score: R = 1, DB = 1, W = 0. Total = 2

Risk of bias

Boraks 1987 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Breivik 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 8 h	
Participants	Orthopaedic surgery (knee, ankle etc) N = 120 Age 18 to 65 years	
Interventions	Aspirin 650 mg, n = 29 Piroxicam 5 mg, n = 30 Piroxicam 10 mg, n = 31 Placebo, n = 30 Rescue medication allowed after 2 h (paracetamol plus codeine)	
Outcomes	PI: standard 4-point scale PI: VAS (none to unbearable pain) PR: standard 5-point scale Global assessment: 5-point scale Use of rescue medication Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double dummy

Calimlim 1977

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 5 h
Participants	Postsurgical patients (exact type of surgery not reported) N = 100 (98 included, but only 74 with global ratings) Age 21 to 65 years
Interventions	Aspirin 650 mg, n = 23 Aspirin 325 mg + pentazocine 25 mg, n = 25 Aspirin 650 mg + pentazocine 50 mg, n = 50 Placebo, n = 26 Rescue medication generally not allowed before 3 h (standard analgesic) (BOCF)
Outcomes	PI: non-standard 5-point scale and VAS 20 cm (no pain at all - worst pain ever experienced) PR: standard 5-point scale Global assessment: 5-point scale Use of rescue medication Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Clark 1989

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h
Participants	Oral surgery N = 248 Age 15 to 63 years
Interventions	Aspirin 600 mg, n ~40 Carprofen 75 mg, n = ~40 Carprofen 100 mg, n = ~40 Carprofen 150 mg, n = ~40 Placebo, n ~40

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

Clark 1989 (Continued)

Rescue medication allowed after 1 h

Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0. Total = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Cooper 1977

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 and hourly to 4 h
Participants	Oral surgery - impacted teeth N = 245 Age 16 to 35 years
Interventions	Aspirin 325 mg, n = 37 Aspirin 650 mg, n = 37 Ibuprofen 200 mg, n = 38 Ibuprofen 400 mg, n = 40 Placebo, n = 40 Rescue medication allowed after 2 h (routine clinic medication) (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Serious adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Cooper 1977 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Medications assigned using a card-shuffling technique"
Allocation concealment (selection bias)	Low risk	"tablets in an envelope identified only by a sequential number"
Blinding (performance bias and detection bias) All outcomes	Low risk	"two identically appearing tablets"

Cooper 1979a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 4 h Study 2	
Participants	Oral surgery N = 254 (201 for efficacy analyses) Age adult	
Interventions	Aspirin 600 mg, n = 47 Indoprofen 100 mg, n = 46 Indoprofen 200 mg, n = 50 Placebo, n = 58 Rescue medication allowed after 1 h (did not report data handling)	
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated codes"
Allocation concealment (selection bias)	Low risk	"medication was placed in an envelope identified only by a sequential number code"
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing capsules"

Cooper 1982

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 4 h
Participants	Dental impaction N = 316 (249 for efficacy analyses) Age 16 to 65 years
Interventions	Aspirin 650 mg, n = 38 Ibuprofen 400 mg, n = 38 Codeine 60 mg, n = 41 Aspirin 650 mg + codeine 60 mg, n = 45 Ibuprofen 400 mg + codeine 60 mg, n = 45 Placebo, n = 46 Rescue medication allowed after 1 h (LOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Tablets "appeared identical for every patient"

Cooper 1983

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 6 h
Participants	Peridontal treatment N = 199 (176 for efficacy analyses) Age adults
Interventions	Aspirin 650 mg, n = 43 Suprofen 200 mg, n = 44

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

Cooper 1983 (Continued)

Suprofen 400 mg, n = 45
Placebo, n = 44

Rescue medication allowed after 1 h (LOCF)

Outcomes

PI: standard 4-point scale
PR: standard 5-point scale
Global assessment: standard 5-point scale

Use of rescue medication

Adverse events

Withdrawals

Notes

Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Cooper 1986

Methods

RCT, DB, single oral dose, parallel groups
Assessed at 0.5, 1 h then hourly to 6 h
Study C

Participants

Dental extraction (third molar)
N = 211 (204 for efficacy analyses)
Age 18 to 46

Interventions

Aspirin 650 mg, n = 40

Aspirin 650 mg + codeine 60 mg, n = 39

Suprofen 200 mg, n = 42

Suprofen 400 mg, n = 42
Placebo, n = 41

Rescue medication allowed after 1 h (paracetamol + codeine) (LOCF)

Outcomes

PI standard 4-point scale
PR standard 5-point scale
Global standard 5-point scale

Use of rescue medication

Adverse events

Cooper 1986 (Continued)

Withdrawals

Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated"
Allocation concealment (selection bias)	Low risk	Identical bottles bearing sequential number
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy technique"

Cooper 1988

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 8 h	
Participants	Dental surgery (impacted third molars) N = 159 (151 for efficacy analyses) Age adult	
Interventions	Aspirin 600 mg, n = 29 Flurbiprofen 50 mg, n = 30 Flurbiprofen 100 mg, n = 30 Flurbiprofen 150 mg, n = 29 Placebo, n = 33 Rescue medication allowed after 1 h (LOCF)	
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Cooper 1988 (Continued)

Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Cooper 1991

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 189 (182 for efficacy) Age ≥ 16 years
Interventions	Aspirin 650 mg, n = 46 Meclofenamate 50 mg, n = 40 Meclofenamate 100 mg, n = 48 Placebo, n = 48 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing single doses"

Cooper 1992

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 8 h
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Single dose oral aspirin for acute postoperative pain in adults (Review)

Cooper 1992 (Continued)

Participants	Dental surgery (impacted third molar) N = 112 (104 for efficacy analyses) Age 16 to 59 years
Interventions	Aspirin 650 mg, n = 28 Oxaprozin 600 mg, n = 28 Oxaprozin 1200 mg, n = 22 placebo n = 26
Outcomes	PI: standard 4-point scale PR: non-standard 6-point scale Global assessment: 5-point standard Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Not described
Allocation concealment (selection bias)	Unclear risk Not described
Blinding (performance bias and detection bias) All outcomes	Low risk "tablets and their packaging were identical"

Coutinho 1976

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 5 h
Participants	Urogenital surgery (various) N = 90 Age 23 to 64 years
Interventions	Aspirin 600 mg n = 15 Fenbufen 400 mg, n = 15 Fenbufen 800 mg, n = 16 Codeine 30 mg, n = 14 Propoxyphene 65 mg, n = 15 Placebo n = 15 Rescue medication allowed after 4 h (coded - aspirin or fenbufen) (LOCF)

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

Coutinho 1976 (Continued)

Outcomes	PI: standard 4-point scale PR: standard 5-point scale Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 0. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing capsules, administered in a single oral dose"

De Vroey 1977

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0 h then hourly for 6 to 8 h
Participants	Episiotomy N = 156 Age 16 to 40 years
Interventions	Aspirin 600 mg, n = 32 Diflunisal 125 mg, n = 33 Diflunisal 250 mg, n = 30 Diflunisal 500 mg, n = 30 Placebo, n = 31 Rescue medication allowed - no further details (PI = 4 carried forward)
Outcomes	PI: standard 4-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

De Vroey 1977 (Continued)

Allocation concealment (selection bias)	Low risk	"individual patient-coded vials"
Blinding (performance bias and detection bias) All outcomes	Low risk	"two identically appearing capsules"

Desjardins 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 6 h
Participants	Dental extraction (impacted third molar) N = 160 (159 for efficacy analyses) Age 18 to 68 years
Interventions	Aspirin 650 mg, n = 40 Propiram fumarate 50 mg, n = 40 Codeine 60 mg, n = 40 Placebo, n = 40 Rescue medication allowed - participants asked to wait as long as possible
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"medications identical in appearance (two capsules)"

Flidner 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 12 h
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Single dose oral aspirin for acute postoperative pain in adults (Review)

Fliedner 1984 (Continued)

Participants	Dental extraction (impacted third molar) N = 384 (380 for efficacy analyses) Age not reported
Interventions	Aspirin 650 mg, n = 83 Etodolac 50 mg, n = 37 Etodolac 100 mg, n = 87 Etodolac 200 mg, n = 86 Placebo n=87 Rescue medication allowed (no further details) (BOCF)
Outcomes	PI: non-standard 5-point scale PR: 5-point scale Global assessment: non-standard 4-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Forbes 1980

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 4 h
Participants	Dental surgery (impacted third molar) N = 247 Age ≥ 15 years
Interventions	Aspirin 650 mg, n = 38 Proquazone 75 mg, n = 40 Proquazone 150 mg, n = 44 Proquazone 300 mg, n = 45 placebo n = 43 Rescue medication allowed after 1 h (BOCF)

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

Forbes 1980 (Continued)

Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"tablets packaged in envelopes identified only by individual numerical code"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All tablets were identical in appearance"

Forbes 1982

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h
Participants	Dental surgery (multiple mandibular or impacted third molar) N = 212 (201 for efficacy analyses) Age ≥ 15 years
Interventions	Aspirin 650 mg, n = 42 Diflunisal 250 mg, n = 39 Diflunisal 500 mg, n = 41 Diflunisal 1000 mg, n = 41 Placebo, n = 38 Rescue medication allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

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

Forbes 1982 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers list
Allocation concealment (selection bias)	Low risk	"treatments ... packaged in envelopes identified only by individual numerical code"
Blinding (performance bias and detection bias) All outcomes	Low risk	"treatments were identical in appearance"

Forbes 1983

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h	
Participants	Dental surgery (impacted third molar) N = 211 (199 for efficacy analyses) Age ≥ 15 years	
Interventions	Aspirin 650 mg, n = 39 Diflunisal 500 mg, n = 39 Diflunisal 1000 mg, n = 40 Zomepirac 100 mg, n = 41 Placebo n = 40 Rescue medication (Tylenol) allowed after 2 h (BOCF)	
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers list
Allocation concealment (selection bias)	Unclear risk	Not described

Forbes 1983 (Continued)

Blinding (performance bias and detection bias)
All outcomes

Low risk

"double dummy technique"

Forbes 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h
Participants	Dental surgery (impacted third molar) N = 115 (109 for efficacy analyses) Age ≥ 15 years
Interventions	Aspirin 650 mg n = 24 Fendosal 200 mg, n = 29 Ibuprofen 400 mg, n = 28 Placebo, n = 28 Rescue medication allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique

Forbes 1986

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h
Participants	Dental surgery (impacted third molar) N = 222 (198 for efficacy analyses)

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

Forbes 1986 (Continued)

	Age ≥ 15 years
Interventions	Aspirin 650 mg, n = 36 Naproxen 550 mg, n = 38 Codeine 60 mg, n = 44 Naproxen 550 mg + codeine 60 mg, n = 38 Placebo, n = 42 Rescue medication (paracetamol + codeine) allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique

Forbes 1989

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 8 h
Participants	Dental surgery (impacted third molar) N = 191 (164 for efficacy) Age ≥ 15 years
Interventions	Aspirin 600 mg, n = 31 Flurbiprofen 25 mg, n = 31 Flurbiprofen 50 mg, n = 33 Flurbiprofen 100 mg, n = 36 Placebo n = 33 Rescue medication (paracetamol + codeine) allowed after 2 h (BOCF)

Forbes 1989 (Continued)

Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"all tablets were identical in appearance"

Forbes 1990a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 6
Participants	Dental surgery (impacted third molar) N = 404 (350 for efficacy analyses) Age ≥ 15 years
Interventions	Aspirin 650 mg, n = 68 Aspirin 1000 mg, n = 71 Caffeine 65 mg, n = 70 Aspirin 650 mg + caffeine 65 mg, n = 66 Placebo n = 75 Rescue medication allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias
Single dose oral aspirin for acute postoperative pain in adults (Review)

Forbes 1990a (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"all tablets were identical in appearance"

Forbes 1990b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 6 h	
Participants	Dental surgery (impacted third molar) N = 153 (128 for efficacy analyses) Age ≥ 15 years	
Interventions	Aspirin 650 mg, n = 32 Ketorolac 10 mg, n = 37 Paracetamol 600 mg + codeine 60 mg, n = 27 Placebo n = 32 Rescue medication (Tylenol) allowed after 2 h (BOCF)	
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"capsules were identical in appearance"

Forbes 1991

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 8 h
Participants	Dental surgery (impacted third molar) N = 276 (241 for efficacy analyses) Age 15 to 44 years
Interventions	Aspirin 650 mg, n = 41 Ibuprofen 400 mg, n = 37 Bromfenac 5 mg, n = 39 Bromfenac 10 mg, n = 43 Bromfenac 25 mg, n = 42 Placebo n = 39 Rescue medication (Vicodin) allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"all capsules were identical in appearance"

Forbes 1992

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 8 h
Participants	Dental surgery (impacted third molar) N = 324 (280 for efficacy analyses) Age 15 to 56 years
Interventions	Aspirin 650 mg, n = 38

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

Forbes 1992 (Continued)

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

Placebo n = 38

Rescue medication (Vicodin) allowed after 2 h (BOCF)

Outcomes

PI: standard 4-point scale

PR: standard 5-point scale

Global assessment: standard 5-point scale

Use of rescue medication

Adverse events

Withdrawals

Notes

Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"all capsules were identical in appearance"

Frame 1986

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 5 h
Participants	Dental surgery (impacted third molar) N = 159 (141 for efficacy analyses) Mean age 24 years
Interventions	Aspirin 600 mg, n = 25
	Ibuprofen 200 mg + codeine 15 mg, n = 32
	Ibuprofen 400 mg + codeine 30 mg, n = 32
	Ibuprofen 800 mg + codeine 60 mg, n = 26
	Placebo n = 26
	Rescue medication (paracetamol) allowed after 2 h
Outcomes	PI: non-standard 9-point scale

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

Frame 1986 (Continued)

PR: standard 5-point scale
Global assessment (no scale reported)

Use of rescue medication
Adverse events

Withdrawals

Notes Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sealed sachets
Blinding (performance bias and detection bias) All outcomes	Low risk	"aspirin specially formulated to match the other drugs"

Gaston 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 8 h
Participants	Oral surgery N = 161 Mean age 27 years
Interventions	Aspirin 650 mg, n = 40 Etodolac 50 mg, n = 39 Etodolac 200 mg, n = 40 Placebo, n = 42 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: non-standard 5-point scale PR: 5-point scale Global assessment: non-standard 4-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Gaston 1984 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Gaston 1986

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 12 h
Participants	Dental surgery (impacted third molar) N = 189 Age 18 to 48 years
Interventions	Aspirin 650 mg, n = 38 Etodolac 50 mg, n = 37 Etodolac 100 mg, n = 38 Etodolac 200 mg, n = 38 Placebo n = 38 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: non-standard 5-point scale PR: 5-point scale Global assessment: non-standard 4-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a randomization code was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Patients allocated sequential code numbers based on order of admission to study
Blinding (performance bias and detection bias) All outcomes	Low risk	"All medications were in the form of identical tablets"

Herbertson 1994

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 8 h
Participants	Gynaecological surgery N = 217 (209 for efficacy analyses) Mean age 43 years
Interventions	Aspirin 650 mg, n = 53 Diclofenac 50 mg, n = 52 Diclofenac 100 mg, n = 52 Placebo n = 52 Rescue medication allowed after 1 h
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0. Total = 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Herrmann 1980a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1, 2, 3, 4 h Study 1
Participants	Episiotomy (not uterine cramps) N = 203 Mean age 27 years
Interventions	Aspirin 1000 mg, n = 50 Fluproquazone 75 mg, n = 52 Fluproquazone 150 mg, n = 51 Placebo n = 50

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

Herrmann 1980a (Continued)

Rescue medication allowed after 1 h (LOCF)

Outcomes	PI: standard 4-point scale PR: standard 5-point scale Adverse events (combined for 4 studies)
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	All medication "prepackaged in code-numbered individual envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All capsules were identical in appearance"

Herrmann 1980b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1, 2, 3, 4 h Study 2
Participants	Episiotomy (not uterine cramps) N = 168 Mean age 27 years
Interventions	Aspirin 1000 mg, n = 40 Fluproquazone 100 mg, n = 42 Fluproquazone 200 mg, n = 44 Placebo, n = 42
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Adverse events (combined for 4 studies)
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	All medication "prepackaged in code-numbered individual envelopes"

Herrmann 1980b (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	"All capsules were identical in appearance"
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Holland 1988

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.25, 0.5, 0.75, 1, 1.5, 2 h then hourly to 5 h
Participants	Dental surgery (impacted third molar) N = 140 Age 18 to 35 years
Interventions	Soluble aspirin 600 mg, n = 20 Soluble aspirin 900 mg, n = 20 Soluble aspirin 1200 mg, n = 20 Aspirin 600 mg, n = 20 Aspirin 900 mg, n = 20 Aspirin 1200 mg, n = 20 Placebo, n = 20 Rescue medication (paracetamol) allowed - no further details
Outcomes	PI: 100 mm VAS Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double dummy technique"

Honig 1978

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 8 h
Participants	Meniscectomy N = 145 Mean age ~30 years

Honig 1978 (Continued)

Interventions	Aspirin 600 mg, n = 30 Diflunisal 125 mg, n = 28 Diflunisal 250 mg, n = 29 Diflunisal 500 mg, n = 30 Placebo n = 28 Rescue medication allowed (time not specified) (participants assigned PI = severe for analysis)
Outcomes	PI: standard 4-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Pre-packaged in individual patient-coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	"All capsules were identical in appearance"

Jain 1985a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 5 h
Participants	Episiotomy N = 120 Mean age 23 years
Interventions	Aspirin 600 mg, n = 30 Indoprofen 50 mg, n = 30 Indoprofen 100 mg, n = 30 Placebo n = 30 Rescue medication allowed (time not specified) (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: non-standard 4-point scale Rescue medication Adverse events Withdrawals

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

Jain 1985a (Continued)

Notes Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching capsules"

Jain 1985b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 4 h
Participants	Dental surgery (impacted third molar) N = 151 (146 for efficacy analyses) Mean age 34 years
Interventions	Aspirin 600 mg, n = 29 Indoprofen 50 mg, n = 29 Indoprofen 100 mg, n = 30 Indoprofen 200 mg, n = 29 Placebo n = 29 Rescue medication allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

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

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Jain 1985b (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
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Jain 1986a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1, 2, 3, 4 h
Participants	Dental surgery (impacted third molar) N = 120 Mean age 24 years
Interventions	Aspirin 600 mg, n = 38 Amfenac 100 mg, n = 40 Placebo n = 40 Rescue medication allowed after 2 h (BOCF)
Outcomes	PI: standard 4-point scale and 10 cm VAS PR: standard 5-point scale Global assessment: non-standard 4-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 1, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random number"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Jain 1986b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 241 (227 for efficacy analyses) Mean age 23 years
Interventions	Aspirin 650 mg, n = 45

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

Jain 1986b (Continued)

Ibuprofen 100 mg, n = 39

Ibuprofen 200 mg, n = 47

Ibuprofen 400 mg, n = 49

Placebo n = 47

Rescue medication allowed after 1 h (LOCF)

Outcomes

PI: standard 4-point scale, 100 mm VAS

PR: non-standard 6-point scale

Global assessment: 5-point scale

Use of rescue medication

Adverse events

Withdrawals

Notes

Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Bottle identified only by a sequential number
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing tablets"

Kempf 1987

Methods

RCT, DB, single oral dose (followed by multiple dose phase), parallel groups

Assessed at 0, 0.5, 1 hourly to 6

Participants

Dental surgery (impacted third molar)

N = 105 (98 for efficacy analysis)

Age 18 to 60 years

Interventions

Buffered aspirin 600 mg, n = 24

Meclofenamate 100 mg, n = 24

Meclofenamate 200 mg, n = 26

Placebo, n = 24

Second dose allowed for inadequate response after 4 h

Rescue medication (paracetamol + codeine) allowed after 1 h (LOCF)

Outcomes

PI: standard 4-point scale

PR: standard 5-point scale

Global assessment: non-standard 3-point scale

Adverse events

Kempf 1987 (Continued)

Withdrawals

Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing capsules"

Lehnert 1990

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h	
Participants	Dental surgery (impacted third molar) N = 150 (139 for efficacy analyses) Age 17 to 54 years	
Interventions	Aspirin 1000 mg, n = 45 Paracetamol 1000 mg, n = 49 Placebo, n = 42 Rescue medication allowed (no further details) (BOCF)	
Outcomes	PI: standard 4-point scale PR: non-standard 4-point scale Global assessment: non-standard 4-point scale Use of rescue medication Adverse events Withdrawals	
Notes	Language: German Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Randomly generated
Allocation concealment (selection bias)	Unclear risk	Not described

Lehnert 1990 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	All capsules were identical in appearance
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London 1983a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 6 h
Participants	Episiotomy N = 166 (160 for efficacy) Age 18 to 40
Interventions	Aspirin 650 mg, n = 40 Fluproquazone 100 mg, n = 41 Fluproquazone 200 mg, n = 39 Placebo, n = 40 Rescue medication allowed - no further details
Outcomes	Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical capsules"

London 1983b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 4 h
Participants	Episiotomy N = 160 Age 18 to 36 years
Interventions	Aspirin 300 mg, n = 40

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

London 1983b (Continued)

Aspirin 600 mg, n = 41
Aspirin 1200 mg, n = 40
Placebo, n = 39

Rescue medication allowed, data up to point of remedication used for analysis

Outcomes	PI: standard 4-point scale Use of rescue medication Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Study medication "individually packaged and identified only by study number and patient number"
Blinding (performance bias and detection bias) All outcomes	Low risk	"all tablets appeared identical"

Mardirossian 1985

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 171 (164 analysed) Mean age 24 years
Interventions	Aspirin 650 mg, n = 40 Flurbiprofen 25 mg, n = 39 Flurbiprofen 50 mg, n = 43 Placebo, n = 42 Rescue medication allowed after 1 h (LOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: non-standard 4-point scale Use of rescue medication Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
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Single dose oral aspirin for acute postoperative pain in adults (Review)

Mardirossian 1985 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing medications"

Markowitz 1985

Methods	RCT, DB, single oral dose (followed by multiple dose phase), parallel groups Assessed at 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 225 (205 analysed) Mean age 24 years
Interventions	Buffered aspirin 600 mg, n = 50 Meclofenamate 100 mg, n = 51 Meclofenamate 200 mg, n = 51 Placebo, n = 53 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: non-standard Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 1, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

McQuay 1987

Methods	RCT, DB, single oral dose, parallel groups
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Single dose oral aspirin for acute postoperative pain in adults (Review)

McQuay 1987 (Continued)

Assessed at 0.5, 1, 1.5, 2, h then hourly to 6 h

Participants	Orthopaedic surgery N = 120 Age 18 to 70 years
Interventions	Aspirin 650 mg, n = 30 Fluradoline 150 mg, n = 30 Fluradoline 300 mg, n = 30 Placebo, n = 30 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale, 100 mm VAS PR: standard 5-point scale, 100 mm VAS Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	All capsules "identical in external appearance"

Mehlisch 1984

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 162 Age 16 to 78 years
Interventions	Aspirin 650 mg, n = 49 Paracetamol 1000 mg, n = 58 Placebo, n = 55 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale

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

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Mehlisch 1984 (Continued)

PR: standard 5-point scale
Global assessment: standard 5-point scale

Use of rescue medication
Withdrawals

Notes Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"capsules were identical in appearance"

Mehlisch 1990

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 161 Mean age 24 years
Interventions	Aspirin 650 mg, n = 40 FS205-397 250 mg, n = 40 FS205-397 500 mg, n = 40 Placebo, n = 41
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-derived randomization schedule"

Mehlisch 1990 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically appearing two-capsule doses"

Mehlisch 1994

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 8 h
Participants	Dental surgery (impacted third molar) N = 208 Age 20 to 90 years
Interventions	Aspirin 650 mg, n = 51 Diclofenac 50 mg, n = 53 Diclofenac 100 mg, n = 52 placebo, n = 52
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: non-standard 3-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Nelson 1985

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 12 h
Participants	Dental surgery (impacted third molar)

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

Nelson 1985 (Continued)

N = 207 (201 for analyses)
Age 17 to 45 years

Interventions	Aspirin 650 mg, n = 40 Etodolac 50 mg, n = 41 Etodolac 100 mg, n = 42 Etodolac 200 mg, n = 39 Placebo, n = 39 Rescue medication allowed (time not specified) (BOCF)
Outcomes	PI: non-standard 5-point scale PR: 5-point scale Global assessment: non-standard 4-point scale Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"two tablets which appeared identical"

Nelson 1994a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.25, 0.5, 0.75, 1, 1.5, 2 h then hourly to 6 h
Participants	Dental surgery (impacted third molar) N = 183 (180 for efficacy analyses) Age 15 to 52 years
Interventions	Aspirin 500 mg, n = 65 Ibuprofen lysine 200 mg, n = 77 Placebo, n = 41 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events

Nelson 1994a (Continued)

Withdrawals

Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"allocation schedule of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy method

Nelson 1994b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 8 h	
Participants	Dental surgery (impacted third molar) N = 255 (252 for analyses) Age 16 to 70 years	
Interventions	Aspirin 650 mg, n = 51 Diclofenac 25 mg, n = 51 Diclofenac 50 mg, n = 51 Diclofenac 100 mg, n = 51 Placebo, n = 51 Rescue medication allowed after 1 h - no further details	
Outcomes	PI: standard 4-point scale PR: 5-point scale Use of rescue medication Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Nelson 1994b (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy technique"
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Olsen 1997

Methods	<p>RCT, DB, single oral dose, parallel groups.</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 0.5, 1 h, then hourly to 8 h</p>
Participants	<p>Episiotomy</p> <p>N = 255</p> <p>All F</p> <p>Mean age 24 years</p>
Interventions	<p>Aspirin 650 mg, n = 50</p> <p>Diclofenac K 25 mg, n = 52</p> <p>Diclofenac K 50 mg, n = 50</p> <p>Diclofenac K 100 mg, n = 51</p> <p>Placebo, n = 52</p> <p>Rescue medication (non-study analgesic) allowed after 1 h</p>
Outcomes	<p>PI: standard 4-point scale</p> <p>PR: standard 5-point scale</p> <p>Global assessment: non-standard 4-point scale</p> <p>Use of rescue medication</p> <p>Adverse events</p> <p>Withdrawals</p>
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique

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

Or 1988

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1, 2, 3, 4 h
Participants	Dental surgery (impacted third molar) N = 120 Mean age 26 years
Interventions	Aspirin 650 mg, n = 27 Mefenamic acid 250 mg, n = 27 Mefenamic acid 250 mg plus aspirin 650 mg, n = 27 Placebo, n = 27
Outcomes	PI: non-standard 5-point scale, 100 mm VAS PR: standard 5-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing two-capsule doses"

Parkhouse 1969

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0. 0.5, 1 h then hourly to 6 h
Participants	Postoperative pain
Interventions	Hospital A Aspirin fast-buffered 600 mg, n = 45 Aspirin standard tablets 600 mg, n = 45 Placebo, n = 46 Hospital B Aspirin fast-buffered 600 mg, n = 42

Parkhouse 1969 (Continued)

Aspirin standard tablets 600 mg, n = 37

Placebo, n = 39

Rescue medication allowed at any time

Outcomes	PI: standard 4-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically formulated"

Patel 1991

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 8 h
Participants	Dental surgery (impacted third molar) N = 150 Mean age 24 years
Interventions	Aspirin 650 mg, n = 30 Lornoxicam 2 mg, n = 30 Lornoxicam 4 mg, n = 30 Lornoxicam 8 mg, n = 30 Placebo, n = 30 Rescue medication allowed at any time (LOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

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

Patel 1991 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Rowe 1985

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h	
Participants	Dental surgery (impacted third molar) N = 174 (167 for efficacy analyses) Age 17 to 58 years	
Interventions	Buffered aspirin 600 mg, n = 43 Meclofenamate 100 mg, n = 44 Meclofenamate 200 mg, n = 39 Placebo, n = 41 Rescue medication allowed after 1 h (no further details)	
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: scale not reported Adverse events	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical appearing medications"

Seymour 1986

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.25, 0.5, 0.45, 1, 1.5, 2 h then hourly to 5 h
Participants	Dental surgery (impacted third molar) N = 90 Age 17 to 40 years
Interventions	Soluble aspirin 1200 mg, n = 30 Aspirin tablets 1200 mg, n = 30 Placebo, n = 30
Outcomes	PI: 100 mm VAS
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy technique"

Seymour 1992

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.25, 0.5, 0.75, 1, 1.5, 2 h then hourly to 5 h
Participants	Dental surgery (impacted third molar) N = 182 Mean age 26 years
Interventions	Buffered aspirin 500 mg, n = 35 Buffered aspirin 1000 mg, n = 38 Aspirin tablets 500 mg, n = 35 Aspirin tablets 1000 mg, n = 37 Placebo, n = 37 Rescue medication allowed (LOCF)
Outcomes	PI: 100 mm VAS Global assessment: 5-point scale Use of rescue medication
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Seymour 1992 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy technique"

Seymour 2003

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2 h	
Participants	Dental surgery (impacted third molar) N = 153 Mean age 25 years	
Interventions	Soluble aspirin 900 mg, n = 59 Paracetamol tablets 1000 mg, n = 62 Placebo, n = 32 Rescue medication (ibuprofen 400 mg) allowed after 1 h (LOCF)	
Outcomes	PI: 100 mm VAS Global assessment: 5-point scale Use of rescue medication Adverse events Withdrawals	
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy method"

Sunshine 1983a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 6 h
Participants	Dental surgery (impacted third molars) N = 148 Mean age 23 years
Interventions	Aspirin 650 mg, n = 41 Aspirin 650 mg + codeine 60 mg, n = 41 Suprofen 200 mg, n = 40 Suprofen 400 mg, n = 41 Placebo, n = 40 Rescue medication allowed after 2 h (LOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing capsules"

Sunshine 1983b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 6 h
Participants	Episiotomy N = 168 (152 for analysis) Mean age 24 years
Interventions	Aspirin 600 mg, n = 29 Flurbiprofen 25 mg, n = 32 Flurbiprofen 50 mg, n = 29

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

Sunshine 1983b (Continued)

	Flurbiprofen 100 mg, n = 31 Placebo, n = 31 Rescue medication allowed after 1 h (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Use of rescue medication Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Tablets were "identical in appearance"

Sunshine 1983c

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 0.5, 1 h then hourly to 4 h Medication administered when pain severe
Participants	Episiotomy N = 120 Mean age 24 years
Interventions	Aspirin 600 mg, n = 30 Ibuprofen 400 mg, n = 30 Zomepirac 100 mg, n = 30 Placebo, n = 30 Rescue medication allowed after 1 h (LOCF)
Outcomes	PI: standard 4-point scale PR: 5-point scale Global assessment: non-standard 7-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

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

Sunshine 1983c (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy technique"

Sunshine 1988

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 12 h
Participants	Study 2 Mixed general surgery (35%) and gynaecological surgery 65%) N = 61 (60 for analysis) Age 31 to 33 years
Interventions	Aspirin 648 mg, n = 15 Piroxicam 20 mg, n = 15 Piroxicam 40 mg, n = 15 Placebo, n = 15 Rescue medication allowed (time not specified) (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Unclear risk	Not described

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

Sunshine 1988 (Continued)

All outcomes

Wang 1982

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 6 h
Participants	Mixed general and orthopaedic surgery N = 100 Age 18 to 61 years
Interventions	Aspirin 650 mg, n = 25 Bicifadine 75 mg, n = 25 Bicifadine 150 mg, n = 25 Placebo n = 25 Rescue medication allowed (time not specified) (BOCF)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"coded single-dose envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing capsules"

Winter 1983a

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0, 1 h then hourly to 8 h
Participants	Dental surgery (complicated or multiple extractions or impactions) N = 105 Age 18 to 65 years
Interventions	Aspirin 650 mg, n = 37 Oxaprozin 1200 mg, n = 33 Placebo, n = 35 Rescue medication (paracetamol plus codeine) allowed after 2 h (data handling not reported)

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

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Winter 1983a (Continued)

Outcomes	PI: standard 4-point scale PR: non-standard scale Global assessment: non-standard 4-point scale Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Winter 1983b

Methods	RCT, DB, single oral dose, parallel groups Assessed at 0.5, 1 h then hourly to 4 h
Participants	Dental surgery (complicated or multiple extractions or impactions) N = 161 Mean age 32 years
Interventions	Aspirin 650 mg, n = 42 Phenyltoloxamine 60 mg + paracetamol 1000 mg, n = 41 Placebo, n = 44 Rescue medication allowed after 2 h (data handling not reported)
Outcomes	PI: standard 4-point scale PR: standard 5-point scale Global assessment: standard 5-point scale Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

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

Winter 1983b (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"identically-appearing 2-capsule single doses"

BOCF = baseline observation carried forward; DB = double-blind; h = hour; LOCF = last observation carried forward; N = number of participants in study; n = number of participants in treatment arm; PI = pain intensity; PR = pain relief; RCT = randomised controlled trial; VAS = visual analogue scale; W = withdrawals

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahlstrom 1968	No extractable data
Ahlstrom 1974	No extractable data
Antonsson 1985	No placebo
Aromaa 1978	No placebo
Barrenechea 1981	Not randomised
Bella 1987	No placebo
Bhounsule 1990	Did not state baseline pain
Bloomfield 1974	No extractable data
Bloomfield 1976	Baseline pain intensity not given so no extractable data
Boerlin 1986	Not randomised (MEDLINE indexed as RCT)
Burguet 1989	No placebo
Campos 1980	Included patients with somatic pain
Capuano 1990	No placebo
Carstens 1987	Unable to obtain the paper locally or through the British Library. Not indexed in MEDLINE as randomised controlled trial
Cooper 1976	Only 3 hours observation time
Cooper 1979b	Inappropriate formulation ?? Probably not randomised (not indexed RCT) and probably no placebo
Cooper 1980a	Inappropriate study design ?? Probably not randomised (not indexed RCT)
Cooper 1980b	Duplicate publication of Cooper 1980a (excluded)
Cordero 1985	Unable to obtain the paper locally or through the British Library

Study	Reason for exclusion
Dahl 1985	No placebo
Desjardins 1983	Inappropriate study design ??
Di Blasi 1980a	No placebo, includes children (< 12 years)
Di Blasi 1980b	No placebo, includes children (< 12 years)
Feldmeier 1982	Non-standard pain measures
Fink 1978	Included patients with 'slight' baseline pain
Fleiss 1979	No extractable data
Friedrich 1983	Non-standard pain measures
Fuccella 1977	Inappropriate study design ??
Gallardo 1982	Observation period only 3 hours
Gallardo 1984	Observation period only 3 hours
Gallardo 1990	Not randomised
Gallardo 1992	Observation period only 3 hours
Gammelgaard 1981	No extractable data
Giglio 1984	Medication administered preoperatively - inadequate baseline pain
Giles 1986	Inappropriate study design - data from patients re-medicated were not handled correctly
Green 1978	Not randomised
Grippaudo 1981	No placebo
Happonen 1987	No placebo
Heimdahl 1979	Inadequate baseline pain
Henrikson 1979	Intervention given immediately after surgery without regard to baseline pain
Hepso 1976	Not double-blind (title says double-blind)
Herrmann 1980c	Includes participants with pain due to trauma
Herrmann 1980d	Includes participants with pain due to trauma
Hill 1969	Inadequate baseline pain
Hutton 1983	No extractable data
Ihalainen 1980	No placebo
Irwin 1984	No placebo

Study	Reason for exclusion
Izquierdo 1995	No placebo, intravenous administration
Jain 1978a	Study 1: combined data for episiotomy and uterine cramps. Study 2: non-standard pain scales
Jain 1978b	No usable data
Joubert 1982	Not randomised
Kamiyama 1980	No placebo
Kantor 1965	Includes participants with pain due to fracture
Kristensen 1986	No placebo
Kristensen 1988	No placebo
Lamphier 1974	Multiple dose study - 1 tablet every 3 hours
Lobo 1983	Observation period only 3 hours long
Maeglin 1979	Observation period only 3 hours long
Mahler 1976	Not randomised, no placebo
Mandujano	Unable to obtain the paper locally or through the British Library
Mehta 1986	No extractable data
Mitchell 1985	Baseline pain not of moderate to severe intensity
Mukherjee 1980	No extractable data
Okun 1979	Includes participants with musculoskeletal pain and fractures
Okun 1982	Non-standard pain scales therefore no extractable data
Or 1985	Unable to obtain the paper locally or through the British Library. Probably no placebo
Ormiston 1981	No placebo
Parker 1986	Baseline pain and age not reported. Dose of aspirin unclear
Parkhouse 1967a	Not double-blind
Parkhouse 1967b	Inadequate baseline pain
Parkhouse 1968	Baseline pain not reported
Perotti 1984	No placebo
Reines 1986	Inadequate baseline pain
Rowe 1981	Inadequate baseline pain
Rye 1978	Duplicate publication; data already included in studies published by Cooper

Study	Reason for exclusion
Sechzer 1977	Included patients with postpartum uterine cramps
Seymour 1982	Inadequate baseline pain
Seymour 1983a	Not randomised
Seymour 1983b	Inadequate baseline pain
Seymour 1984	Inadequate baseline pain
Sindet 1986	No placebo
Skjelbred 1977	No placebo
Skjelbred 1984	Inadequate baseline pain
Slatis 1980	No placebo
Spivach 1984	No placebo
Sunshine 1975	Included patients with somatic pain
Sunshine 1978a	Included patients with somatic pain
Sunshine 1978b	Included patients with somatic pain
Sunshine 1986	Included patients with postpartum uterine cramps
Sveen 1975	Inadequate baseline pain
Szmyd 1959	Inadequate baseline pain
Todorovic 1982	No placebo
Trop 1983	Non-standard pain scales therefore no extractable data
Vaidya 1974	Non-standard pain scales therefore no extractable data
Versichelen 1982	No extractable data
Von Graffenried 1980	Observation period only 3 hours long
Walker 1960	Not randomised
Wang 1979	Includes participants with fracture. No separate results for postoperative pain
Wilkinson 1960	No placebo
Winter 1978	Observation period only 3 hours long
Wojcicki 1977	Observation period only 1 hour long
Zederfeldt 1977	Inadequate baseline pain

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. Aspirin 500 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	2	213	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.82, 2.00]

Analysis 1.1. Comparison 1 Aspirin 500 mg versus placebo, Outcome 1 Participants with at least 50% pain relief.

Comparison 2. Aspirin 600 or 650 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	59	4644	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [2.22, 2.72]
1.1 Dental surgery	43	3433	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [2.23, 2.88]
1.2 Non-dental surgery	17	1211	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.93, 2.75]
2 Participants using rescue medication at 4 to 5 h	11	982	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.50, 0.67]
3 Participants using rescue medication at 6 h	20	1923	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.73, 0.82]
4 Participants using rescue medication at 12 h	4	291	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.05]
5 Any adverse event	46	3633	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.00, 1.44]

Analysis 2.1. Comparison 2 Aspirin 600 or 650 mg versus placebo, Outcome 1 Participants with at least 50% pain relief.

Analysis 2.2. Comparison 2 Aspirin 600 or 650 mg versus placebo, Outcome 2 Participants using rescue medication at 4 to 5 h.

Analysis 2.3. Comparison 2 Aspirin 600 or 650 mg versus placebo, Outcome 3 Participants using rescue medication at 6 h.

Analysis 2.4. Comparison 2 Aspirin 600 or 650 mg versus placebo, Outcome 4 Participants using rescue medication at 12 h.

Analysis 2.5. Comparison 2 Aspirin 600 or 650 mg versus placebo, Outcome 5 Any adverse event.

Comparison 3. Aspirin 900 or 1000 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	6	618	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [2.00, 3.64]
2 Participants using rescue medication at 4 to 5 h	5	501	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.56, 0.74]
3 Participants using rescue medication at 6 h	2	233	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.95]
4 Any adverse event	4	404	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.05, 2.30]

Analysis 3.1. Comparison 3 Aspirin 900 or 1000 mg versus placebo, Outcome 1 Participants with at least 50% pain relief.

Analysis 3.2. Comparison 3 Aspirin 900 or 1000 mg versus placebo, Outcome 2 Participants using rescue medication at 4 to 5 h.

Analysis 3.3. Comparison 3 Aspirin 900 or 1000 mg versus placebo, Outcome 3 Participants using rescue medication at 6 h.

Analysis 3.4. Comparison 3 Aspirin 900 or 1000 mg versus placebo, Outcome 4 Any adverse event.

Comparison 4. Aspirin 1200 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	3	249	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.95, 4.20]

Analysis 4.1. Comparison 4 Aspirin 1200 mg versus placebo, Outcome 1 Participants with at least 50% pain relief.

APPENDICES

Appendix 1. Search strategy

- Aspirin/
- (aspirin OR acetylsalicylic acid).ti,ab,kw.
- OR/1-2
- Postoperative pain/
- ((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.
- ((post-surgical adj4 pain\$) or ("post surgical" adj4 pain\$) or (post-surgery adj4 pain\$)).ti,ab,kw.
- ("pain-relief after surg\$") or ("pain following surg\$") or ("pain control after\$")).ti,ab,kw.
- ("post surg\$" or post-surg\$) AND (pain\$ or discomfort)).ti,ab,kw.
- ((pain\$ adj4 "after surg\$") or (pain\$ adj4 "after operat\$") or (pain\$ adj4 "follow\$ operat\$") or (pain\$ adj4 "follow\$ surg\$")).ti,ab,kw.
- ((analgesi\$ adj4 "after surg\$") or (analgesi\$ adj4 "after operat\$") or (analgesi\$ adj4 "follow\$ operat\$") or (analgesi\$ adj4 "follow\$ surg\$")).ti,ab,kw.
- OR/4-10
- clinical trials.sh.
- 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 2. Search strategy for EMBASE (via OVID)

1. Acetylsalicylic acid/
2. (aspirin OR acetylsalicylic acid).ti,ab,kw.
3. OR/1-2
4. Postoperative pain/
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 CENTRAL

1. MESH descriptor Aspirin
2. (aspirin OR acetylsalicylic 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 are 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 co-ordination are needed, which can be difficult postoperatively 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](#)).

Appendix 5. Summary of outcomes: analgesia and rescue medication

Study ID	Treatment	Analgesia		Rescue medication	
		PI or PR	Number with 50% PR	Median time to use (h)	% using
Bloomfield 1967	(1) aspirin 600 mg, n = 16 (2) placebo, n = 18 Also 3 doses of chlorphenesin (n = 50)	SPID 6	(1) 9/16	No data	No data
		(1) 6.71	(2) 6/18		
		(2) 4.29			
Boraks 1987	(1) aspirin 650 mg, n = 41 (2) placebo, n = 39 Also flurbiprofen and dipyrrone	TOTPAR 6	(1) 23/41	No data	Over 4 h:
		(1) 12.39	(2) 10/39		(1) 2.4%
		(2) 6.89			(2) 51%
Breivik 1984	(1) aspirin 650 mg, n = 29 (2) placebo, n = 30 Also 2 doses of piroxicam	SPID 6	(1) 9/29	No data	Over 6 h:
		(1) 3.61	(2) 5/30		(1) 41%
		(2) 1.98			(2) 67%

(Continued)

Calimlim 1977	(1) aspirin 650 mg, n = 23 (2) placebo, n = 26 Also 2 doses of pentazocine plus aspirin	TOTPAR 5 (1) 12.11 (2) 9.24	(1) 16/23 (2) 13/26	No data	Over 5 h: (1) 35% (2) 69%
Clark 1989	(1) aspirin 600 mg, n = 40 (2) placebo, n = 40 Also 3 doses of carprofen, 1 of diflunisal	TOTPAR 6 (1) 7.5 (2) 4.4	(1) 12/40 (2) 5/40	(1) 4.7 (2) 3.8	Over 6 h: (1) 55% (2) 65%, Over 8 h: (1) 60% (2) 78% Over 12 h: (1) 65% (2) 87%
Cooper 1977	(1) aspirin 325 mg, n = 37 (2) aspirin 650 mg, n = 37 (3) placebo, n = 40 Also 2 doses ibuprofen	TOTPAR 4 (1) 5.35 (2) 3.36	(1) 13/37 (2) 7/40	No data	No data
Cooper 1979a	Study 2: (1) aspirin 600 mg, n = 47 (2) placebo, n = 58 Also 2 doses indoprofen (n = 96)	TOTPAR 4 (1) 8.4 (2) 4.3	(1) 27/47 (2) 14/58	No data	No data
Cooper 1982	(1) aspirin 650 mg, n = 38 (2) placebo, n = 46 Also codeine, codeine plus aspirin, ibuprofen, codeine plus ibuprofen (n = 165)	TOTPAR 4 (1) 5.66 (2) 2.65	(1) 14/38 (2) 5/46	Mean (1) 2.97 (2) 2.38	No data
Cooper 1983	(1) aspirin 650 mg, n = 43 (2) placebo, n = 44 Also 2 doses of suprofen (n = 89)	TOTPAR 6 (1) 11.0 (2) 7.27	(1) 21/43 (2) 13/44	Mean (1) 242 min (2) 194 min	No data
Cooper 1986a	Study C (1) aspirin 650 mg, n = 40 (2) placebo, n = 41 Also aspirin plus codeine and 2 doses of suprofen (n = 123)	TOTPAR 6 (1) 8.13 (2) 3.59	(1) 13/40 (2) 3/41	Mean (1) 165 min (2) 136 min	No data
Cooper 1988	(1) aspirin 600 mg, n = 29 (2) placebo, n = 33 Also 3 doses of flurbiprofen (n = 89)	TOTPAR 6 (1) 4.61 (2) 2.60	(1) 4/29 (2) 1/33	Mean (1) 203 min (2) 142 min	No data
Cooper 1991b	(1) aspirin 650 mg, n = 46 (2) placebo, n = 48 Also 2 doses of meclofenamate	TOTPAR 6 (1) 6.22 (2) 3.79	(1) 11/46 (2) 5/48	Mean (1) 3.1 (2) 2.9	No data
Cooper 1992	(1) aspirin 650 mg, n = 28 (2) placebo, n = 26 Also 2 doses oxaprozin (n = 50)	SPID 6 (1) 1.67	(1) 4/28 (2) 0/26	(1) 2.8 (2) 1.8	Over 6 h: (1) 80% (2) 88%,

(Continued)

		(2) 0.19			Over 8 h: (1) 92% (2) 92%
Coutinho 1976	(1) aspirin 650 mg, n = 15 (2) placebo, n = 15 Also codeine, propoxyphene, 2 doses fen- bufen (n = 60)	SPID 5 (1) 6.8 (2) 3.3	(1) 13/15 (2) 6/15	No data	No data
De Vroey 1977	(1) aspirin 650 mg, n = 32 (2) placebo, n = 31 Also 3 doses diflunisal	SPID 6 (1) 8.1 (2) 2.87	(1) 19/32 (2) 1/31	No data	No data
Desjardins 1983a	(1) aspirin 650 mg, n = 40 (2) placebo, n = 39 Also codeine and propiram fumarate (n = 80)	TOTPAR 6 (1) 9.65 (2) 3.23	(1) 17/40 (2) 2/39	Mean (1) 184 min (2) 117 min	No data
Fliedner 1984	(1) aspirin 650 mg, n = 83 (2) placebo, n = 87 Also 3 doses etodolac (n = 210)	TOTPAR 6 (1) 7.5 (2) 4.0	(1) 25/83 (2) 9/87	Aspirin longer than placebo	No data
Forbes 1980	(1) aspirin 650 mg, n = 38 (2) placebo, n = 43 Also 3 doses proquazone (n = 129)	TOTPAR 4 (1) 6.08 (2) 2.4	(1) 15/38 (2) 4/43	Mean (1) 3.1 (2) 2.4	No data
Forbes 1982	(1) aspirin 650 mg, n = 42 (2) placebo, n = 38	TOTPAR 4 (1) 6.26 (2) 4.21	(1) 17/42 (2) 9/38	Mean (1) 3.1 (2) 2.4	Over 12 h: (1) 74% (2) 76%
Forbes 1983	(1) aspirin 650 mg, n = 39 (2) placebo, n = 40 Also zomepirac and 2 doses of diflunisal (n = 120)	TOTPAR 6 (1) 7.46 (2) 4.07	(1) 12/39 (2) 4/40	Mean (1) 5.0 (2) 4.6	Over 6 h: (1) 79% (2) 80% Over 8 h: (1) 90% (2) 83% Over 12 h: (1) 97% (2) 90%
Forbes 1984	(1) aspirin 650 mg, n = 24 (2) placebo, n = 28 Also ibuprofen and fendosal (n = 57)	TOTPAR 6 (1) 6.67 (2) 3.79	(1) 6/24 (2) 3/28	Mean (1) 5.3 (2) 4.5	Over 12 h: (1) 92% (2) 89%
Forbes 1986	(1) aspirin 650 mg, n = 36 (2) placebo, n = 42 Also naproxen, codeine and naproxen plus codeine (n = 158)	TOTPAR 6 (1) 6.89 (2) 4.07	(1) 10/36 (2) 5/42	Mean (1) 5.4 (2) 5.3	No data
Forbes 1989	(1) aspirin 600 mg, n = 31	TOTPAR 6	(1) 9/31	Mean	Over 8 h:

(Continued)

	(2) placebo, n = 33 Also 3 doses flurbiprofen (n = 100)	(1) 7.12 (2) 3.49	(2) 3/33	(1) 5.1 (2) 3.3	(1) 77% (2) 94%
Forbes 1990a	(1) aspirin 650 mg, n = 68 (2) aspirin 1000 mg, n = 71 (3) placebo, n = 75 Also aspirin plus caffeine (n = 66)	TOTPAR 6 (1) 6.57 (2) 6.35 (3) 1.99	(1) 17/68 (2) 17/71 (3) 0/75	Mean (1) 3.9 (2) 3.9 (2) 2.8	Over 6 h: (1) 65% (2) 77% (3) 93%
Forbes 1990b	(1) aspirin 650 mg, n = 32 (2) placebo, n = 32 Also ketorolac and paracetamol plus codeine (n = 64)	TOTPAR 6 (1) 6.5 (2) 2.91	(1) 8/32 (2) 1/32	Mean (1) 4.2 (2) 3.1	Over 6 h: (1) 81% (2) 84%
Forbes 1991	(1) aspirin 650 mg, n = 41 (2) placebo, n = 39 Also 3 doses bromfenac	TOTPAR 6 (1) 5.15 (2) 2.49	(1) 7/41 (2) 1/39	Mean (1) 3.5 (2) 2.8	Over 8 h: (1) 98% (2) 97%
Forbes 1992	(1) aspirin 650 mg, n = 38 (2) placebo, n = 38 Also ibuprofen and 3 doses bromfenac (n = 204)	TOTPAR 6 (1) 5.81 (2) 2.06	(1) 8/38 (2) 0/38	Mean (1) 3.9 (2) 2.7	Over 8 h: (1) 97% (2) 97%
Frame 1986	(1) aspirin 600 mg, n = 25 (2) placebo, n = 26 Also 3 doses ibuprofen plus codeine (n = 4)	TOTPAR 5 (1) 10.06 (2) 8.7	(1) 14/25 (2) 12/26	(1) 2.9 (2) 2.6	Over 5 h: (1) 64% (2) 78%
Gaston 1984	(1) aspirin 650 mg, n = 40 (2) placebo, n = 42	TOTPAR 6 (1) 5.99 (2) 4.8	(1) 9/40 (2) 6/42	No data	No data
Gaston 1986	(1) aspirin 650 mg, n = 38 (2) placebo, n = 38 Also 3 doses etodolac (n = 113)	TOTPAR 6 (1) 5.8 (2) 3.9	(1) 8/38 (2) 4/38	No data	No data
Herbertson 1994	(1) aspirin 650 mg, n = 53 (2) placebo, n = 52 Also 2 doses diclofenac	TOTPAR 6 (1) 10.2 (2) 3.54	(1) 23/50 (2) 4/47	(1) 4.4 (2) 1.4	Over 6 h: (1) 70% (2) 80% Over 8 h: (1) 90% (2) 80%
Herrmann 1980a Study 1	(1) aspirin 1000 mg, n = 50 (2) placebo, n = 50 Also 2 doses fluproquazone (n = 103)	TOTPAR 4 (1) 9.2 (2) 5.3	(1) 32/50 (2) 16/50	No data	Over 4 h: (1) 20% (2) 50%
Herrmann 1980b Study 2	(1) aspirin 1000 mg, n = 40 (2) placebo, n = 42 Also 2 doses fluproquazone (n = 86)	TOTPAR 4 (1) 7.0 (2) 2.62	(1) 19/40 (2) 4/42	No data	Over 4 h: (1) 10% (2) 67%
Holland 1988	(1) aspirin 600 mg, n = 20 (2) sol aspirin 600 mg, n = 20 (3) aspirin 900 mg, n = 20	VAS SPID 5 (1) 107.4	(1) 6/20 (2) 12/20	No data	No data

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	(4) sol aspirin 900 mg, n = 20	(2) 200.8	(3) 8/20		
	(5) aspirin 1200 mg, n = 20				
	(6) sol aspirin 1200 mg, n = 20	(3) 123.9	(4) 14/20		
	(7) placebo, n = 20	(4) 215.0	(5) 13/20		
	(8) sol placebo, n = 20	(5) 194.8	(6) 15/20		
		(6) 226.7	(7) 4/20		
		(7) 75.1	(8) 4/20		
		(8) 69.4			
<hr/>					
Honig 1978a	(1) aspirin 600 mg, n = 30	SPID 6	(1) 9/30	No data	No data
	(2) placebo, n = 28				
	Also 3 doses diflunisal (n = 151)	(1) 3.74	(2) 1/28		
		(2) 0.96			
<hr/>					
Jain 1985a	(1) aspirin 600 mg, n = 30	TOTPAR 5	(1) 19/30	No data	No data
	(2) placebo, n = 30	(1) 11.1			
	Also 2 doses indoprofen (n = 60)	(2) 4.0	(2) 4/30		
<hr/>					
Jain 1985b	(1) aspirin 600 mg, n = 29	TOTPAR 4	(1) 19/29	No data	Over 4 h:
	(2) placebo, n = 29	(1) 9.4			(1) 10%
	Also 3 doses indoprofen (n = 88)	(2) 6.2	(2) 12/29		(2) 41%
<hr/>					
Jain 1986a	(1) aspirin 600 mg, n = 38	TOTPAR 4	(1) 17/37	No data	Over 4 h:
	(2) placebo, n = 40	(1) 6.94			(1) 37%
	Also amfenac (n = 40)	(2) 4.79	(2) 11/39		(2) 60%
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Jain 1986b	(1) aspirin 650 mg, n = 45	SPID 6	(1) 6/45	Mean	Over 6 h:
	(2) placebo, n = 47	(1) 2.11		(1) 240 min	(1) 73%
	Also 3 doses ibuprofen (n = 136)	(2) -1.73	(2) 0/47	(2) 121 min	(2) 96%
<hr/>					
Kempf 1987	(1) aspirin buffered 600 mg, n = 24	TOTPAR 4	(1) 6/24	No data	No data
	(2) placebo, n = 24	(1) 4.54			
	Also 2 doses meclofenamate (n = 50)	(2) 2.3	(2) 2/23		
<hr/>					
Lehnert 1990	(1) aspirin 1000 mg, n = 45	SPID 6	(1) 20/45	No data	Over 6 h:
	(2) placebo, n = 42				(1) 50%
	Also paracetamol 1000 mg (n = 49)	(1) 5.0	(2) 5/42		(2) 65%
		(2) 1.5			
<hr/>					
London 1983a	(1) aspirin 650 mg, n = 40	PGE very good or excellent	(1) 12/40	No data	Over 4 h:
	(2) placebo, n = 40				(1) 15%
	Also 2 doses fluproquazone (n = 80)		(2) 7/40		(2) 40%
		(1) 12/40			Over 6 h:
		(2) 7/40			(1) 28%
					(2) 63%
<hr/>					
London 1983b	(1) aspirin 300 mg, n = 40	SPID 4	(1) 19/40	No data	Over 4 h:
	(2) aspirin 600 mg, n = 41				(1) 5%
	(3) aspirin 1200 mg, n = 40	(1) 3.29	(2) 22/41		(2) 7%
	(4) placebo, n = 39	(2) 3.73	(3) 25/40		(3) 3%
		(3) 4.38	(4) 14/39		(4) 25%
		(4) 2.61			

(Continued)

Mardirossian 1985	(1) aspirin 650 mg, n = 40 (2) placebo, n = 42 Also 2 doses of flurbiprofen (n = 82)	TOTPAR 6 (1) 7.15 (2) 3.29	(1) 11/40 (2) 3/42	Mean (1) 216 min (2) 175 min	No data
Markowitz 1985	(1) aspirin buffered 600 mg, n = 50 (2) placebo, n = 53 Also 2 doses meclofenamate (n = 102)	TOTPAR 6 (1) 4.74 (2) 1.87	(1) 5/47 (2) 0/53	No data	No data
McQuay 1987	(1) aspirin 650 mg, n = 30 (2) placebo, n = 30 Also 2 doses fluradoline (n = 60)	TOTPAR 6 (1) 5.62 (2) 2.57	(1) 6/30 (2) 1/30	(1) 3.5 (2) 2.0	Over 6 h: (1) 70% (2) 87%
Mehlisch 1984	(1) aspirin 650 mg, n = 49 (2) placebo, n = 55 Also paracetamol (n = 58)	TOTPAR 6 (1) 5.51 (2) 1.75	(1) 9/49 (2) 0/55	No data	Over 4 h: (1) 71% (2) 89% Over 6 h: (1) 76% (2) 95%
Mehlisch 1990	(1) aspirin 650 mg, n = 40 (2) placebo, n = 41 Also 2 doses FS 205-397 (n = 80)	TOTPAR 6 (1) 13.28 (2) 9.32	(1) 25/40 (2) 16/41	Mean (1) 3.5 (2) 2.4	No data
Mehlisch 1994	(1) aspirin 650 mg, n = 51 (2) placebo, n = 52 Also 2 doses diclofenac (n = 105)	TOTPAR 6 (1) 8.53 (2) 3.09	(1) 18/51 (2) 3/52	(1) 4.0 (2) 1.8	Over 4 h: (1) 60% (2) 80% Over 6 h: (1) 75% (2) 87% Over 6 h: (1) 86% (2) 94%
Nelson 1985	(1) aspirin 650 mg, n = 40 (2) placebo, n = 39 Also 3 doses etodolac (n = 122)	TOTPAR 6 (1) 6.13 (2) 3.28	(1) 9/40 (2) 3/39	No data	No data
Nelson 1994a	(1) aspirin 500 mg, n = 65 (2) placebo, n = 41 Also ibu lysine (n = 77)	TOTPAR 6 (1) 7.65 (2) 5.56	(1) 20/65 (2) 8/41	(1) 235 min (2) 174 min	Over 6 h: (1) 66% (2) 70%
Nelson 1994b	(1) aspirin 650 mg, n = 51 (2) placebo, n = 51 Also 3 doses diclofenac (153)	TOTPAR 6 (1) 11.3 (2) 3.65	(1) 26/50 (2) 4/50	(1) 8.0 (2) 2.7	Over 8 h: (1) 51% (2) 76%
Olsen 1997	(1) aspirin 650 mg, n = 40 (2) placebo, n = 90	TOTPAR 4 (1) 8.0 (2) 4.9	(1) 27/50 (2) 15/52	(1) 3.5 (2) 2.3	At 6 h: (1) 10% (2) 37%
Or 1988	(1) aspirin 650 mg, n = 27 (2) placebo, n = 27 Also mefenamic acid and mefenamic acid plus aspirin (n = 54)	TOTPAR 4 (1) 8.3 (2) 5.1	(1) 16/27 (2) 8/27	No data	No data
Parkhouse 1969	(1) aspirin 600 mg tab, n = 82 (2) aspirin 600 mg fast buffered, n = 87 (2) placebo, n = 85	TOTPAR 6 (1) 13.0 (2) 9.1	(1) 31/82 (2) 54/87 (3) 29/85	> 6 h for all treatments	Over 4 h: (1) 17% (2) 17% (3) 28% Over 6 h:

(Continued)

		(3) 8.1			(1) 28% (2) 28% (3) 40%
Patel 1991	(1) aspirin 650 mg, n = 30 (2) placebo, n = 30 Also 3 doses lornoxicam (n = 90)	TOTPAR 6 (1) 8.9 (2) 7.8	(1) 11/30 (2) 10/30	No data	No data
Rowe 1985	(1) aspirin 600 mg, n = 43 (2) placebo, n = 41 Also 2 doses meclofenate	TOTPAR 6 (1) 5.84 (2) 3.47	(1) 9/43 (2) 3/41	No data	No data
Seymour 1986	(1) aspirin sol 1200 mg, n = 30 (2) aspirin tabs 1200 mg, n = 30 (3) placebo, n = 30	SPID 5	(1) 32/60 (2) 2/30	No data	No data
Seymour 1992	(1) aspirin buffered 500 mg, n = 35 (2) aspirin buffered 1000 mg, n = 38 (3) aspirin tabs 500 mg, n = 35 (4) aspirin tabs 1000 mg, n = 37 (5) placebo, n = 37	VAS SPID 5 (1) 65.0 (2) 72.25 (3) 117.5 (4) 91.5 (5) 88.25	(1)+(3) 25/70 (2)+(4) 25/75 (5) 12/37	(1) 135 min (2) 135 min (3) 100 min (4) 95 min (5) 70 min	Over 5 h: (1) 30/35 (2) 28/38 (3) 25/35 (4) 30/37 (5) 33/37
Seymour 2003	(1) aspirin 900 mg, n = 59 (2) placebo, n = 32	VAS SPID 4 (1) 87.3 (2) 22.6	(1) 25/59 (2) 3/32	1) 1.9 2) 1.1	At 4 hrs: 1) 81% 2) 91%
Sunshine 1983a	(1) aspirin 650 mg, n = 41 (2) placebo, n = 40 Also aspirin plus codeine, and 2 doses suprofen	TOTPAR 4 (1) 12.25 (2) 6.67	(1) 27/30 (2) 11/26	No data	Over 4 h: (1) 7% (2) 48% Over 6 h: (1) 7% (2) 48%
Sunshine 1983b	(1) aspirin 600 mg, n = 29 (2) placebo, n = 31 Also 3 doses flurbiprofen (n = 92)	TOTPAR 6 (1) 10.6 (2) 2.3	(1) 14/29 (2) 0/31	No data	Over 4 h: (1) 0% (2) 23% Over 6 h: (1) 3% (2) 45%
Sunshine 1983c	(1) aspirin 600 mg, n = 30 (2) placebo, n = 30 Also zomepirac and ibuprofen (n = 60)	TOTPAR 6 (1) 7.18 (2) 1.55	(1) 14/30 (2) 0/30	No data	Over 4 h: (1) 13% (2) 17%
Sunshine 1988	(1) aspirin 648 mg, n = 15 (2) placebo, n = 15 Also 2 doses piroxicam (n = 30)	TOTPAR 6 (1) 15.3 (2) 7.3	(1) 11/15 (2) 4/15	(1) 9.1 (2) 5.6	Over 24 h: (1) 87% (2) no data
Wang 1982	(1) aspirin 650 mg, n = 2 (2) placebo, n = 25	TOTPAR 6	(1) 10/25	No data	No data

(Continued)

	Also 2 doses bicifadine (n = 50)	(1) 8.95 (2) 3.83	(2) 2/25		
Winter 1983a	(1) aspirin 650 mg, n = 37 (2) placebo, n = 35 Also oxaprozin (n = 33)	SPID 6 (1) 7.9 (2) 4.3	(1) 24/37 (2) 12/35	No data	Over 8 h: (1) 41% (2) 60%
Winter 1983b	(1) aspirin 650 mg, n = 42 (2) placebo, n = 44 Also phenyltoloxamine plus paracetamol (n = 41)	TOTPAR 4 (1) 6.19 (2) 4.76	(1) 17/42 (2) 12/44	No data	No data

PGE = patient global assessment of efficacy; PI = pain intensity; PR = pain relief; SPID = summed pain intensity difference; TOTPAR = summed total pain relief; VAS = visual analogue scale

Appendix 6. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Adverse events		Withdrawals	
		Any	Serious	Adverse event	Other
Bloomfield 1967	(1) aspirin 600 mg, n = 16 (2) placebo, n = 18 Also 3 doses of chlorphenesin (n = 50)	(1) 3/16 (2) 1/18	No data	No data	4 pts randomised, but did not complete study and excluded from analyses
Boraks 1987	(1) aspirin 650 mg, n = 41 (2) placebo, n = 39 Also flurbiprofen and dipyrrone	No usable data	No data	No data	No data
Breivik 1984	(1) aspirin 650 mg, n = 29 (2) placebo, n = 30 Also 2 doses of piroxicam	No GI discomfort or nausea, or other symptom attributable to study medication	None	None reported	None
Calimlim 1977	(1) aspirin 650 mg, n = 23 (2) placebo, n = 26 Also 2 doses of pentazocine plus aspirin	No usable data	No data	None reported	2 pts randomised but did not provide data (not linked to study med)
Clark 1989	(1) aspirin 600 mg, n = 40 (2) placebo, n = 40 Also 3 doses of carprofen, 1 of diflunisal	(1) 9/40 (2) 4/40 Most mild or moderate	None reported	None	30 pts did not take medication, 11 pts had invalid data due to protocol violations
Cooper 1977	(1) aspirin 325 mg, n = 37 (2) aspirin 650 mg, n = 37 (3) placebo, n = 40	No significant difference be-	None	None	53 pts excluded for uninterpretable form (17), confounding medication (12),

(Continued)

	Also 2 doses ibuprofen	tween treatment groups			loss to follow-up (10), inadequate baseline pain (9), asleep after 1 h (5)
Cooper 1979a	Study 2: (1) aspirin 600 mg, n = 47 (2) placebo, n = 58 Also 2 doses indoprofen (n = 96)	(1) 8/54 (2) 0/61 All mild	None	None	27 pts excluded for falling asleep (10), inaccurate timing (8), incorrect medication (7), confounding medication (2)
Cooper 1982	(1) aspirin 650 mg, n = 38 (2) placebo, n = 46 Also codeine, codeine plus aspirin, ibuprofen, codeine plus ibuprofen (n = 165)	(1) 9/38 (2) 5/46 Most mild or moderate	None reported	None	67 pts originally randomised excluded for loss to follow-up (30), incorrect administration of medication (31), missing observations (6)
Cooper 1983	(1) aspirin 650 mg, n = 43 (2) placebo, n = 44 Also 2 doses of suprofen (n = 89)	(1) 3/43 (2) 5/44 Generally "minor"	None reported	None	60 pts originally randomised excluded for loss to follow-up (3), did not take medication (37), took rescue medication < 1 h (7), other protocol violations (13)
Cooper 1986a	Study C (1) aspirin 650 mg, n = 40 (2) placebo, n = 41 Also aspirin plus codeine and 2 doses of suprofen (n = 123)	(1) 4/40 (2) 5/41	None reported	None	7 pts randomised, but excluded from analyses for loss to follow-up (4), took rescue medication < 1 h (3)
Cooper 1988	(1) aspirin 600 mg, n = 29 (2) placebo, n = 33 Also 3 doses of flurbiprofen (n = 89)	(1) 10/30 (2) 12/33 No unexpected events, none could be directly linked to study drugs	None reported	None	8 pts randomised but excluded from analyses for loss to follow-up, rescue medication < 1 h, asleep during observation times, uninterpretable responses, surgical complication, confounding medication, inappropriate administration, vomiting soon after taking medication
Cooper 1991b	(1) aspirin 650 mg, n = 46 (2) placebo, n = 48 Also 2 doses of meclofenamate	(1) 8/46 (2) 6/48 Most mild to moderate	None reported	None	7 pts randomised, but excluded from analyses for protocol violations - missing observations, early remediation
Cooper 1992	(1) aspirin 650 mg, n = 28 (2) placebo, n = 26 Also 2 doses oxaprozin (n = 50)	(1) 3/28 (2) 3/26 All mild and transient	None	None	8 pts randomised but excluded from analyses for loss to follow-up, rescue medication < 1 h, insufficient baseline pain
Coutinho 1976	(1) aspirin 650 mg, n = 15 (2) placebo, n = 15 Also codeine, propoxyphene, 2 doses fenbufen (n = 60)	(1) 4/15 (2) 0/15 But this assumes no-	None	None reported	21 pts did not complete trial - no further details

(Continued)

		body had > 1 event			
De Vroey 1977	(1) aspirin 650 mg, n = 32 (2) placebo, n = 31 Also 3 doses diflunisal	(1) 1/32 (2) 0/31	None	None	LoE: (1) 0/32 (2) 3/31
Desjardins 1983a	(1) aspirin 650 mg, n = 40 (2) placebo, n = 39 Also codeine and propiram fumarate (n = 80)	(1) 14/40 (2) 7/39	None	None	1 pt randomised to placebo was lost to follow up
Fliedner 1984	(1) aspirin 650 mg, n = 83 (2) placebo, n = 87 Also 3 doses etodolac (n = 210)	(1) 13/85 (2) 9/87 Most mild and self limiting	None	None	4 pts randomised, but excluded from analyses for loss to follow-up and confounding medication LoE: 1 pt (etodolac)
Forbes 1980	(1) aspirin 650 mg, n = 38 (2) placebo, n = 43 Also 3 doses proquazone (n = 129)	(1) 2/38 (2) 2/43 (before rescue medication) All transitory	None	None	4 pts lost to follow-up, 15 did not need analgesic, 20 pts had invalid efficacy data (fell asleep, early remedication, code broken, invalid entry, vomiting soon after taking study medication)
Forbes 1982	(1) aspirin 650 mg, n = 42 (2) placebo, n = 38	(1) 0/42 (2) no usable data All transient	None	None	11 pts from all groups excluded from efficacy analyses due to protocol violations
Forbes 1983	(1) aspirin 650 mg, n = 39 (2) placebo, n = 40 Also zomepirac and 2 doses of diflunisal (n = 120)	(1) 4/42 (2) 9/42 All transitory	None	None	2 pts did not return forms, 11 did not need analgesic, 10 had invalid efficacy data (early remedication, did not follow instructions)
Forbes 1984	(1) aspirin 650 mg, n = 24 (2) placebo, n = 28 Also ibuprofen and fendosal (n = 57)	(1) 3/25 (2) 3/30 All transitory, did not require treatment	None	None	21 pts did not need analgesic, 6 had invalid efficacy data
Forbes 1986	(1) aspirin 650 mg, n = 36 (2) placebo, n = 42 Also naproxen, codeine, and naproxen plus codeine (n = 158)	(1) 3/41 (2) 7/46 (before rescue medication) All transitory	None	None	46 pts did not need analgesic, 24 had invalid efficacy data (inappropriate medication, incomplete evaluations, surgical complication)
Forbes 1989	(1) aspirin 600 mg, n = 31 (2) placebo, n = 33 Also 3 doses flurbiprofen (n = 100)	(1) 5/38 (2) 1/39 (before rescue medication) All transitory	None	None	26 pts did not need analgesic, 24 had invalid efficacy data (inappropriate medication or rescue medication, incomplete evaluations)

(Continued)

Forbes 1990a	(1) aspirin 650 mg, n = 68 (2) aspirin 1000 mg, n = 71 (3) placebo, n = 75 Also aspirin plus caffeine (n = 66)	(1) 8/68 (2) 5/71 (3) 6/75 (before rescue medication) All transitory, did not require treatment	None	None	3 pts lost to follow-up, 43 did not need analgesic, 51 had invalid efficacy data (inappropriate medication or rescue medication, inconsistent data, vomiting soon after taking medication)
Forbes 1990b	(1) aspirin 650 mg, n = 32 (2) placebo, n = 32 Also ketorolac and paracetamol plus codeine (n = 64)	(1) 4/38 (2) 5/34 (before 2nd dose)	None	None	19 pts did not need analgesic, 14 had invalid efficacy data (inappropriate medication or rescue medication, vomiting soon after taking study medication)
Forbes 1991	(1) aspirin 650 mg, n = 41 (2) placebo, n = 39 Also 3 doses bromfenac	(1) 3/46 (2) 3/47 (before rescue medication) All transitory, did not require treatment	None	None	7 pts lost to follow up, 12 did not need analgesic, 28 had invalid efficacy data (inappropriate medication or rescue med, inconsistent or incomplete data)
Forbes 1992	(1) aspirin 650 mg, n = 38 (2) placebo, n = 38 Also ibuprofen and 3 doses bromfenac (n = 204)	(1) 5/44 (2) 2/46 (before rescue medication) All transitory, did not require treatment	None	None	3 pts lost to follow-up, 14 did not need analgesic, 41 had invalid efficacy data (inappropriate rescue medication, incomplete or inconsistent data)
Frame 1986	(1) aspirin 600 mg, n = 25 (2) placebo, n = 26 Also 3 doses ibuprofen plus codeine (n = 4)	(1) 2/25 (2) 1/26	None	None	6 pts did not need analgesic, 12 took medication incorrectly, 12 lost to follow-up or incomplete data
Gaston 1984	(1) aspirin 650 mg, n = 40 (2) placebo, n = 42	(1) 1/40 (2) 0/42	None	None	None reported
Gaston 1986	(1) aspirin 650 mg, n = 38 (2) placebo, n = 38 Also 3 doses etodolac (n = 113)	(1) 3/38 (2) 3/38 Most mild to moderate, all self limiting	None	None	All pts who took drug were included in analyses
Herbertson 1994	(1) aspirin 650 mg, n = 53 (2) placebo, n = 52 Also 2 doses diclofenac	"medical problems" (1) 5/54 (2) 2/54 All considered possibly drug-related	None	8 pts withdrew due to "medical problems", only 1 was drug-related (nausea +	None reported

(Continued)

		All mild or moderate		vomiting with diclofenac)	
Herrmann 1980a Study 1	(1) aspirin 1000 mg, n = 50 (2) placebo, n = 50 Also 2 doses fluproquazone (n = 103)	Data are provided for 4 studies combined, 2 of which are excluded studies			
Herrmann 1980b Study 2	(1) aspirin 1000 mg, n = 40 (2) placebo, n = 42 Also 2 doses fluproquazone (n = 86)				
Holland 1988	(1) aspirin 600 mg, n = 20 (2) sol aspirin 600 mg, n = 20 (3) aspirin 900 mg, n = 20 (4) sol aspirin 900 mg, n = 20 (5) aspirin 1200 mg, n = 20 (6) sol aspirin 1200 mg, n = 20 (7) placebo, n = 20 (8) sol placebo, n = 20	(3) 1/20 (6) 2/20 Mild and transient	None	None	None
Honig 1978a	(1) aspirin 600 mg, n = 30 (2) placebo, n = 28 Also 3 doses diflunisal (n = 151)	(1) 0/30 (2) 0/28	None	None	5 pts randomised but excluded from efficacy due to failing to meet inclusion criteria (3) or reasons unrelated to study (2) LoE (very severe pain): (1) 5/30 (2) 10/28
Jain 1985a	(1) aspirin 600 mg, n = 30 (2) placebo, n = 30 Also 2 doses indoprofen (n = 60)	None	None	None	None
Jain 1985b	(1) aspirin 600 mg, n = 29 (2) placebo, n = 29 Also 3 doses indoprofen (n = 88)	(1) 1/29 (2) 0/30	None	None	5 pts randomised but excluded from analyses due to early remedication (2), confounding medication (2), failure to follow instructions
Jain 1986a	(1) aspirin 600 mg, n = 38 (2) placebo, n = 40 Also amfenac (n = 40)	(1) 0/39 (2) 5/41	None	None	2 pts in (1) used confounding medication so excluded from all analyses 1 pt in each group had missing data so excluded from efficacy analyses
Jain 1986b	(1) aspirin 650 mg, n = 45 (2) placebo, n = 47 Also 3 doses ibuprofen (n = 136)	(1) 6/52 (2) 12/52	None	None	33 pts randomised but excluded from efficacy analyses due to early remedication (10), did not need analgesic or loss to follow-up (19), missing data, confounding medication, mild baseline pain

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Kempf 1987	(1) aspirin buffered 600 mg, n = 24 (2) placebo, n = 24 Also 2 doses meclofenamate (n = 50)	(1) 3/26 (2) 1/26	None	None	7 pts had missing data for PI, 11 for PR - excluded from efficacy analyses
Lehnert 1990	(1) aspirin 1000 mg, n = 45 (2) placebo, n = 42 Also paracetamol 1000 mg (n = 49)	(1) 5/45 (2) 4/42	None	None	17 pts excluded from analyses due to loss to follow-up (3), did not need analgesic (11), violation of procedures (3)
London 1983a	(1) aspirin 650 mg, n = 40 (2) placebo, n = 40 Also 2 doses fluproquazone (n = 80)	(1) 2/40 (2) 3/40 All mild or moderate	None	None	6 pts randomised but excluded from analyses since did not follow protocol
London 1983b	(1) aspirin 300 mg, n = 40 (2) aspirin 600 mg, n = 41 (3) aspirin 1200 mg, n = 40 (4) placebo, n = 39	None	None	None	No data
Mardirossian 1985	(1) aspirin 650 mg, n = 40 (2) placebo, n = 42 Also 2 doses of flurbiprofen (n = 82)	(1) 13/40 (2) 16/42 No unexpected events, none could be directly linked to study drugs	None	None	7 pts randomised but excluded from analyses for loss to follow-up (2), inappropriate remedication (2), confounding medication (1), broke code (1), did not take medication (1)
Markowitz 1985	(1) aspirin buffered 600 mg, n = 50 (2) placebo, n = 53 Also 2 doses meclofenamate (n = 102)	(1) 1/50 (2) 0/53 Generally mild	None	None	23 pts randomised but excluded from analyses due to loss to follow-up, deemed unreliable, or taking confounding medication
McQuay 1987	(1) aspirin 650 mg, n = 30 (2) placebo, n = 30 Also 2 doses fluradoline (n = 60)	(1) 9/30 (2) 11/30	None	None	None
Mehlisch 1984	(1) aspirin 650 mg, n = 49 (2) placebo, n = 55 Also paracetamol (n = 58)	No usable data No significant difference between aspirin and placebo	No data	None	12 pts randomised but excluded from analyses because loss to follow-up (3), did not comply with protocol (9)
Mehlisch 1990	(1) aspirin 650 mg, n = 40 (2) placebo, n = 41 Also 2 doses FS 205-397 (n = 80)	(1) 6/40 (2) 7/41 All mild or moderate	None	None	None
Mehlisch 1994	(1) aspirin 650 mg, n = 51 (2) placebo, n = 52 Also 2 doses diclofenac (n = 105)	(1) 7/51 (2) 4/52 All mild or moderate	None	None	None

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Nelson 1985	(1) aspirin 650 mg, n = 40 (2) placebo, n = 39 Also 3 doses etodolac (n = 122)	No usable data No significant difference between aspirin and placebo	No data	None	6 pts randomised but excluded from analyses because 3 lost to follow-up, 3 dropped out before 1 h evaluation
Nelson 1994a	(1) aspirin 500 mg, n = 65 (2) placebo, n = 41 Also ibu lysine (n = 77)	(1) 13/65 (2) 11/41	None	None	3 pts randomised but excluded from efficacy analyses due to early remedication (2), failure to record baseline pain (1)
Nelson 1994b	(1) aspirin 650 mg, n = 51 (2) placebo, n = 51 Also 3 doses diclofenac (153)	(1) 4/51 (2) 6/51	None	None	3 pts excluded from efficacy analyses - no reason given
Olsen 1997	(1) aspirin 650 mg, n = 40 (2) placebo, n = 90	Probably judged treatment-related (1) 1/50 (2) 1/52	None	None	None
Or 1988	(1) aspirin 650 mg, n = 27 (2) placebo, n = 27 Also mefenamic acid and mefenamic acid plus aspirin (n = 54)	(1) 5/27 (2) 1/27 All mild and transient	None	None	12 pts had invalid efficacy data, 8 did not follow protocol, 4 took confounding medication
Parkhouse 1969	(1) aspirin 600 mg tab, n = 82 (2) aspirin 600 mg fast buffered, n = 87 (2) placebo, n = 85	No usable data Most mild or moderate	No data	No data	No data
Patel 1991	(1) aspirin 650 mg, n = 30 (2) placebo, n = 30 Also 3 doses lornoxicam (n = 90)	(1) 2/30 (2) 2/30	None	None	Data reported for those who completed trial according to protocol
Rowe 1985	(1) aspirin 600 mg, n = 43 (2) placebo, n = 41 Also 2 doses meclofenate	No usable data	None reported	None	Only LoE reported
Seymour 1986	(1) aspirin sol 1200 mg, n = 30 (2) aspirin tabs 1200 mg, n = 30 (3) placebo, n = 30	No data	No data	No data	No data
Seymour 1992	(1) aspirin buffered 500 mg, n = 35 (2) aspirin buffered 1000 mg, n = 38 (3) aspirin tabs 500 mg, n = 35 (4) aspirin tabs 1000 mg, n = 37 (5) placebo, n = 37	No data	No data	No data	No data
Seymour 2003	(1) aspirin 900 mg, n = 59 (2) placebo, n = 32	At 4 h: 1) 51/59	None	None	14 pts enrolled but not randomised:

(Continued)

		2) 28/32			10 - insufficient pain 2 - withdrew consent 1 - adverse reaction to anaesthetic 1 - protocol violator
Sunshine 1983a	(1) aspirin 650 mg, n = 41 (2) placebo, n = 40 Also aspirin plus codeine, and 2 doses suprofen	(1) 3/42 (2) 1/40	None	None	46 pts participated in study twice. Results not used for efficacy, but included in safety. 9 pts excluded from efficacy analyses for early remedication
Sunshine 1983b	(1) aspirin 600 mg, n = 29 (2) placebo, n = 31 Also 3 doses flurbiprofen (n = 92)	No data	No data	None	16 pts excluded from all analyses due to confounding medication
Sunshine 1983c	(1) aspirin 600 mg, n = 30 (2) placebo, n = 30 Also zomepirac and ibuprofen (n = 60)	None	None	None	None
Sunshine 1988	(1) aspirin 648 mg, n = 15 (2) placebo, n = 15 Also 2 doses piroxicam (n = 30)	(1) 8/15 (2) 5/15	None reported	None	1 pt excluded due to history of drug abuse
Wang 1982	(1) aspirin 650 mg, n = 2 (2) placebo, n = 25 Also 2 doses bicifadine (n = 50)	No data	No data	No data	No data
Winter 1983a	(1) aspirin 650 mg, n = 37 (2) placebo, n = 35 Also oxaprozin (n = 33)	No data	No data	None	22 pts randomised but did not experience moderate/severe pain
Winter 1983b	(1) aspirin 650 mg, n = 42 (2) placebo, n = 44 Also phenyltoloxamine plus paracetamol (n = 41)	No usable data	None	None	34 pts randomised but excluded from analyses due to lost to follow-up, did not need analgesic, early remedication, fell asleep, confused answers

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 3, 2000

Date	Event	Description
16 April 2015	Review declared as stable	To be assessed for further updating in 2020.
25 January 2012	New citation required but conclusions have not changed	<p>New search with slightly more restrictive inclusion criteria, which excluded a small number of studies that included participants with pain following trauma rather than surgery. One new study identified, and included (Seymour 2003). New outcomes relating to use of rescue medication added: number of participants using rescue medication within specified times, and mean or median time to use of rescue medication. These are additional measures of efficacy, providing information on duration of analgesia, that have been identified as clinically useful by healthcare workers. We excluded five studies that were included in the earlier review because they included participants with pain due to trauma (Herrmann 1980c; Herrmann 1980d), fracture (Kantor 1965; Wang 1979) or fracture and musculoskeletal pain (Okun 1979), which are outside the scope of this update.</p> <p>Results for participants with at least 50% pain relief over 4 to 6 hours, and participants experiencing adverse events, were not changed. The median time to use of rescue medication was about 5 hours with 600/650 mg aspirin, and the number needed to treat to prevent one participant needing rescue medication was 5 over 4 to 8 hours.</p>
25 January 2012	New search has been performed	The search was brought up to date to January 2012.
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.
4 July 2010	Amended	Jayne Rees reverted to Jayne Edwards so that Cochrane Library citations will match bibliographic databases outside Cochrane
5 November 2008	Amended	Minor amendment to what's new and to rest of text
21 April 2008	Amended	Converted to new review format and synopsis included.

CONTRIBUTIONS OF AUTHORS

RAM and SD both carried out searches and reassessed the original trials for inclusion and new outcomes. SD entered the data into RevMan. Both authors were involved in analyses and writing. RAM and SD are responsible for updates.

DECLARATIONS OF INTEREST

RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. RAM and SD have received research support from charities, government and industry sources at various times. Support for this review came from Oxford Pain Research Funds.

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For original review

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For original review

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For original review

- Biotechnology and Biological Sciences Research Council, UK.

For original review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between protocol and review. The original review was conducted before the need for protocols, but it conforms in all essentials with protocols for recent reviews in this series for which protocols were prepared.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage] [adverse effects]; Aspirin [*administration & dosage] [adverse effects]; Pain, Postoperative [*drug therapy]

MeSH check words

Adult; Humans