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Single dose oral paracetamol (acetaminophen) for postoperative pain in adults (Review)

Toms L, McQuay HJ, Derry S, Moore RA

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[Intervention Review]

Single dose oral paracetamol (acetaminophen) for postoperative pain in adults

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 1, 2004 - this original review had been split from a previous title on 'Single dose paracetamol (acetaminophen) with and without codeine for postoperative pain'. The last version of this review concluded that paracetamol is an effective analgesic for postoperative pain, but additional trials have since been published. This review sought to evaluate the efficacy and safety of paracetamol using current data, and to compare the findings with other analgesics evaluated in the same way.

Objectives

To assess the efficacy of single dose oral paracetamol for the treatment of acute postoperative pain.

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE, the Oxford Pain Relief Database and reference lists of articles to update an existing version of the review in July 2008.

Selection criteria

Randomised, double-blind, placebo-controlled clinical trials of paracetamol for acute postoperative pain in adults.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Area under the “pain relief versus time” curve was used to derive the proportion of participants with paracetamol or placebo experiencing at least 50% pain relief over four to six hours, using validated equations. Number-needed-to-treat-to-benefit (NNT) was calculated, with 95% confidence intervals (CI). The proportion of participants using rescue analgesia over a specified time period, and time to use, were sought as measures of duration of analgesia. Information on adverse events and withdrawals was also collected.

Main results

Fifty-one studies, with 5762 participants, were included: 3277 participants were treated with a single oral dose of paracetamol and 2425 with placebo. About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo. NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 500 mg NNT 3.5 (2.7 to 4.8); 600 to 650 mg NNT 4.6 (3.9 to 5.5); 975 to 1000 mg NNT 3.6 (3.4 to 4.0). There was no dose response. Sensitivity analysis showed no significant effect of trial size or quality on this outcome.

About half of participants needed additional analgesia over four to six hours, compared with about 70% with placebo. Five people would need to be treated with 1000 mg paracetamol, the most commonly used dose, to prevent one needing rescue medication over four to six hours, who would have needed it with placebo. Adverse event reporting was inconsistent and often incomplete. Reported adverse events were mainly mild and transient, and occurred at similar rates with 1000 mg paracetamol and placebo. No serious adverse events were reported. Withdrawals due to adverse events were uncommon and occurred in both paracetamol and placebo treatment arms.

Authors' conclusions

A single dose of paracetamol provides effective analgesia for about half of patients with acute postoperative pain, for a period of about four hours, and is associated with few, mainly mild, adverse events.

PLAIN LANGUAGE SUMMARY

Single dose oral paracetamol (acetaminophen) for postoperative pain relief in adults

Pain is commonly experienced after surgical procedures, and is not always well controlled. This review assessed data from fifty-one studies and found that paracetamol provided effective pain relief for about half of participants experiencing moderate to severe pain after an operation, including dental surgery for a period of about four hours. There were no clear differences between doses of paracetamol typically used. These single dose studies did not associate paracetamol with any serious side effects.

BACKGROUND

This is an update of a review published in *The Cochrane Library* in Issue 1, 2004 on 'Single dose oral paracetamol (acetaminophen) for postoperative pain' (Barden 2004a). The title now states that the review is limited to adults.

In the clinical development of analgesics, the first step is to demonstrate that they alleviate pain. This can only be done by testing them in people with established pain, and experience has shown that this must be clinical, rather than experimentally-induced, pain. 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, also called rescue analgesia, if the pain has not diminished after about an hour. This is appropriate, because not all participants given analgesic will have significant pain relief, and about 18% of participants given placebo will have significant pain relief (Moore 2006).

The demonstration that a drug is an analgesic in an acute pain situation is important. In itself, such demonstration does not determine the utility of the tested drug in any particular situation. However, because drugs that work well in one pain condition generally work well in others, with a similar relative efficacy, acute pain trials provide useful information relevant to many other pain conditions. 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 2004b).

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 or pain relief scales immediately before the intervention, 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. Patients with inadequate pain relief after 60 to 120 minutes are given rescue medication. For these patients 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.

Paracetamol (acetaminophen) was first identified as the active metabolite of two older antipyretic drugs, acetanilide and phenacetin in the late nineteenth century. It became available in the UK on prescription in 1956, and over-the-counter in 1963 (PIC 2008). Since then it has become one of the most popular antipyretic and analgesic drugs worldwide, and is often also used in combination with other drugs.

The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of non-steroidal anti-inflammatory drugs (NSAIDs) yet, despite years of use and research, the mechanisms of action of paracetamol are not fully understood. NSAIDs act by inhibiting the activity of cyclooxygenase (COX), now recognised to consist of two isoforms, COX-1 and COX-2, which catalyses the production of prostaglandins responsible for pain and inflammation. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but is now being considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis' wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002; PIC 2008) now has little credibility, and a central mode action of paracetamol is thought to be likely (Graham 2005).

Despite a low incidence of adverse effects, paracetamol has a recognised potential for hepatotoxicity and is thought to be responsible for approximately half of all cases of liver failure in the UK (Hawton 2001), and about 40% in the USA (Norris 2008). Acute paracetamol hepatotoxicity at therapeutic doses is extremely unlikely despite reports of so-called therapeutic misadventure (Prescott 2000). In recent years legislative changes restricting pack sizes and the maximum number of tablets permitted in over-the-counter sales were introduced in the UK (CSM 1997) on the basis of evidence that poisoning is lower in countries that restrict availability (Gunnell 1997; Hawton 2001). The contribution of these changes, which are inconvenient and more costly (particularly to chronic pain sufferers), to any observed reductions in incidence of liver failure or death, remains uncertain (Hawkins 2007). There have been concerns over the safety of paracetamol in patients with compromised hepatic function (those with severe alcoholism, cirrhosis or hepatitis) but these have not been substantiated (Dart 2000; PIC 2008).

Low technology interventions such as oral paracetamol administration, used appropriately, have the potential to reduce unnecessary pain. Paracetamol is the analgesic of choice for adult patients in whom salicylates or other NSAIDs are contraindicated. Such patients include asthmatics, those with salicylate allergies, and those with a history of peptic ulcer. Paracetamol is useful for children with febrile viral illnesses, in whom aspirin is contraindicated due to the risk of Reye's syndrome (swelling of the brain that may lead to coma and death).

The previous version of this Cochrane systematic review (Barden 2004a) concluded that paracetamol is effective for postoperative pain, but additional trials have since been published. This review aims to provide robust estimates of both efficacy and harm, in a format facilitating direct comparison with other analgesics.

OBJECTIVES

To assess the efficacy and adverse effects of single dose paracetamol for acute postoperative pain using methods that permit comparison with other analgesics evaluated in the same way, using wider criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005).

METHODS

Criteria for considering studies for this review

Types of studies

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

Studies were excluded if they were:

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

Types of participants

Trials of adult patients (15 years and older) with postoperative pain of moderate to severe intensity following day surgery or inpatient surgery were included. For studies using a visual analogue scale (VAS), pain intensity was assumed to be of at least moderate intensity when the VAS score was greater than 30 mm (Collins 1997). Trials of patients with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp). Trials investigating pain due to uterine cramps alone were excluded.

Types of interventions

Oral paracetamol or matched placebo for relief of postoperative pain.

Types of outcome measures

Data were collected on the following outcomes:

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

Details of the outcomes sought and scales used to measure them are in the glossary (Appendix 4).

Search methods for identification of studies

The following electronic databases were searched:

- Cochrane CENTRAL (November 2002 for original search and July 2008 for the update).
- MEDLINE via Ovid (1966 to November 2002 for the original review and July 2008 for the update).
- EMBASE via Ovid (1966 to November 2002 for the original review and May 2008 for the update).
- Oxford Pain Database (Jadad 1996a).

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

Reference lists of retrieved studies were also manually searched. Other databases searched for the original review were not searched for the update.

Language

No language restriction was applied.

Unpublished studies

Abstracts, conference proceedings and other grey literature were not searched. Manufacturers were not contacted.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies that might be included in the updated review

Quality assessment

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

The scale used is as follows:

- Is the study randomised? If yes - 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 'Methodological quality of included studies' section below

Data management

Data were extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling were entered into RevMan 5.0.13.

Data analysis

QUOROM guidelines were followed (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one valid post-baseline assessment. For safety analyses we used number of participants randomised to each treatment group who took the study medication. Analyses were planned for different doses (where there were at least 200 participants). Sensitivity analyses were planned for pain model (dental versus other postoperative pain), trial size (39 or fewer versus 40 or more per treatment arm), and quality score (two versus three or more).

Primary outcome: number of participants achieving at least 50% pain relief

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

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

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

Secondary outcomes:

1. Use of rescue medication

(Moore 2005)

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

2. Adverse events

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

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

3. Other withdrawals

Withdrawals for reasons other than lack of efficacy (participants using rescue medication - see above) and adverse events were noted.

Relative benefit/risk estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT/NNH and 95% CI were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the relative benefit did not include the number one.

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

RESULTS

Description of studies

Fifty-one studies, with 5762 participants in total, fulfilled the entry criteria. Forty-six studies were included in the 2004 review (Bentley 1987; Berry 1975; Bhounsule 1990; Bjune 1996; Cooper 1980; Cooper 1981; Cooper 1986; Cooper 1988; Cooper 1989; Cooper 1991; Cooper 1998; Dionne 1994; Dolci 1994; Edwards 2002; Fassolt 1983; Forbes 1982; Forbes 1983; Forbes 1984a; Forbes 1984b; Forbes 1989; Forbes 1990a; Hersh 2000; Honig 1984; Jain 1986; Kiersch 1994; Laska 1983 (Study 3); Lehnert 1990; McQuay 1988; Mehlisch 1984; Mehlisch 1990; Mehlisch 1995; Moller 2000; Pinto 1984; Rubin 1984; Rubinstein 1986; Sakata 1986; Santos Pereira 1986; Schachtel 1989; Seymour 1996; Sunshine 1986; Sunshine 1989; Sunshine 1993; Winnem 1981; Winter 1979; Winter 1983; Young 1979). Five new studies (Haglund 2006; Kubitzek 2003; Moller 2005; Olson 2001; Seymour 2003) were added to this update. Details of included and excluded studies are in the corresponding "Characteristics of included studies" tables.

It is worth noting that one study (Forbes 1990b), which appeared in the 2004 review, was not included in our analysis. It does not have a paracetamol only arm and it is not clear why it appeared in the 2004 review.

Two studies contained two relevant active treatment arms, (Moller 2000; Seymour 1996) and one contained three (Laska 1983 (Study 3)). One study was a review reporting two separate groups of randomised controlled trials (RCTs) with separate placebo groups (Edwards 2002) hence the total number of comparisons for analysis was 56.

Paracetamol 500 mg was used in six studies with 561 participants (Cooper 1980; Dolci 1994; Laska 1983 (Study 3); Pinto 1984; Rubinstein 1986; Seymour 1996).

Paracetamol 600 or 650 mg was used in 19 studies with 1886 participants (Bhounsule 1990; Cooper 1981; Cooper 1988; Cooper 1991; Dionne 1994; Edwards 2002; Fassolt 1983; Forbes 1982; Forbes 1983; Forbes 1984a; Forbes 1984b; Forbes 1989; Forbes 1990a; Honig 1984; Jain 1986; Sunshine 1986; Sunshine 1989; Sunshine 1993; Young 1979).

Paracetamol 975 or 1000 mg was used in 28 studies with 3232 participants (Bentley 1987; Berry 1975; Bjune 1996; Cooper 1986; Cooper 1989; Cooper 1998; Edwards 2002; Haglund 2006; Hersh 2000; Kubitzek 2003; Kiersch 1994; Laska 1983 (Study 3); Lehnert 1990; McQuay 1988; Mehlisch 1984; Mehlisch 1990; Mehlisch 1995; Moller 2000; Moller 2005; Olson 2001; Rubin 1984; Sakata 1986; Santos Pereira 1986; Schachtel 1989; Seymour 1996; Seymour 2003; Winnem 1981; Winter 1983).

One study used a dose of 325 mg (Winter 1979) and one used a dose of 1500 mg (Laska 1983 (Study 3).

Thirty-two studies enrolled participants with dental pain following extraction of at least one impacted third molar (Bentley 1987; Cooper 1980; Cooper 1981; Cooper 1986; Cooper 1988; Cooper 1989; Cooper 1991; Cooper 1998; Dionne 1994; Dolci 1994; Edwards 2002; Forbes 1982; Forbes 1984a; Forbes 1989; Forbes 1990a; Haglund 2006; Hersh 2000; Kiersch 1994; Kubitzek 2003; Lehnert 1990; Mehlisch 1984; Mehlisch 1990; Mehlisch 1995; Moller 2000; Moller 2005; Olson 2001; Seymour 1996; Seymour 2003; Sunshine 1986; Winter 1979; Winter 1983).

Twenty-three studies involved participants with pain following 'other surgical' procedures (Berry 1975; Bhounsule 1990; Bjune 1996; Edwards 2002; Fassolt 1983; Forbes 1983; Forbes 1984b; Honig 1984; Jain 1986; Laska 1983 (Study 3); McQuay 1988; Pinto 1984; Rubin 1984; Rubinstein 1986; Sakata 1986; Santos Pereira 1986 Schachtel 1989; Sunshine 1989; Sunshine 1993; Winnem 1981; Young 1979). These were episiotomy (8/23), caesarian section (2/23) and minor gynaecological/orthopaedic/general surgical procedures (13/23).

Study duration was four hours in 15 studies, five hours in one study, six hours in 27 studies, eight hours in two studies, and 12 hours in five studies. Information about duration was unavailable for one study (Edwards 2002), although this study allowed extraction of appropriate data for the four to six hour study period.

One study (Forbes 1990a) included a multiple dose phase, but reported results for the first dose separately for at least some relevant outcomes. All other studies used only single doses.

Risk of bias in included studies

Each of the 51 studies were scored for methodological quality.

Eleven studies were given a quality score of five (Cooper 1989; Edwards 2002; Forbes 1983; Forbes 1984a; Forbes 1989; Forbes 1990a; Haglund 2006; Lehnert 1990; Moller 2005; Olson 2001; Sunshine 1986).

Twenty-five studies were given a score of four (Cooper 1980; Cooper 1981; Cooper 1988; Cooper 1998; Dolci 1994; Forbes 1984b; Hersh 2000; Jain 1986; Kiersch 1994; Kubitzek 2003; Laska 1983 (Study 3); McQuay 1988; Mehlisch 1984; Mehlisch 1990; Moller 2000; Rubin 1984; Rubinstein 1986; Schachtel 1989; Seymour 1996; Seymour 2003; Sunshine 1989; Sunshine 1993; Winnem 1981; Winter 1983; Young 1979).

Twelve studies were given a score of three (Bentley 1987; Berry 1975; Bhounsule 1990; Bjune 1996; Cooper 1986; Cooper 1991; Dionne 1994; Forbes 1982; Honig 1984; Mehlisch 1995; Pinto 1984; Santos Pereira 1986).

Three studies were given a score of two (Fassolt 1983; Sakata 1986; Winter 1979).

Full details can be found in the 'Characteristics of included studies'.

Effects of interventions

Details of study efficacy outcomes (analgesia and use of rescue medication) are in Table 1, and details of adverse events and withdrawals are in Table 2. Summary tables are provided within the text.

Number of participants achieving at least 50% pain relief

Paracetamol (all doses) versus placebo

(*see* Table 1, Summary of results A)

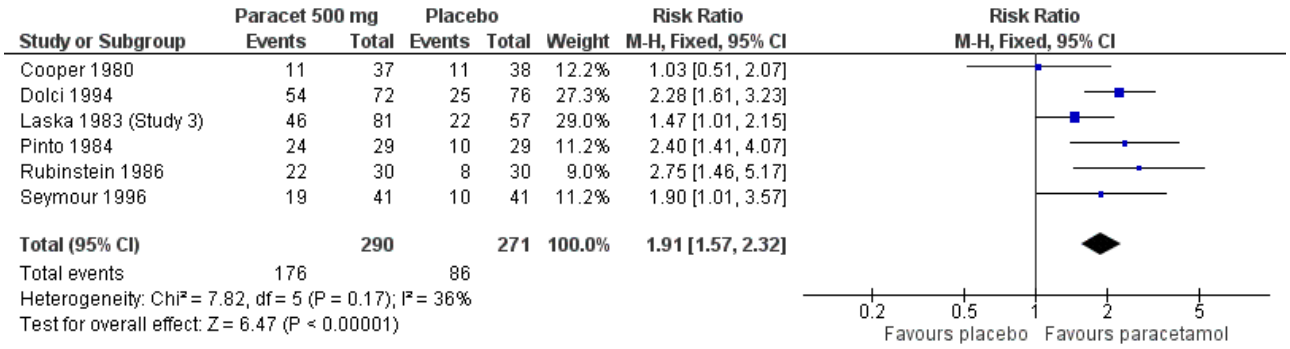
- Fifty-one studies provided data. There were 3277 participants who were treated with between 325 and 1500 mg of paracetamol and 2425 were treated with placebo.
- The proportion of participants experiencing at least 50% pain relief over four to six hours with paracetamol (325 to 1500 mg) was 46% (1507/3277).
- The proportion of participants experiencing at least 50% pain relief over four to six hours with placebo was 20% (485/2425).
- The relative benefit of treatment compared with placebo was 2.4 (2.2 to 2.6).
- The NNT for at least 50% pain relief over four to six hours was 3.9 (3.6 to 5.3). For every four participants treated with any dose of paracetamol, one would experience at least 50% pain relief who would not have done so with placebo.

Data was analysed by dose of paracetamol, and for each dose the data for dental and other surgical studies was analysed separately for the purposes of sensitivity analysis.

Paracetamol 500 mg versus placebo

(*see* Table 1; Figure 1, Summary of results A)

Figure 1. Forest plot of comparison: 3 Paracetamol 500 mg versus placebo, outcome: 3.1 Participants with at least 50% pain relief over 4 to 6 hours.

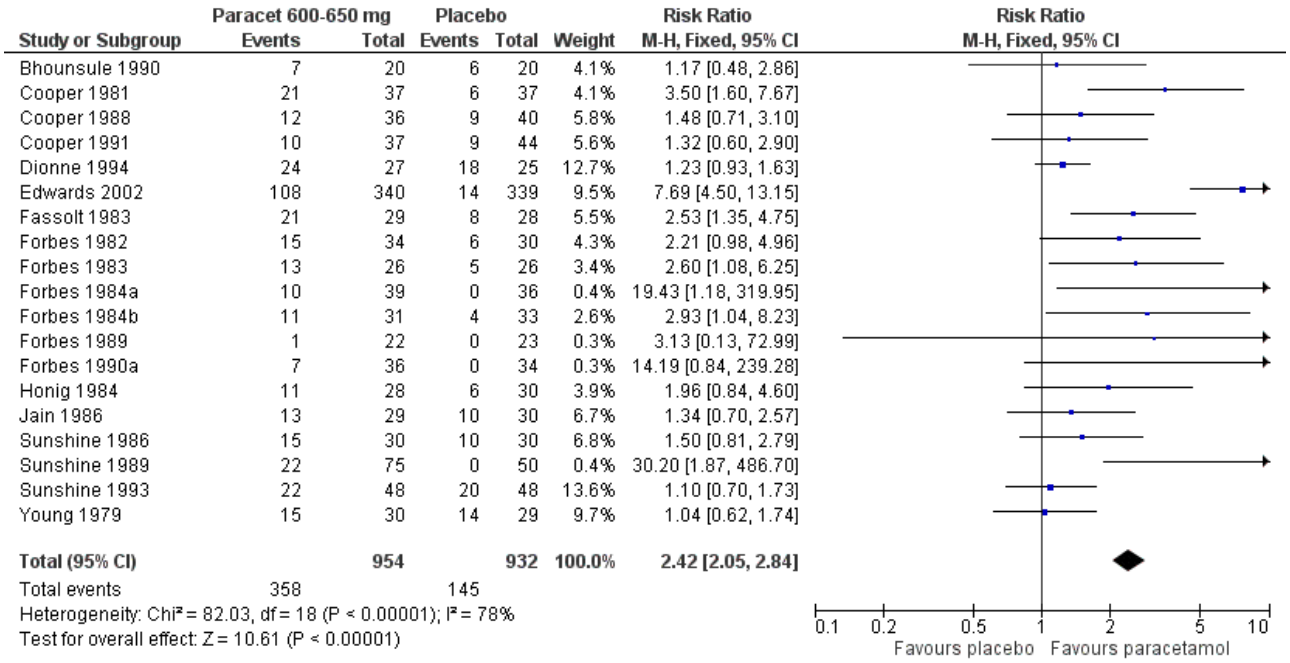


- Six studies provided data (Cooper 1980; Dolci 1994; Laska 1983 (Study 3); Pinto 1984; Rubinstein 1986; Seymour 1996). There were 290 participants who were treated with 500 mg paracetamol and 271 with placebo.
- The proportion of patients experiencing at least 50% pain relief over four to six hours with 500 mg paracetamol was 61% (176/290).
- The proportion of patients experiencing at least 50% pain relief over four to six hours with placebo was 32% (86/271).
- The relative benefit of paracetamol 500 mg compared with placebo was 1.9 (1.6 to 2.3).
- The NNT for at least 50% pain relief over four to six hours was 3.5 (2.7 to 4.8). For every four participants treated with 500 mg paracetamol, one would experience at least 50% pain relief who would not have done so with placebo.
- For dental trials only, the relative benefit of paracetamol versus placebo was 1.9 (1.4 to 2.5) and the NNT was 3.8 (2.7 to 6.4). For the other surgical trials only, the relative benefit was 1.9 (1.5 to 2.5) and the NNT was 3.2 (2.3 to 5.1).

Paracetamol 600 to 650 mg versus placebo

(*see* Table 1; Figure 2, Summary of results A)

Figure 2. Forest plot of comparison: 4 Paracetamol 600-650 mg versus placebo, outcome: 4.1 Participants with at least 50% pain relief over 4 to 6 hours.



- Nineteen studies provided data (Bhounsule 1990; Cooper 1981; Cooper 1988; Cooper 1991; Dionne 1994; Edwards 2002; Fassolt 1983; Forbes 1982; Forbes 1983; Forbes 1984a; Forbes 1984b; Forbes 1989; Forbes 1990a; Honig 1984; Jain 1986; Sunshine 1986; Sunshine 1989; Sunshine 1993; Young 1979). There were 954 participants who were treated with 600 to 650 mg paracetamol and 932 with placebo.
- The proportion of participants experiencing at least 50% pain relief over four to six hours with 600 to 650 mg paracetamol was 38% (358/954).

- The proportion of participants experiencing at least 50% pain relief over four to six hours with placebo was 16% (145/932).
- The relative benefit of paracetamol 600 to 650 mg compared with placebo was 2.4 (2.0 to 2.8).
- The NNT for at least 50% pain relief over 4 to 6 hours was 4.6 (3.9 to 5.5). For every five participants treated with 600 to 650 mg paracetamol, one would experience at least 50% pain relief who would not have done so with placebo.
- For dental trials only, the relative benefit of paracetamol 600 to 650 mg versus placebo was 3.1 (2.4 to 3.8) and the NNT was 4.2 (3.6 to 5.2). For the other surgical trials only, the relative benefit was 1.8 (1.4 to 2.3) and the NNT was 5.6 (4.0 to 9.5).

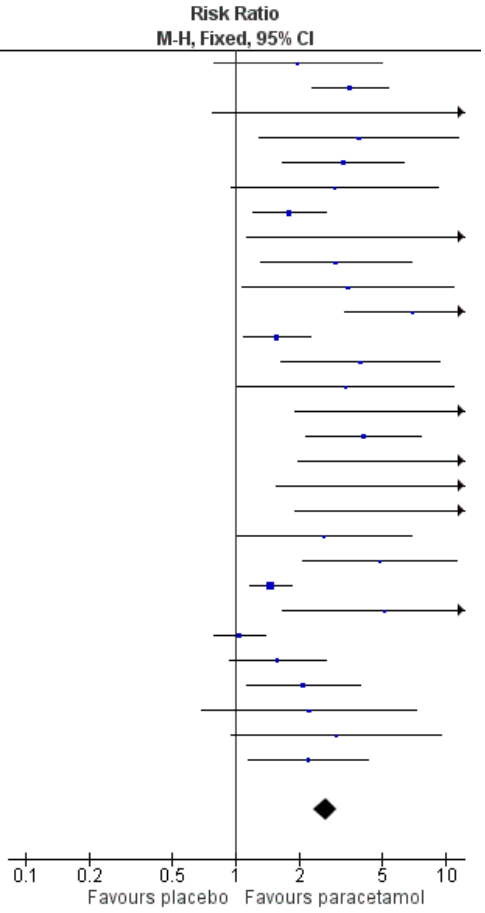
Paracetamol 975 to 1000 mg versus placebo

(*see* Table 1; Figure 3, Summary of results A)

Figure 3. Forest plot of comparison: 5 Paracetamol 975-1000 mg versus placebo, outcome: 5.1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or Subgroup	Paracet 975-1000 Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	19	41	4	17	2.1%	1.97 [0.79, 4.93]
Berry 1975	63	76	18	76	6.8%	3.50 [2.31, 5.31]
Bjune 1996	12	43	0	21	0.3%	12.50 [0.78, 201.48]
Cooper 1986	20	38	3	22	1.4%	3.86 [1.29, 11.53]
Cooper 1989	27	59	9	64	3.2%	3.25 [1.67, 6.34]
Cooper 1998	17	50	3	26	1.5%	2.95 [0.95, 9.14]
Edwards 2002	45	100	25	100	9.4%	1.80 [1.20, 2.69]
Haglund 2006	10	20	0	17	0.2%	18.00 [1.13, 286.20]
Hersh 2000	35	63	5	27	2.6%	3.00 [1.32, 6.82]
Kiersch 1994	21	92	3	45	1.5%	3.42 [1.08, 10.88]
Kubitzek 2003	45	78	7	84	2.5%	6.92 [3.32, 14.43]
Laska 1983 (Study 3)	49	81	22	57	9.7%	1.57 [1.08, 2.27]
Lehnert 1990	24	49	5	40	2.1%	3.92 [1.64, 9.34]
McQuay 1988	10	30	3	30	1.1%	3.33 [1.02, 10.92]
Mehlisch 1984	16	58	0	55	0.2%	31.32 [1.92, 509.77]
Mehlisch 1990	131	306	9	85	5.3%	4.04 [2.15, 7.60]
Mehlisch 1995	35	101	1	40	0.5%	13.86 [1.96, 97.79]
Moller 2000	12	60	0	62	0.2%	25.82 [1.56, 426.59]
Moller 2000	15	60	0	60	0.2%	31.00 [1.90, 506.59]
Moller 2005	21	50	4	25	2.0%	2.63 [1.01, 6.82]
Olson 2001	41	66	5	39	2.4%	4.85 [2.09, 11.22]
Rubin 1984	86	123	52	109	20.8%	1.47 [1.17, 1.84]
Sakata 1986	17	30	3	27	1.2%	5.10 [1.68, 15.50]
Santos Pereira 1986	22	28	22	29	8.1%	1.04 [0.78, 1.37]
Schachtel 1989	20	37	13	38	4.8%	1.58 [0.93, 2.69]
Seymour 1996	21	41	10	41	3.8%	2.10 [1.13, 3.89]
Seymour 2003	13	62	3	32	1.5%	2.24 [0.69, 7.28]
Winnem 1981	9	20	3	20	1.1%	3.00 [0.95, 9.48]
Winter 1979	20	41	9	41	3.4%	2.22 [1.15, 4.29]
Total (95% CI)		**1903**		**1329**	**100.0%**	**2.67 [2.36, 3.02]**
Total events	876		241			

Heterogeneity: Chi² = 115.64, df = 28 (P < 0.00001); I² = 76%
Test for overall effect: Z = 15.72 (P < 0.00001)



- Twenty-eight studies (29 comparisons) provided data (Bentley 1987; Berry 1975; Bjune 1996; Cooper 1986; Cooper 1989; Cooper 1998; Edwards 2002; Haglund 2006; Hersh 2000; Kiersch 1994; Kubitzek 2003; Laska 1983 (Study 3); Lehnert 1990; McQuay 1988; Mehlisch 1984; Mehlisch 1990; Mehlisch 1995; Moller 2000; Moller 2005; Olson 2001; Rubin 1984; Sakata 1986; Santos Pereira 1986; Schachtel 1989; Seymour 1996; Seymour 2003; Winnem 1981; Winter 1983). There were 1903 participants who were treated with 975 to 1000 mg paracetamol and 1329 with placebo.
- The proportion of participants experiencing at least 50% pain relief over four to six hours with 975 to 1000 mg paracetamol was 46% (876/1903).
- The proportion of participants experiencing at least 50% pain relief over four to six hours with placebo was 18% (241/1329).
- The relative benefit of paracetamol 975 to 1000 mg compared with placebo was 2.7 (2.4 to 3.0).
- The NNT for at least 50% pain relief over four to six hours was 3.6 (3.2 to 4.1). For every four participants treated with 975 to 1000 mg paracetamol, one would experience at least 50% pain relief who would not have done so with placebo.
- For dental trials only, the relative benefit of paracetamol 975 to 1000 mg versus placebo was 4.1 (3.3 to 5.2) and the NNT was 3.2 (2.9 to 3.6). For the other surgical trials only, the relative benefit was 1.7 (1.5 to 2.0) and the number needed to treat was 3.7. (3.1 to 4.7).

Paracetamol 325 mg and 1500 mg each had only one study.

No dose response was demonstrated for the outcome of at least 50% pain relief. Approximately four people would need to be

treated with paracetamol for one to experience at least 50% pain relief over four to six hours who would not have done so with placebo.

Summary of results A - participants with at least 50% pain relief

Group	No of studies	Number of participants	50% PR paracetamol	50% PR placebo	RB (95% CI)	NNT (95% CI)
All (325 to 1500 mg)	51	5762	46	20	2.4 (2.2 to 2.6)	4.1 (3.7 to 4.5)
500 mg All	6	561	61	32	1.9 (1.6 to 2.3)	3.5 (2.7 to 4.8)
500 mg Dental	3	305	56	30	1.9 (1.4 to 2.5)	3.8 (2.7 to 6.4)
500 mg Other surgical	3	256	66	34	1.9 (1.5 to 2.5)	3.2 (2.3 to 5.1)
600-650 mg All	19	1886	38	16	2.4 (2.1 to 2.8)	4.6 (3.9 to 5.5)
600-650 mg Dental	10	1276	35	12	3.1 (2.4 to 3.8)	4.2 (3.6 to 5.2)
600-650 mg Other surgical	9	610	43	25	1.8 (1.4 to 2.3)	5.6 (4.0 to 9.5)
975-1000 mg All	28	3232	46	18	2.7 (2.4 to 3.0)	3.6 (3.2 to 4.1)
975-1000 mg Dental	19	2157	41	10	4.1 (3.3 to 5.2)	3.2 (2.9 to 3.6)
975-1000 mg Other surgical	10	1075	59	32	1.7 (1.5 to 2.0)	3.7 (3.1 to 4.7)

Use of rescue medication

Number of participants using rescue medication in four to six hours

(*see* Table 1)

Thirty-two of the 51 studies reported the numbers of participants using rescue medication.

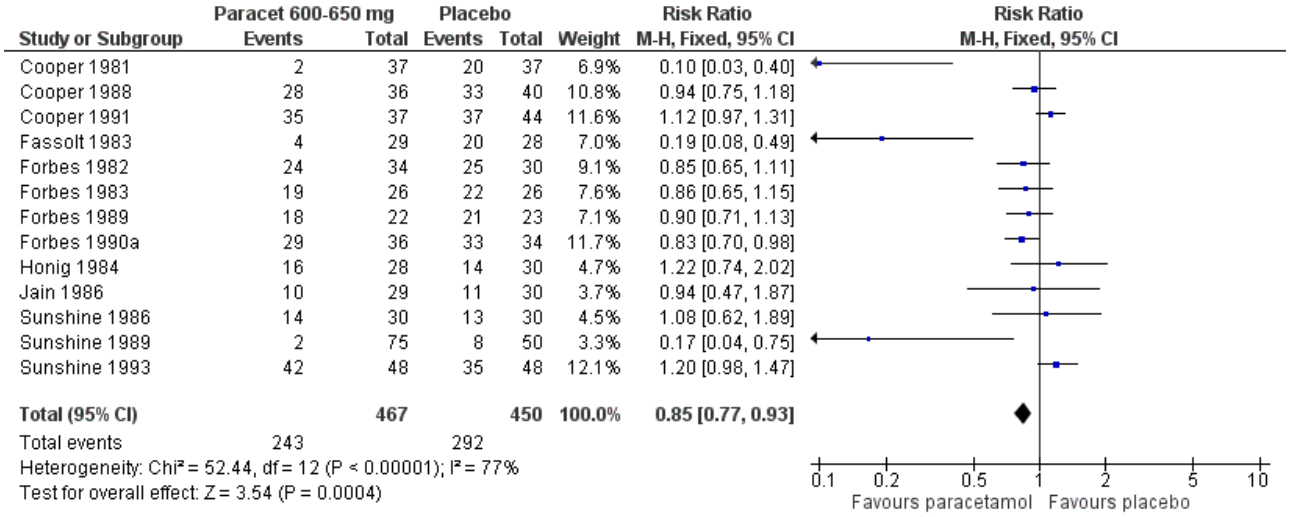
For all doses of paracetamol, the weighted mean proportion of patients using rescue medication over four to six hours was 51% for patients treated with paracetamol versus 69% for those given placebo. This gives a number needed to treat to prevent (NNTp) remedication of 5.6 (4.7 to 7.0). Six participants need to be treated with paracetamol to prevent one using rescue medication within 4 to 6 hours.

For 500 mg paracetamol, three studies reported data on use of rescue medication. The weighted mean proportion for paracetamol was 35% and for placebo 63%, giving an NNTp of 3.6 (2.6 to 6.0) (Figure 4).

Figure 4. Forest plot of comparison: 3 Paracetamol 500 mg versus placebo, outcome: 3.4 Participants using rescue medication over 4 to 6 hours.

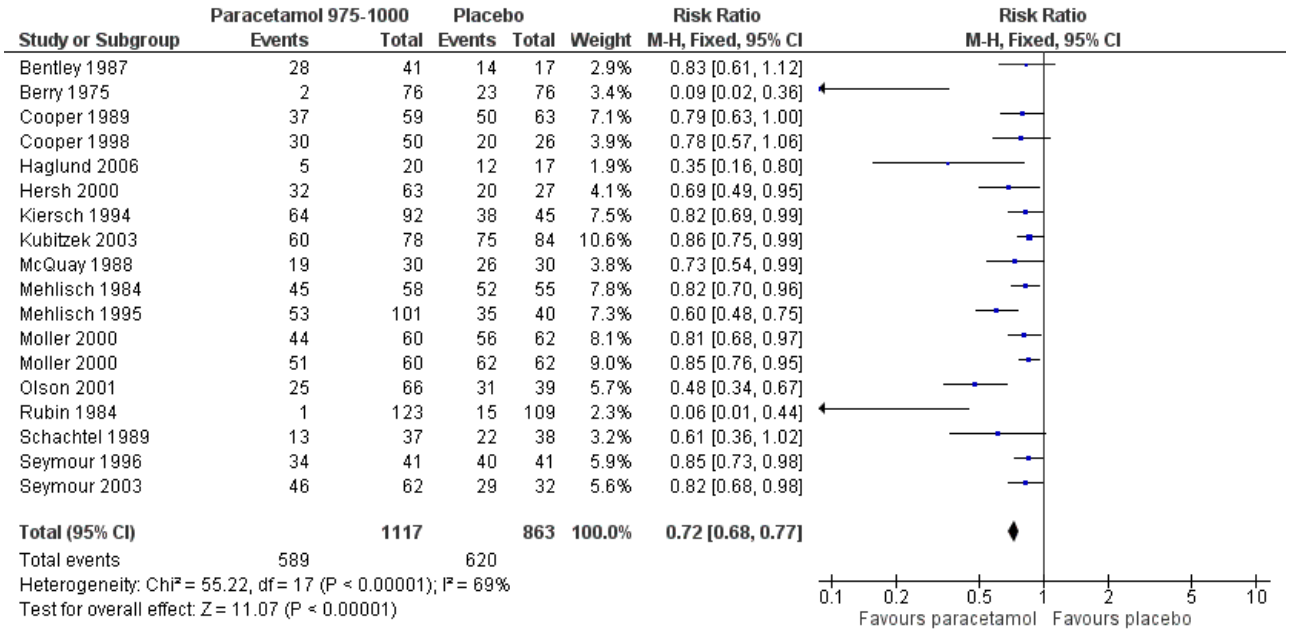
For 600 to 650 mg paracetamol, 12 studies reported data on use of rescue medication. The weighted mean proportion for paracetamol was 52% and for placebo 65%, giving an NNTp of 7.8 (5.2 to 15) (Figure 5).

Figure 5. Forest plot of comparison: 4 Paracetamol 600-650 mg versus placebo, outcome: 4.4 Participants using rescue medication over 4 to 6 hours.



For 975 to 1000 mg paracetamol, 18 studies reported data on use of rescue medication. The weighted mean proportion for paracetamol was 53% and for placebo 72%, giving an NNTp of 5.2 (4.3 to 6.7) (Figure 6).

Figure 6. Forest plot of comparison: 5 Paracetamol 975-1000 mg versus placebo, outcome: 5.4 Participants using rescue medication over 4 to 6 hours.



There was no clear dose response for this outcome, with 95% CIs for NNTp overlapping. Five people would need to be treated with 1000 mg paracetamol, the most commonly used dose, to prevent one needing rescue medication over 4 to 6 hours, who would have needed it with placebo.

Summary of results B - number using rescue medication over 4 to 6 hours

Dose	Studies	Participants	Paracetamol (%)	Placebo (%)	NNTp
All	32	3079	51	68	5.6 (4.7 to 7.0)
500 mg	3	290	35	63	3.6 (3.0 to 6.0)
600-650 mg	13	917	52	65	7.8 (5.2 to 15)
1000 mg	18	1919	53	72	5.2 (4.3 to 6.7)

Time to use of rescue medication

(see Table 1, Summary of results C)

Data for the time to use of rescue medication was not available for all studies that reported the number of participants using it. A total of 17 studies reported the median, five studies the mean, and three studies both median and mean time to use of rescue medication. Median time to rescue medication varied between 2.1 and more than six hours for active treatment and 1.0 to 3.0 hours for placebo. The weighted mean of the median time to use of rescue medication was 3.8 hours for paracetamol (all doses) versus 1.6 hours for placebo. Mean time to rescue medication varied between 2.8 and 4.7 hours for active treatment and 2.5 and 3.5 hours for placebo. The weighted mean of the mean times to use of rescue medication was 3.8 hours for paracetamol (all doses) versus 2.9 hours for placebo. There were insufficient data to analyse use of rescue medication by dose of paracetamol.

Half of the participants required rescue medication by 3.8 hours if treated with paracetamol, compared to 1.6 hours if treated with placebo.

Summary of results C - weighted mean of time to use of rescue medication

Weighted mean	Paracetamol (hr)	Placebo (hr)
Median time to rescue medication	3.8	1.6
Mean time to rescue medication	3.8	2.9

Adverse events

(*see* Table 2; Figure 7; Figure 8; Figure 9; Figure 10, Summary of results D)

Figure 7. Forest plot of comparison: 1 Paracetamol all doses versus placebo, outcome: 1.3 Participants with any adverse event.

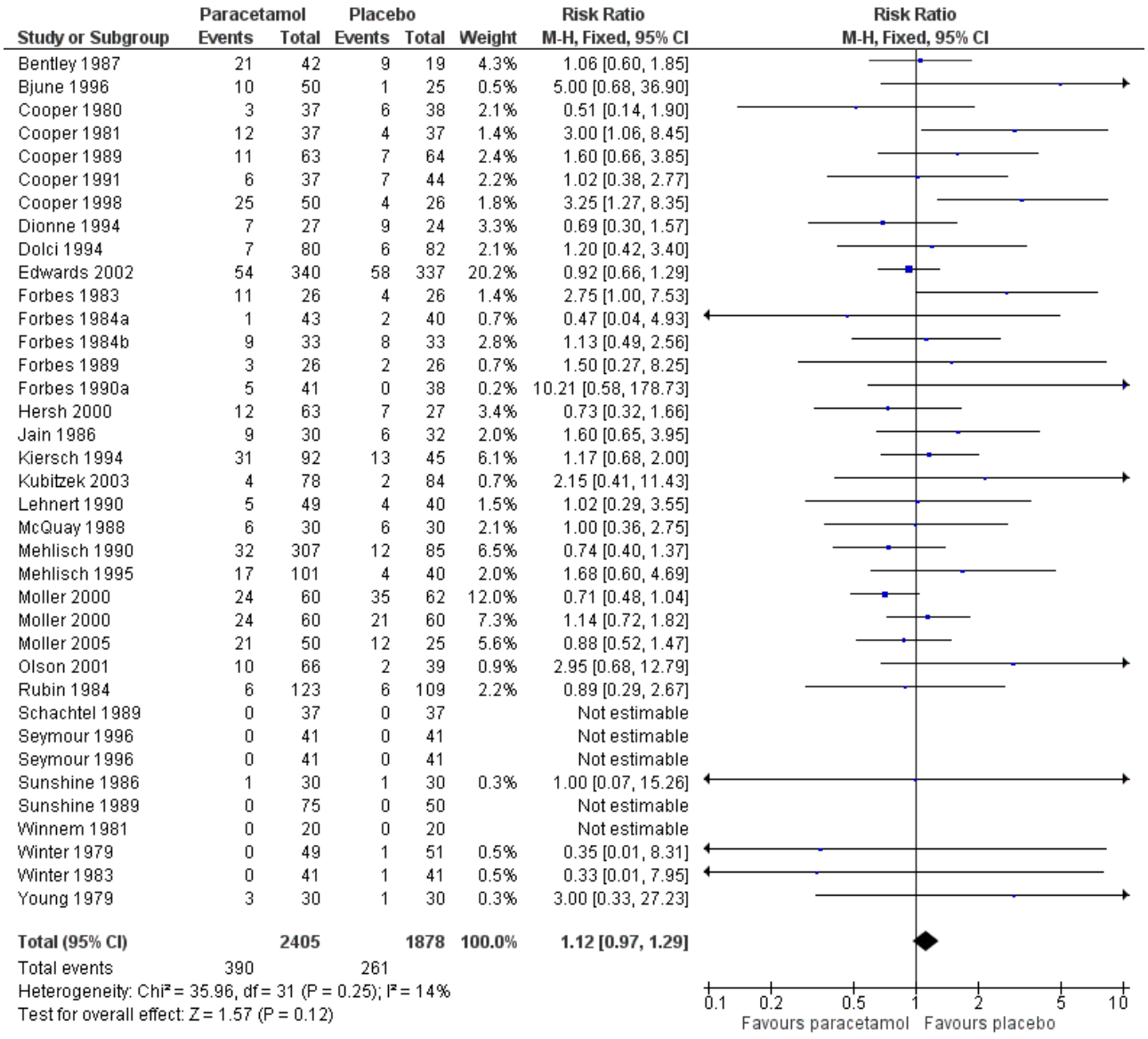


Figure 8. Forest plot of comparison: 3 Paracetamol 500 mg versus placebo, outcome: 3.5 Participants with any adverse event.

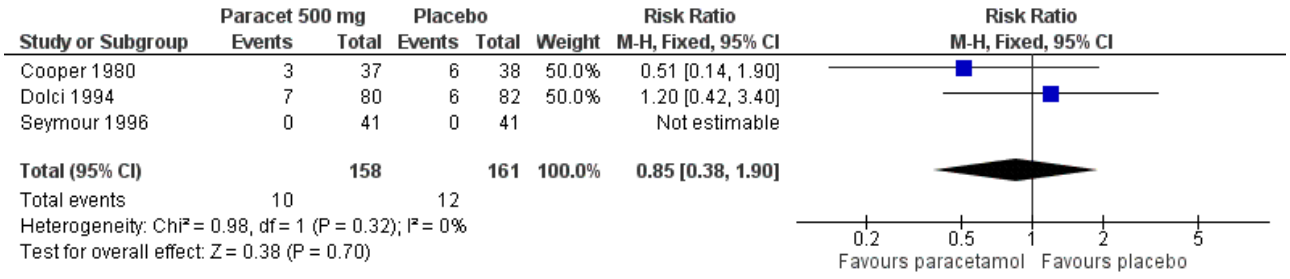


Figure 9. Forest plot of comparison: 4 Paracetamol 600-650 mg versus placebo, outcome: 4.5 Participants with any adverse event.

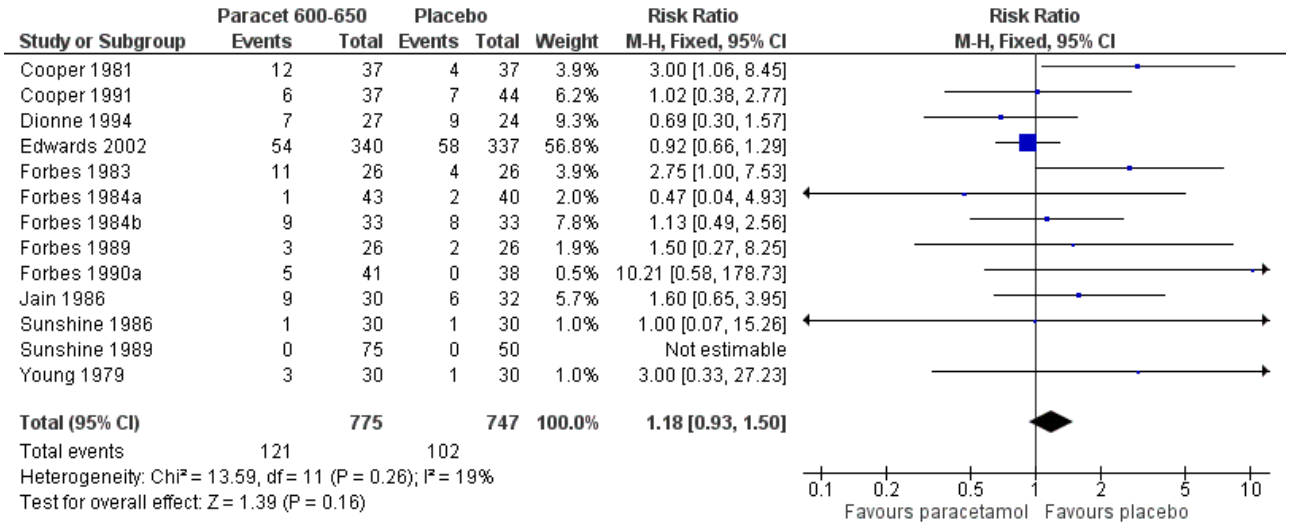
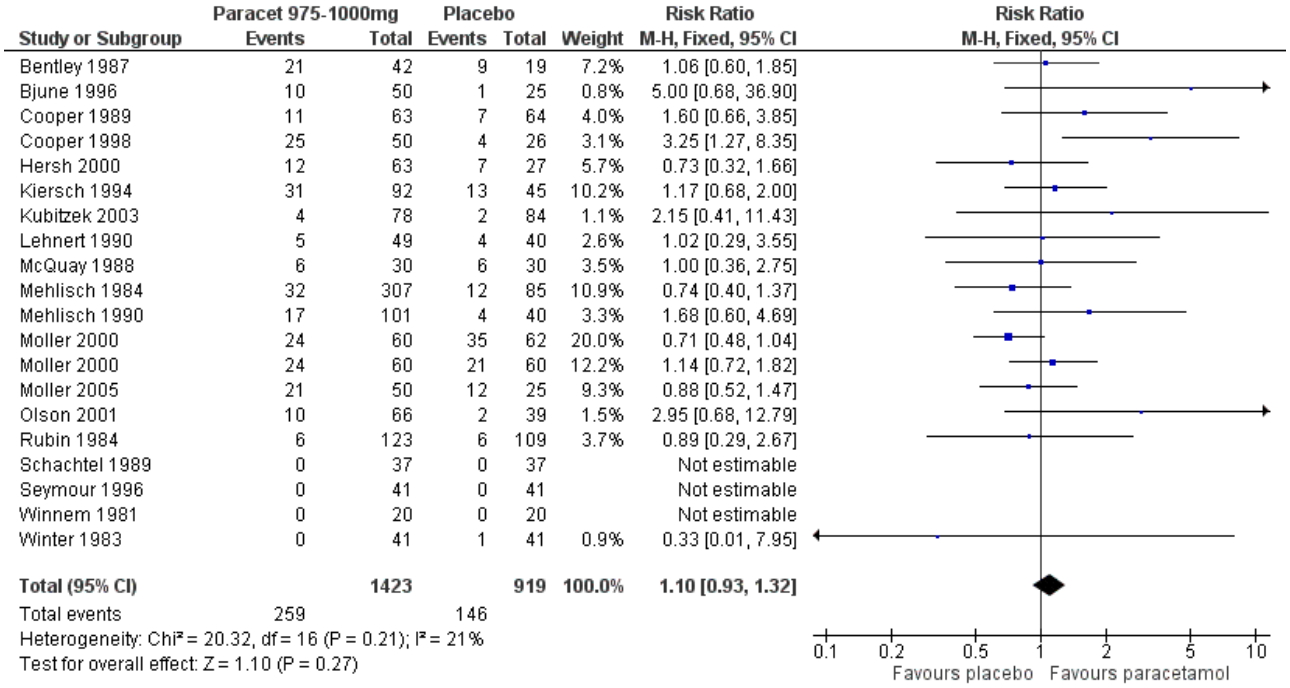


Figure 10. Forest plot of comparison: 5 Paracetamol 975-1000 mg versus placebo, outcome: 5.5 Participants with any adverse event.



Thirty-five studies reported numbers of patients with any adverse event (Bentley 1987; Bjune 1996; Cooper 1980; Cooper 1981; Cooper 1989; Cooper 1991; Cooper 1998; Dionne 1994; Dolci 1994; Edwards 2002; Forbes 1983; Forbes 1984a; Forbes 1984b; Forbes 1989; Forbes 1990a; Hersh 2000; Jain 1986; Kiersch 1994; Kubitzek 2003; Lehnert 1990; McQuay 1988; Mehlisch 1990; Mehlisch 1995; Moller 2000; Moller 2005; Olson 2001; Rubin 1984; Schachtel 1989; Seymour 1996; Sunshine 1986; Sunshine 1989; Winnem 1981; Winter 1979; Winter 1983; Young 1979).

The time over which adverse event data were collected varied from four hours to seven days. It was unclear in some studies whether the adverse event reports covered the duration of the trial, or whether they included any adverse events occurring between the end of the trial and a follow-up visit some days later. Few studies reported whether adverse event data continued to be collected after rescue medication had been taken. Reported adverse events were mainly mild and transient, and occurred at similar rates of around 16% in both paracetamol and placebo groups. There was no dose response.

One study reported a serious adverse event (Moller 2005). However, this was in a patient in a treatment arm not relevant to the review (intravenous propacetamol).

Summary of results D - participants with one or more adverse events

Dose	Studies	Participants	Paracetamol (%)	Placebo (%)	NNH (95%CI) any AE
All (325 to 1500 mg)	35	4283	16	14	not calculated
500 mg	3	319	7	6	not calculated
600-650 mg	13	1522	16	14	not calculated
975-1000 mg	19	2342	18	16	not calculated

Withdrawals

(*see* Table 2)

Patients who took rescue medication were classified as withdrawals due to lack of efficacy, and are reported under 'use of rescue medication' above.

Data on other withdrawals were generally poorly reported, probably because these were single dose studies where withdrawals for reasons other than lack of efficacy are uncommon. Some studies reported participants who had invalid data due to inadequate baseline pain, who violated a protocol, or took rescue medication within the first hour, as withdrawals or exclusions. Whether these should be included in the intention-to-treat population is arguable. Attrition due to invalid data is unlikely to affect results.

A total of six patients were reported as withdrawing due to adverse events: one each with nausea and vomiting after paracetamol 500 mg and one with fever, nausea and diarrhoea after placebo (Dolci 1994), two with vomiting after paracetamol 1000 mg (Kiersch 1994), and one for an unspecified reason after paracetamol 650 mg (Edwards 2002).

Sensitivity analysis

Sensitivity analyses were carried out to investigate the effect of various study characteristics on the primary efficacy outcome.

Pain model

Efficacy of pain relief in dental versus other surgical pain models was analysed as part of the main efficacy analysis. There were sufficient data to perform this analysis for each dose. The results are shown with the summary of results A table in the text.

Three studies with 305 participants used 500 mg in dental pain. The NNT for at least 50% pain relief over four to six hours was 3.8 (2.7 to 6.4). Three studies with 256 participants used 500 mg paracetamol in other surgical pain, with an NNT of 3.2 (2.3 to 5.1).

Ten studies with 1276 participants used 600 to 650 mg in dental pain. The NNT was 4.2 (3.6 to 5.2). Nine studies with 610 participants used 600 to 650 mg paracetamol in other surgical pain, with an NNT of 5.6 (4.0 to 9.5).

Nineteen studies with 2157 participants used 975 to 1000 mg in dental pain. The NNT was 3.2 (2.9 to 3.6). Ten studies with 1075 participants used 975 to 1000 mg paracetamol in other surgical pain, with an NNT of 3.7 (3.1 to 4.7).

There were differences between pain models in RR, but not in NNT. Response rates for active treatment were similar in both models, but placebo response rates were lower in dental than other surgery.

Study quality

A quality score of three out of five was considered adequate, given that for inclusion in the review each study had to score at least one point for being randomised and one for being blinded. There were insufficient numbers of participants in studies scoring less than three points to permit analysis by dose within each quality group.

Three studies with 214 participants had a quality score of less than three. The NNT for at least 50% pain relief over four to six hours was 2.8 (2.1 to 4.4). Fourty-eight studies with 5332 participants had quality scores of three or more, giving an NNT of 3.7 (3.4 to 4.1). Trials with lower quality scores, which are more likely to be subject to bias, produced a slightly greater, but not significantly different, treatment effect, though based on relatively small numbers (Summary of results E).

Study size

A threshold of 40 or more participants in both the treatment and placebo arms was used to assess the effect of study size on the primary outcome of at least 50% pain relief over four to six hours. Twenty-one studies had fewer than 40 participants in both treatment arms giving an NNT of 4.3 (3.5 to 5.5), whilst 30 studies (32 comparisons) had 40 or more participants in each treatment arm giving an NNT of 3.7 (3.4 to 4.2). Restricting the analysis to studies using 1000 mg paracetamol gave an NNT of 3.3 (2.5 to 5.1) for studies with fewer than 40 participants per treatment arm, and 3.6 (3.2 to 4.1) for studies with 40 or more participants per treatment arm (Summary of results E).

No significant effect of size on the primary outcome was demonstrated using 40 participants per treatment arm as the threshold.

Summary of results E - sensitivity analyses

Study characteristic	Studies	Participants	Paracetamol %	Placebo %	NNT (95%CI) 50% PR
Quality of 2	3	214	67	31	2.8 (2.1 to 4.4)
Quality 3 or more	53	5332	45	18	3.7 (3.4 to 4.1)
<40pts/arm (all doses)	21	1236	45	22	4.3 (3.5 to 5.5)
≥40pts/arm (all doses)	30	4468	45	18	3.7 (3.2 to 4.2)
<40pts/arm, 1000 mg	5	272	48	17	3.3 (2.5 to 5.1)
≥40pts/arm, 1000 mg	21	2826	45	17	3.6 (3.2 to 4.1)

DISCUSSION

Since the previous review a number of new larger studies of good methodological quality have been published, all using 1000 mg of paracetamol, which is generally regarded as the most useful dose clinically. This updated review included 561 participants treated with a single dose of paracetamol 500 mg and 1886 participants treated with 600 to 650 mg, both unchanged form the previous review. For the 975 to 1000 mg dose, 3252 participants were treated, 495 more than the earlier review (Barden 2004a) giving a more robust (Moore 1998a), but almost identical result.

The primary measure of efficacy was the proportion of patients achieving at least 50% pain relief over four to six hours. This is now generally regarded as a useful level of pain relief in acute pain, and also in chronic pain conditions such as arthritis (Moore 2008a) and neuropathic pain (Straube 2008). It has the advantage that it also highlights that not all of those given an analgesic have useful pain relief, and that interventions do not work in everyone. Participants not having a useful level of pain relief are important because therapeutic failure is to be avoided. Figures and tables therefore provide percentages of patients with outcomes, as well as statistical comparisons.

There was no significant difference in the relative benefit or NNT for at least 50% pain relief by dose. Values for NNT were 3.5 (2.7 to 4.8) for 500 mg, 4.6 (3.9 to 5.5) for 600 to 650 mg , and 3.6 (3.2 to 4.1) for 975 to 1000 mg. About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo. The differences between dental and other postsurgical pain have been noted before (Barden 2004c). Consistently lower placebo responses in the dental pain model do not effect the NNT as a measurement of efficacy. Dose response may be more sensitively determined using trials that directly compare two doses, as has been done for paracetamol 1000 mg compared with 500 mg (McQuay 2007).

Because the same methods of analyses have been used, it is possible to compare the NNT for a single dose of oral paracetamol with that of a single dose of other NSAIDs (Bandolier 2008).

- Analgesics with comparable efficacy to paracetamol include ibuprofen 100 mg (NNT 3.7 (2.9 to 4.9)), celecoxib 200 mg (NNT 3.5 (2.9 to 4.4)), naproxen 200 to 220 mg (NNT 3.4 (2.4 to 5.8), and aspirin 600 to 650 mg (NNT 4.4 (4.0 to 4.9);
- Analgesics with lower efficacy include codeine 60 mg (NNT 17 (11 to 48)) and tramadol 50 mg (NNT 8.3 (6.0 to 13));
- Analgesics with superior efficacy include ibuprofen 200 mg (NNT 2.7 (2.5 to 2.9)), naproxen 500 mg (NNT 2.7 (2.3 to 3.3)), diclofenac 50 mg (NNT 2.7 (2.4 to 3.1)), celecoxib 400 mg (NNT 2.1 (1.8 to 2.5), and etoricoxib 180 to 240 mg (NNT 1.5 (1.3 to 1.7)).

We have effective analgesics, but clinical practice finds it difficult to use effective analgesics effectively. More immediately relevant outcomes are needed than relative benefit and even numbers needed to treat. One is the time before participants with adequate pain relief require additional analgesic because the pain has returned. This can be measured in terms of the mean or median time to remedication, or the percentage of participants needing more analgesic over a particular time. This update includes both these outcomes. Previous versions of this review have not reported data on participants using rescue medication, and not all studies (32/51) provided this information.

The median time to use of rescue medication varied greatly between trials, particularly for the active treatment arms, but was generally longer for paracetamol than placebo. The weighted mean of the median time to use of rescue medication (all doses of paracetamol) at 3.8 hours is equal to or shorter than most non-selective NSAIDs (diclofenac 50 mg 3.8 hours, ibuprofen 400 mg 5.3 hours, naproxen 9.8 hours) and much shorter than etoricoxib 120 mg and rofecoxib 50 mg (20 hours or more). There was insufficient data to analyse this by separate paracetamol dose, as not all studies reporting number of patients remedicating also reported this outcome. However, the short time to remedication is unlikely to

be a result of the over-representation of low dose studies providing median time to use of rescue medication data (those using 500 mg paracetamol, which is not commonly used), as only 3 of the 17 studies in this analysis used 500 mg paracetamol, and almost 90% of the data was from studies of 600 mg or more.

About half of participants needed additional analgesia over four to six hours, compared with about 70% with placebo. Significantly fewer participants required rescue medication with paracetamol than with placebo across all doses. There was no dose response. The numbers needed to treat to prevent one patient needing rescue medication within 4 to 6 hours were: 3.6 (3.0 to 6.0) for paracetamol 500 mg, 7.8 (5.2 to 15) for 600 to 650 mg, and 5.2 (4.3 to 6.7) for 975 to 1000 mg .

Longer duration of action is desirable in an analgesic, particularly in a postoperative setting where the patient may experience postoperative nausea, or be dependent on a third party to respond to a request for rescue medication. Duration of pain relief and requirement of rescue medication information have only recently been recognised as important outcomes (Moore 2005), and a fuller evaluation of the importance of these outcomes will depend on more data being collected from other, ongoing, systematic reviews.

Assessment of adverse events is limited in single dose studies as the size and duration of the trials permits only the simplest analysis, as has been emphasised previously (Edwards 1999). Combining results was potentially hampered by the different periods over which the data was collected. There was also and uncertainty about whether adverse event data continued to be collected after rescue medication had been taken. This could disproportionately inflate adverse events in the placebo groups, which tended to use more rescue medication. Most adverse events were reported as mild to moderate in intensity, and were most likely to be related to the anaesthetic or surgical procedure (e.g. nausea, vomiting and somnolence). Although the original review compares individual adverse events, we deemed there to be insufficient data in for this analysis to be valid.

We did calculate the NNH for any adverse event, and found no significant difference between paracetamol and placebo for numbers of participants experiencing any adverse event in the hours immediately following a single dose of the study medication. No serious adverse events were reported. Withdrawals due to adverse events occurred in both paracetamol and placebo treatment arms, but were uncommon, and too few for any statistical analysis. It is important to recognise that adverse event analysis after single dose oral administration will not reflect possible adverse events occurring with use of drugs for longer periods of time. In addition, the relatively small numbers of participants, even when all the trials were combined, and short duration of studies is insufficient to detect rare but serious adverse events, which typically occur with longer use, and at rates of much less than 1 in 1000 (Moore 2008b).

The sensitivity analysis did not demonstrate an effect of trial size or quality on relative benefit or NNT. It is noteworthy that there were only three trials (214 participants) of low quality so this analysis lacked sensitivity. The evidence base is overwhelmingly of good quality, and efficacy results are unlikely to be affected by these characteristics.

The main limitation is that these were single-dose studies, and they could be criticised because pain relief, even in the acute setting, usually requires multiple dosing. That is true, but, in very general terms, pain is pain, and these single diose studies have been used for over 60 years to establish that a drug is actually an analgesic. The relative effectiveness of drugs and other interventions in this setting translates well to other settings like migraine, or musculoskeletal pain.

AUTHORS' CONCLUSIONS

Implications for practice

Paracetamol is effective for about half of patients with moderate to severe postoperative pain following various types of surgery, and has a low incidence of associated adverse effects.

Implications for research

We now have a considerable body of evidence for the efficacy of paracetamol at doses between 600 and 1000 mg. It is unlikely that further studies will alter the estimates for the primary outcome of at least 50% pain relief over four to six hours. More recent trials were generally of good quality, and efficacy data, where collected, was well reported. More consistent data on use of rescue medication, would provide better estimates of duration of analgesia, which in turn may help to decide which analgesics are most effective in the clinical setting. The quality of adverse event reporting remains problematical.

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CHARACTERISTICS OF STUDIES

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

Bentley 1987

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached moderate to severe intensity Pain assessment at baseline then hourly to 5 hours
Participants	Impacted third molar removal Mean age mid 20s N = 128
Interventions	Paracetamol 1000 mg, n = 41 Paracetamol+codeine 1000/60 mg, n = 41 Codeine 60 mg, n = 21 Placebo, n = 17
Outcomes	PI: non std 10 point scale PR: std 5 point scale Time to use of rescue medication Number of patients using rescue medication
Notes	Oxford Quality Score: R1, DB1, W1

Berry 1975

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly to 4 hours
Participants	Episiotomy Age 15+ years N = 225
Interventions	Paracetamol 1000 mg, n = 76

Berry 1975 *(Continued)*

	Propoxyphene 65 mg, n = 73
	Placebo, n = 76
Outcomes	PI: non std 4 point scale
	PR: non std 5 point scale
	PGE: std 5 pt scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
Notes	Oxford Quality Score: R1, DB1, W1
	After a reasonable period rescue analgesia could be prescribed at the investigator's discretion

Bhounsule 1990

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline base reached moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly to 6 hours
Participants	Episiotomy
	Age: adult
	N = 100
Interventions	Paracetamol 1000 mg, n = 20
	Ibuprofen 400 mg, n = 20
	Aspirin 600 mg, n = 20
	Analgin 500 mg, n = 20
	Placebo, n = 20
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
Notes	Oxford Quality Score: R1, DB2, W1

Bjune 1996

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline base reached moderate to severe intensity
	Pain assessment at 0, 30, 60 mins then hourly to 6 hours
Participants	Caesarean section Age 27 - 37 years N = 125
Interventions	Paracetamol 1000 mg, n = 50

Bjune 1996 *(Continued)*

	Paracetamol+codeine 800/60 mg, n = 50
	Placebo, n = 25
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1
	Patients asked to refrain from rescue medication for 1 hour

Cooper 1980

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment at baseline then hourly to 4 hrs
Participants	Removal of impacted 3rd Molar Mean age early 20s
	N = 298
Interventions	Paracetamol 500 mg, n = 37
	Oxycodone 5 mg, n = 42
	Paracetamol+oxycodone 500/5 mg, n = 45
	Paracetamol+oxycodone 1000/5 mg, n = 40
	Paracetamol+oxycodone 1000/10 mg, n = 45
	Placebo, n = 38
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	Time to use of rescue medication
	PGE: std 5 pt scale (patients reporting "very good" or "excellent")
Notes	Oxford Quality Score: R1, DB2, W1
	Patients asked to refrain from rescue medication for 1 hour

Cooper 1981

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity

Cooper 1981 *(Continued)*

	Pain assessment at baseline then hourly to 4 hours
Participants	Impacted third molar Mean age early 20s N = 248
Interventions	Paracetamol 650 mg, n = 37 Paracetamol+codeine 650/60 mg, n = 42 Paracetamol+d-propoxyphene 650/100 mg, n = 42 Ibuprofen 200 mg, n = 42 Placebo, n = 37
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 pt scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Cooper 1986

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at baseline then hourly to 6 hours
Participants	Oral surgery (involving bone removal) Age 16+ years N = 112
Interventions	Paracetamol 1000 mg, n = 38 Paracetamol+codeine+caffeine 1000/16/30 mg, n = 39 Placebo, n = 22
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication Number of patients reporting serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W1

Cooper 1986 *(Continued)*

	Patients asked to refrain from rescue medication for 1 hour

Cooper 1988

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 minutes then hourly to 6 hours
Participants	Impacted third molar extraction Age 18-57 years N = 165
Interventions	Paracetamol 600 mg, n = 36 Paracetamol+codeine 600+60 mg, n = 31 Placebo, n = 40
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Cooper 1989

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 minutes then hourly to 6 hours
Participants	Impacted third molar removal Age 16+ years N = 194
Interventions	Paracetamol 1000 mg, n = 59 Ibuprofen 400 mg, n = 61 Placebo, n = 64
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication

Cooper 1989 *(Continued)*

	PGE: std 5 pt scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1
	Patients asked to refrain from rescue medication for 1 hour

Cooper 1991

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed at home at 0, 30, 60 mins then hourly for 6 hours
Participants	Impacted tooth removal Age "young adults'
	N = 247
Interventions	Paracetamol 650 mg, n = 37 Paracetamol+codeine 650/60 mg, n = 39
	Zomepirac 100 mg, n = 23
	Flurbiprofen 50 mg, n = 42
	Flurbiprofen 100 mg, n = 41
	Placebo, n = 44
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	Time to use of rescue medication
	PGE: std 5 point scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W1
	Patients asked to refrain from rescue medication for 1 hour

Cooper 1998

Methods	R, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain reached moderate to severe intensity

Cooper 1998 *(Continued)*

	Pain assessed at 0, 15, 30, 45, 60 mins, then hourly to 6 hours
Participants	Impacted third molar removal Mean age 23 years N = 177 M = 75, F = 102
Interventions	Paracetamol 1000 mg, n = 50 Ketoprofen 25 mg, n = 50 Ketoprofen 100 mg, n = 51 Placebo, n=26
Outcomes	PI: std 4 pt scale and std 100m VAS PR: std 5 point scale Time to use of rescue medication Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1

Dionne 1994

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached moderate to severe intensity Pain assessed at clinic at baseline then hourly for at least the first 2 hours, then at home hourly to 6 hours
Participants	Impacted third molar removal Age 16+ years N = 135
Interventions	Paracetamol 500 mg, n = 72 Piroxicam 20 mg, n = 76 Piroxicam cyclodextrin =20 mg, n = 74 Placebo, n = 76
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event

Dionne 1994 *(Continued)*

Notes	Oxford Quality Score: R1, DB2, W1

Dolci 1994

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 minutes, then hourly to 4 hours
Participants	Impacted third molar removal Age 18+ years N = 336
Interventions	Paracetamol 500 mg, n = 72 Piroxicam 20 mg, n = 76 Piroxicam cyclodextrin =20 mg, n = 74 Placebo, n = 76
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1.5 hours

Edwards 2002

Methods	6 RCTs, DB, single oral dose Medication administered when baseline pain reached a moderate to severe intensity
Participants	Dental and gynaecologic or orthopaedic pain patients Age 16-83 years N = 879
Interventions	Dental: Paracetamol 650 mg, n = 340 Placebo, n = 339 Gynae/ortho: Paracetamol 975 mg, n = 100

Edwards 2002 *(Continued)*

	Placebo, n = 100
Outcomes	PI: non std 5 point scale and std 100 mm VAS PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Dental trials only: Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1

Fassolt 1983

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly to 6 hours
Participants	"Simple surgery" : 15+ named surgical interventions Age 18+ years N = 146
Interventions	Paracetamol 650 mg, n = 29 Suprofen 200 mg, n = 32 Suprofen 400 mg, n = 28 Paracet+suprofen 650/100 mg, n = 29 Placebo, n = 28
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication
Notes	Oxford Quality Score: R1, DB1, W0 Patients asked to refrain from rescue medication for 2 hours

Forbes 1982

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at baseline then hourly to 12 hours

Forbes 1982 *(Continued)*

Participants	Impacted third molar removal Age 15+ years N = 177
Interventions	Paracetamol 600 mg, n = 34 Paracetamol+codeine 600/60 mg, n = 31 Diflusinal 500 mg, n = 32 Diflusinal 1000 mg, n = 32 Placebo, n = 30
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 2 hours

Forbes 1983

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0, 30, 60 ,90, 120 mins then hourly to 12 hours
Participants	General, gynaecological or orthopaedic surgery Age 19+ years N = 132
Interventions	Paracetamol+codeine 600/60 mg, n = 26 Paracetamol 600 mg, n = 26 Diflusinal 500 mg, n = 26 Diflusinal 1000 mg, n = 28 Placebo, n = 26
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication

Forbes 1983 *(Continued)*

	PGE: std 5 point scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1
	Patients asked to refrain from rescue medication for 1 hour

Forbes 1984a

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment at baseline then hourly for 6 hours
Participants	Impacted third molar removal Age 15+ years
	N = 191
Interventions	Paracetamol 650 mg, n = 39
	Phenyltoloxamine 60 mg, n = 33
	Patacetamol+phenyltoxolamine 650/60 mg, n = 40
	Placebo, n = 36
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	Time to use of rescue medication
	PGE: std 5 point scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1
	Patients asked to refrain from rescue medication for 2 hours

Forbes 1984b

Methods	RCT, DB, single oral dose, 5 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed 0, 15, 30, 60 mins then hourly to 6 hours

Forbes 1984b *(Continued)*

Participants	General, gynaecological or orthopaedic surgery Age 18 + years N = 132
Interventions	Paracetamol 650 mg, n = 31 Nalbuphine 30 mg, n = 32 Paracetamol+nalbuphine 650/30 mg, n = 33 Placebo, n = 33
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1 Patients asked to refrain from rescue medication for 2 hours

Forbes 1989

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at baseline then hourly to 12 hours
Participants	Impacted third molar removal Age 15+ years N = 107
Interventions	Paracetamol 600 mg, n = 22 Paracetamol+codeine 600/60 mg, n = 17 Flurbiprofen 100 mg, n = 26 Placebo, n = 23
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication

Forbes 1989 *(Continued)*

	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB2, W1
	Patients asked to refrain from rescue medication for 2 hours

Forbes 1990a

Methods	RCT, DB, single oral dose, 6 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessed at baseline then hourly to 6 hours
Participants	Impacted third molar extraction
	Age 15+ years
	N = 269
Interventions	Paracetamol 600 mg, n=36 Paracetamol + Codeine 600/60 mg, n=38
	Ibuprofen 400 mg, n = 32
	Ketorolac 10 mg, n = 31
	Ketorolac 20 mg, n = 35
	Placebo, n = 34
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication
Notes	Oxford Quality Score: R2, DB2, W1
	Rescue medication permitted after 2 hours

Haglund 2006

Methods	RCT, DB, single and multiple oral dose, 6 parallel groups
	Medication administered when pain reached a moderate to severe intensity
	Pain assessment at baseline then at every 30 mins up to 8 hours
Participants	Impacted third molar extraction
	Mean age 27 years
	N =112
	M = 50, F= 37

Haglund 2006 *(Continued)*

Interventions	Rofecoxib/paracetamol 50/1000 mg, n = 34 Rofecoxib 50 mg, n = 36 Paracetamol 1000 mg, n = 20 Placebo, n = 17
Outcomes	PI: std 100mm VAS PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") at 4 and 8 hours Number of patients using rescue medication Number of patients reporting any adverse events, and serious adverse events Number if patients withdrawing due to adverse events
Notes	Oxford quality score: R2, DB2, W1

Hersh 2000

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 15, 30, 45, 60, 90 and 120 mins then hourly to 12 hours
Participants	Removal of impacted third molar Age: 16+ years N = 210
Interventions	Paracetamol capsule 1000 mg, n = 63 Ibuprofen liquigel 200 mg, n = 61 Ibuprofen liquigel, 400 mg n = 59 Placebo, n = 27
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Honig 1984

Methods	RCT, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly to 6 hours
Participants	Elective surgery: abdominal, orthopaedic, rectal, thoracic & vascular Age 19-87 years N = 116
Interventions	Paracetamol 600 mg, n = 28 Paracetamol+codeine 600/60 mg, n = 28 Codeine 60 mg, n = 28 Placebo, n = 25
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of serious adverse events
Notes	Oxford Quality Score: R1, DB2, W0

Jain 1986

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 15, 30, 60 mins then hourly to 6 hours
Participants	General, gynaecological or orthopaedic surgery Age 18 - 70 years N = 128
Interventions	Paracetamol 650 mg, n = 30 Nalbuphine 30 mg, n = 34 Paracet+nalbuphine 650/30 mg, n = 32 Placebo, n = 32
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events
Notes	Oxford Quality Score: R2, DB1, W1

Jain 1986 *(Continued)*

	Patients asked to refrain from rescue medication for 2 hours

Kiersch 1994

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 20, 30, 40, 60 mins then hourly to 12 hours
Participants	Removal of impacted 3rd molar Age 14+ years N = 232
Interventions	Paracetamol 1000 mg, n = 92 Naproxen Na 440 mg, n = 89 Placebo, n = 45
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W1 Patients asked to refrain from rescue medication for 2 hours

Kubitzek 2003

Methods	RCT, DB, Single oral dose, three parallel groups Medication administered when baseline pain reached a moderate to severe intensity within 8 hours Pain assessment at 0, 30, 60 mins then hourly up to 6 hours
Participants	Removal of impacted third molars Mean age 26 years N = 245 M ~ 40%, F ~ 60%
Interventions	Paracetamol 1000 mg, n = 78 Diclofenac K 25 mg, n = 83 Placebo, n = 84

Kubitzek 2003 *(Continued)*

Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "good and "excellent") Time to use of rescue medication Number of patients using rescue medication Number of patients reporting any adverse events and serious adverse events Number of patients withdrawing due to adverse events
Notes	Oxford Quality Score: R2, DB2, W1

Laska 1983 (Study 3)

Methods	RCT, DB, single oral dose, 7 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly for 4 hours
Participants	Post partum (post episiotomy and post-surgical) Age: not stated N = 552
Interventions	Paracetamol 500 mg, n = 81 Paracetamol 1000 mg, n = 81 Paracetamol 1500 mg, n = 81 Paracetamol+caffeine 500/65 mg, n = 80 Paracetamol+caffeine 1000/130 mg, n = 78 Paracetamol+caffeine 1500/195 mg, n = 80 Placebo, n = 57
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Lehnert 1990

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 minutes then hourly to 6 hours

Lehnert 1990 *(Continued)*

Participants	Removal of impacted 3rd molar Age: not stated N = 150
Interventions	Paracetamol 1000 mg, n = 49 Aspirin 1000 mg, n = 45 Placebo, n = 40
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non std 5 point scale Time to use of rescue medication Number of patients reporting any adverse event
Notes	Oxford Quality Score: R2, DB1, W1

McQuay 1988

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60, 90, and 120 minutes then hourly to 6 hours
Participants	Post elective orthopaedic surgery Age 18 - 70 years N = 158
Interventions	Paracetamol 1000 mg, n = 30 Bromfenac 5 mg, n = 30 Bromfenac 10 mg, n = 30 Bromfenac 25 mg, n = 30 Placebo, n = 30
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Mehlisch 1984

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached moderate to severe intensity Pain assessment at 0, 30 mins then hourly to 6 hours
Participants	Oral surgery (involving bone removal) Age 16+ years N = 174
Interventions	Paracetamol 1000 mg, n = 58 Aspirin 650 mg, n = 49 Placebo, n = 55
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W1 Patients asked to refrain from rescue medication for 1 hour

Mehlisch 1990

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, and 60 minutes then hourly for 6 hours
Participants	Oral surgery (various procedures) Age 17 - 64 years N = 706
Interventions	Paracetamol 1000 mg, n = 306 Ibuprofen 400 mg, n = 306 Placebo, n = 85
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients reporting any adverse event and serious adverse events
Notes	Oxford Quality Score: R1, DB2, W1

Mehlisch 1995

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 15, 45, 60, 90 and 120 minutes the hourly to 6 hours
Participants	Removal of impacted third molar Age 15+ years N = 240
Interventions	Paracetamol 1000 mg, n = 101 Ibuprofen 400 mg, n = 98 Placebo, n = 40
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W1 Patients asked to refrain from rescue medication for 1 hour

Moller 2000

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 10, 20, 30, 45, 60 mins, then hourly to 4 hours
Participants	Removal of impacted third molar Mean age 25 years N = 315
Interventions	Paracetamol tablet 1000 mg, n = 60 Placebo tablet, n = 60 Paracetamol effervescent, n = 60 Placebo effervescent, n = 62
Outcomes	PI: std 4 point scale, std 100 mm VAS PR: std 5 point scale PGE std 5 point scale (patients reporting "good and "excellent")

Moller 2000 *(Continued)*

	Time to use of rescue medication
Notes	Oxford Quality Score: R1, DB2, W1

Moller 2005

Methods	RCT, DB, Single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 15, 30, 45, 60 mins then hourly to 6 hours
Participants	Removal of impacted third molars Mean age 24 years N = 175 M = 72, F = 103
Interventions	Paracetamol tablet 1000 mg, n = 50 Propacetamol 2 g iv bolus, n = 50 Propacetamol 2 g 15 min infusion, n = 50 Placebo, n = 25
Outcomes	PI: std 100 mm VAS PR: std 5 point scale PGE: std 5 point scale (patients reporting "good and "excellent") Time to use of rescue medication Number of patients using rescue medication Number of patients reporting any adverse events and serious adverse events Number of patients withdrawing due to adverse events
Notes	Oxford Quality Score: R2, DB2, W1

Olson 2001

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Patient assessment at 0, 15, 30, 45, 60 mins then hourly to 6 hours
Participants	Removal of impacted third molars Mean age: 23 years N = 239 M = 76, F = 163

Olson 2001 *(Continued)*

Interventions	Paracetamol 1000 mg, n = 66 Ketoprofen 25 mg, n = 67 Ibuprofen liquigel 400 mg, n = 67 Placebo, n = 39
Outcomes	PI: std 4 point scale and std 100 mm VAS PR: std 5 point scale PGE std 5 point scale (patients reporting "good and "excellent") Time to use of rescue medication Number of patients using rescue medication Number of patients reporting any adverse events and serious adverse events Number of patients withdrawing due to adverse events
Notes	Oxford Quality Score: R2, DB2, W1

Pinto 1984

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 mins then hourly to 4 hours
Participants	Tonsillectomy Mean age: 23 years N = 85
Interventions	Paracetamol 500 mg, n = 29 Dipyrone 500 mg, n = 29 Placebo, n = 29
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non std 5 point scale Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse eventst
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 2 hours

Rubin 1984

Methods	RCT, DB, single oral dose, 4 parallel groups

Rubin 1984 *(Continued)*

	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment at 0, 30, 60 mins then hourly to 4 hours
Participants	Episiotomy (post uncomplicated delivery) Age 13 - 40 years
	N = 500
Interventions	Paracetamol 1000 mg, n = 123
	Paracetamol+aspirin 648/648 mg, n = 123
	Aspirin+caffeine 800/6.5 mg, n = 121
	Placebo, n = 109
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1
	Patients asked to refrain from rescue medication for 2 hours

Rubinstein 1986

Methods	RCT, DB, single oral dose, 3 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment at 0, 30 mins, then hourly to 4 hours
Participants	Urological surgery
	Age: 18-94 years
	N = 90
Interventions	Paracetamol 500 mg, n = 30
	Dypyrone 500 mg, n = 30
	Placebo, n = 30
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event

Rubinstein 1986 *(Continued)*

	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1

Sakata 1986

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 30, 60 mins, then hourly to 4 hours
Participants	Mainly orthopaedic surgery Mean age: 32 years N = 86
Interventions	Paracetamol 1000 mg, n = 30 Dipyrone 1000 mg, n = 30 Placebo, n = 27
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non standard scale
Notes	Oxford Quality Score: R1, DB1, W0

Santos Pereira 1986

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0, 15, 30, 60 mins the hourly to 4 hours
Participants	Orthopaedic surgery Age: 37-40 years N = 85
Interventions	Paracetamol 1000 mg, n = 28 Dipyrone 1000 mg, n = 28 Placebo, n = 29
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication

Santos Pereira 1986 *(Continued)*

Notes	Oxford Quality Score: R1, DB2, W1

Schachtel 1989

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0, 30, 60 mins the hourly to 4 hours
Participants	Episiotomy (post uncomplicated delivery) Age 16 - 37 years N = 115
Interventions	Paracetamol 1000 mg, n = 37 Ibuprofen 400 mg, n = 36 Placebo, n = 38
Outcomes	PI: std 4 point scale PR: std 5 point scale Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R2, DB1, W1 Patients asked to refrain from rescue medication for 1 hour

Seymour 1996

Methods	RCT, DB, single oral dose, 5 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 15, 30, 45, 60 mins, then hourly to 6 hours
Participants	Removal of impacted third molar Age: adult N = 206
Interventions	Paracetamol 500 mg, n = 41 Paracetamol 1000 mg, n = 41 Ketoprofen 12.5mg, n = 42 ketoprofen 25 mg, n = 41 Placebo, n = 41

Seymour 1996 *(Continued)*

Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Seymour 2003

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessment at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120 and 240 mins
Participants	Removal of impacted third molar Mean age: 25 years N =153 M = 63, F = 104
Interventions	Paracetamol 1000 mg, n = 62 Aspirin (soluble) 900 mg, n = 59 Placebo, n = 32
Outcomes	PI: std 100 mm VAS PGE: non std 5 point scale Time to use of rescue medication Number of patients using rescue medication Number of patients reporting any adverse events and serious adverse events Number of patients withdrawing due to adverse events
Notes	Oxford Quality Score: R1, DB2, W1

Sunshine 1986

Methods	RCT, DB, single oral dose, 6 parallel groups Medication administered when baseline pain reached a moderate to severe intensity

Sunshine 1986 *(Continued)*

	Pain assessment at 0, 30 mins, then hourly to 6 hours
Participants	Removal of impacted third molar Age 16+ years N = 182
Interventions	Paracetamol 650 mg, n = 30 Paracetamol+codeine 650/60 mg, n = 31 Flurbiprofen 50 mg, n = 31 Flurbiprofen 100 mg, n = 29 Zomepirac 100 mg, n = 31 Placebo, n = 30
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale (patients reporting "very good" or "excellent") Number of patients using rescue medication Number of patients reporting any adverse event and serious adverse events Number of patients withdrawing due to adverse event 'Overall improvement': non std 7 point scale
Notes	Oxford Quality Score: R2, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Sunshine 1989

Methods	RCT, DB, single oral dose, 3 parallel groups Medication administered when baseline pain reached severe intensity only Pain assessment at 0, 30, 60 mins, then hourly to 6 hours
Participants	Episiotomy (multiparous inpatients) Age 18+ years N = 200
Interventions	Paracetamol 650 mg, n = 75 Placebo, n = 50
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non std 4 point scale 'Overall improvement' 7 point scale Time to use of rescue medication

Sunshine 1989 *(Continued)*

Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 2 hours

Sunshine 1993

Methods	RCT, DB, single oral dose then multi-dose, 5 parallel groups Medication administered when baseline pain reached severe intensity Pain assessment at 0, 30, 60 mins then hourly to 8 hours
Participants	Caesarean Section Age 18+ years N = 240 All F
Interventions	Paracetamol 650 mg, n = 48 Paracetamol/oxycodone 650/10 mg, n = 48 Ketoprofen 50 mg, n = 48 Ketoprofen 100 mg, n = 48 Placebo, n = 48
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE std 5 point scale (patients reporting "good and "excellent") Number of patients using rescue medication
Notes	Oxford Quality Score: R1, DB2, W1 Patients asked to refrain from rescue medication for 1 hour

Winnem 1981

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0, 30, 60 mins then hourly to 6 hours
Participants	Orthopaedic surgery Age 17 - 63 years N = 80
Interventions	Paracetamol 1000 mg, n = 20 Tiaramide 100 mg, n = 20

Winnem 1981 *(Continued)*

	Tiaramide 200 mg, n = 19
	Placebo, n = 20
Outcomes	PI: std 4 point scale and std 100 mm VAS
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1
	Patients asked to refrain from rescue medication for 2 hours

Winter 1979

Methods	RCT, DB, single oral blind, 4 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment 0, 30, 60 mins then hourly to 4 hours and at 6 hours
Participants	Oral surgery (various procedures)
	Age: 18-65 years
	N = 231
Interventions	Paracetamol 325 mg, n = 49
	Orphenadrine 25 mg, n = 50
	Paracetamol/orphenadrine 325/25 mg, n = 50
	Placebo, n = 51
Outcomes	PI: std 4 point scale
	Time to use of rescue medication
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB1, W0
	Patients asked to refrain from rescue medication for 2 hours

Winter 1983

Methods	RCT, DB, single oral dose, 4 parallel groups
	Pain assessed at 0 and 60 mins then hourly to 4 hours
Participants	Oral Surgery (various procedures)

Winter 1983 *(Continued)*

	Age 16 - 75 years
	N = 168
Interventions	Paracetamol 1000 mg, n = 41
	Paracetamol+caffeine 1000/130 mg, n = 40
	Caffeine 130 mg, n = 42
	Placebo, n = 41
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std 5 point scale (patients reporting "very good" or "excellent")
	Number of patients using rescue medication
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1
	Patients asked to refrain from rescue medication for 2 hours

Young 1979

Methods	RCT, DB, single oral dose, 4 parallel groups
	Medication administered when baseline pain reached a moderate to severe intensity
	Pain assessment at 0, 30, 60 mins then hourly up to 4 hours
Participants	Various elective procedures Age 12-83 years
	N = 120
Interventions	Paracetamol 650 mg, n = 30
	Paracetamol+butorphanol 650/4 mg, n = 30
	Butorphanol 4 mg, n = 30
	Placebo, n = 29
Outcomes	PI: std 4 point scale
	PR: std 5 point scale
	PGE: std point scale (patients reporting "very good" or "excellent")
	Number of patients reporting any adverse event and serious adverse events
	Number of patients withdrawing due to adverse event
Notes	Oxford Quality Score: R1, DB2, W1

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

Study	Reason for exclusion
Becker 1990	Pain only assessed for 2 hours after administration of the interventions
Behotas 1992	Interventions were given when pain was "of sufficient intensity that analgesia would normally be given" and data was only presented for pain relief over the first hour
Bjørnsson 2003a	No placebo group (paracetamol vs naproxen)
Bjørnsson 2003b	No placebo group (paracetamol vs ibuprofen)
Breivik 1998	Regular 3 hr medication. Unable to extract single dose data for 4 to 6 hour period
Breivik 1999	No placebo group (paracetamol vs. paracetamol codeine vs. diclofenac)
Cooper 1984	Inadequate description of method. Excluded as did not state whether allocation was randomised or if the studies (summary of five trials) were double blind
Daftary 1980	Inadequate description of method. Excluded as did not state whether allocation was randomised
Davie 1978	Inadequate description of method. Excluded as did not state whether allocation was randomised
Dolci 1993	Contains a subset of patients from another included report [Dolci 1994]. Confirmed by author as duplication
Filtzer 1980	No placebo control (paracetamol v naproxen v pentazocine)
Forbes 1990b	Did not include paracetamol alone
Frerich 1981	Inadequate description of method. Excluded as did not state whether allocation was randomised
Gallardo 1980	Inadequate description of method. Excluded as did not state whether allocation was randomised
Gallardo 1990	Pain only assessed for 3 hours after administration of the interventions
Gomez-Jimenez 1980	Dental study; no placebo control. Episiotomy study; pain scale used was 5 point - therefore not validated for the data extraction method used
Hopkinson 1973	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient
Hopkinson 1974	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient
Hopkinson 1976	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient
Huang 1986	Intervention administered preoperatively. Therefore inadequate baseline pain
Irvine 1982	No placebo control (paracetamol vs diflunisal)

Study	Reason for exclusion
Lasagna 1967	Analysis presented does not provide SPID or TOTPAR or sufficient data to allow their calculation. Therefore there is no data presented which is validated for the data extraction method used
Lecointre 1991	No placebo control (paracetamol vs tiaprofenic acid)
Levin 1974	PI scale was 5 point and therefore not validated for the data extraction method. No results for pain relief which would allow the calculation of TOTPAR were presented. Global evaluation was in the opinion of the investigator and not the patient
Lokken 1980	Intervention given 4 times a day postoperatively irrespective of baseline pain
Marti 1993	No placebo control (paracetamol vs lysine clonixinate)
Matthews 1984	Intervention administered immediately after surgery before anaesthetic wore off. Therefore inadequate baseline pain
Mayer 1984	Did not include paracetamol alone
McMahon 1987	Used a 4 point pain relief scale which is not validated for the data extraction method used. No information was provided about the pain intensity scale used
Melzack 1983	All patients requesting another medication during the study were excluded from the analysis. Therefore the derived outcomes (SPID/TOTPAR) calculated from this data is probably not comparable with those calculated the standard way. The standard practice is to exclude patients remedicating in the first hour to hour and a half. Those taking alternative medication after that are included in the analysis, allocating the pain intensity score at time of remedication for all remaining time points to calculate SPID, or a pain relief score of "none" for all further timepoints in the calculation of TOTPAR
Melzack 1985	Intervention given 3- to 45 mins after surgery, irrespective of baseline pain
Muckle 1984	No placebo control (paracetamol vs flurbiprofen). Also is a multiple dose trial which does not provide separate data for the first dose
Ottinger 1990	Did not include paracetamol alone
Ouellette 1986	No placebo control (paracetamol plus codeine v naproxen)
Parkhouse 1967	Inadequate description of method. Report did not state whether allocation was randomised. Also there was no description of the scales used. Hourly pain relief data provided was in the opinion of the investigator no the patient
Quiding 1983	Patients instructed to take tablets "when pain relief was needed". Mean baseline pain minus 2 standard deviations was less than 30 mm for all interventions (>30 mm equates to at least moderate pain), therefore it is probable that patients with mild pain were included
Ragot 1991	No placebo control (paracetamol vs mefenamic acid)
Rodrigo 1987	Two dose study. Second dose was permitted two hours after the first. No data was provided to allow the calculation of SPID over 4 to 6 hours for the first dose
Rodrigo 1989	No placebo control (paracetamol vs diflunisal)
Scoren 1987	Did not include paracetamol alone
Seymour 1983	Multiple dose trial. No data gathered on the first dose

Study	Reason for exclusion
Skjelbred 1977	No placebo control (paracetamol vs aspirin)
Skoglund 1991	Interventions administered 3 hours after surgery irrespective of baseline pain
Skovlund 1991	Patients were included if they asked for an analgesic. There is no further information provided on the baseline pain level except in figure 3 which shows pain recorded at t = 0 of less than 30 mm. Therefore it must be excluded as some included patients did not experience at least moderate baseline pain
Smith 1975	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient
Spivach 1984	No placebo control (paracetamol vs aspirin vs caffeine vs a combination of the three)
Sunshine 1988	Outline of 5 studies. Study 3 and 4 compare paracetamol plus codeine to placebo. Study 4 is a duplicate of an included RCT. Study 3 cannot be included as the report fails to state whether the allocation to each intervention was randomised
Sveen 1975	Intervention administered immediately after surgery before anaesthetic wore off. Therefore inadequate baseline pain
Terrence 1983	Inadequate description of method. Report did not state whether allocation was randomised
Torabinejad 1994	Intervention administered immediately after surgery before anaesthetic wore off. Therefore inadequate baseline pain
Vangen 1988	Did not include paracetamol alone
Veltmann 1980	No placebo control (paracetamol v paracetamol plus phenylephrine)
Wittenberg 1984	Did not include paracetamol alone

DATA AND ANALYSES

Comparison 1. Paracetamol all doses versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	51	5762	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [2.21, 2.64]
2 Participants using rescue medication over 4 to 6 hours	32	3182	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.71, 0.78]
3 Participants with any adverse event	35	4283	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.97, 1.29]
4 Participants with any adverse event, dental	25	3439	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]

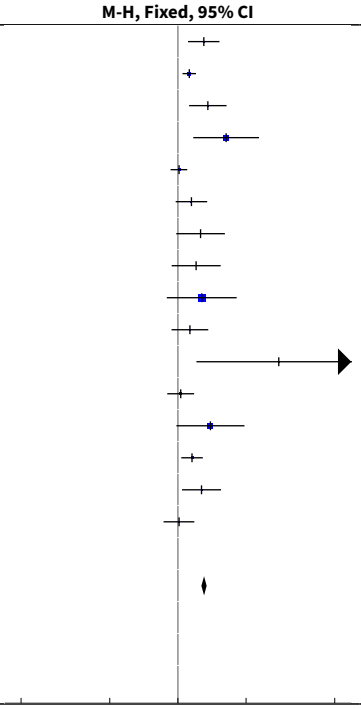
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Participants with any adverse event, surgical	10	846	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.04, 2.33]

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

Study or subgroup	Paracetamol, all doses n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	19/41	4/17		1.11%	1.97[0.79,4.93]
Berry 1975	63/76	18/76		3.53%	3.5[2.31,5.31]
Bhounsule 1990	7/20	6/20		1.18%	1.17[0.48,2.86]
Bjune 1996	12/43	0/21		0.13%	12.5[0.78,201.48]
Cooper 1980	11/37	11/38		2.13%	1.03[0.51,2.07]
Cooper 1981	21/37	6/37		1.18%	3.5[1.6,7.67]
Cooper 1986	20/38	3/22		0.75%	3.86[1.29,11.53]
Cooper 1988	12/36	9/40		1.67%	1.48[0.71,3.1]
Cooper 1989	27/59	9/64		1.69%	3.25[1.67,6.34]
Cooper 1991	10/37	9/44		1.61%	1.32[0.6,2.9]
Cooper 1998	17/50	3/26		0.77%	2.95[0.95,9.14]
Dionne 1994	24/27	18/25		3.66%	1.23[0.93,1.63]
Dolci 1994	54/72	25/76		4.77%	2.28[1.61,3.23]
Edwards 2002	45/100	25/100		4.9%	1.8[1.2,2.69]
Edwards 2002	108/340	14/339		2.75%	7.69[4.5,13.15]
Fassolt 1983	21/29	8/28		1.6%	2.53[1.35,4.75]
Forbes 1982	15/34	6/30		1.25%	2.21[0.98,4.96]
Forbes 1983	13/26	5/26		0.98%	2.6[1.08,6.25]
Forbes 1984a	10/39	0/36		0.1%	19.43[1.18,319.95]
Forbes 1984b	11/31	4/33		0.76%	2.93[1.04,8.23]
Forbes 1989	1/22	0/23		0.1%	3.13[0.13,72.99]
Forbes 1990a	7/36	0/34		0.1%	14.19[0.84,239.28]
Haglund 2006	10/20	0/17		0.11%	18[1.13,286.2]
Hersh 2000	35/63	5/27		1.37%	3[1.32,6.82]
Honig 1984	11/28	6/30		1.14%	1.96[0.84,4.6]
Jain 1986	13/29	10/30		1.93%	1.34[0.7,2.57]
Kiersch 1994	21/92	3/45		0.79%	3.42[1.08,10.88]
Kubitzek 2003	45/78	17/84		3.21%	2.85[1.79,4.54]
Laska 1983 (Study 3)	49/81	8/19		2.54%	1.44[0.82,2.5]
Laska 1983 (Study 3)	46/81	7/19		2.22%	1.54[0.83,2.86]
Laska 1983 (Study 3)	53/81	7/19		2.22%	1.78[0.97,3.27]
Lehnert 1990	24/49	5/40		1.08%	3.92[1.64,9.34]
McQuay 1988	10/30	3/30		0.59%	3.33[1.02,10.92]
Mehlisch 1984	16/58	0/55		0.1%	31.32[1.92,509.77]
Mehlisch 1990	131/306	9/85		2.76%	4.04[2.15,7.6]
Mehlisch 1995	35/101	1/40		0.28%	13.86[1.96,97.79]
Moller 2000	12/60	0/62		0.1%	25.82[1.56,426.59]
Moller 2000	15/60	0/60		0.1%	31[1.9,506.59]
Moller 2005	21/50	4/25		1.05%	2.63[1.01,6.82]
Olson 2001	41/66	5/39		1.23%	4.85[2.09,11.22]

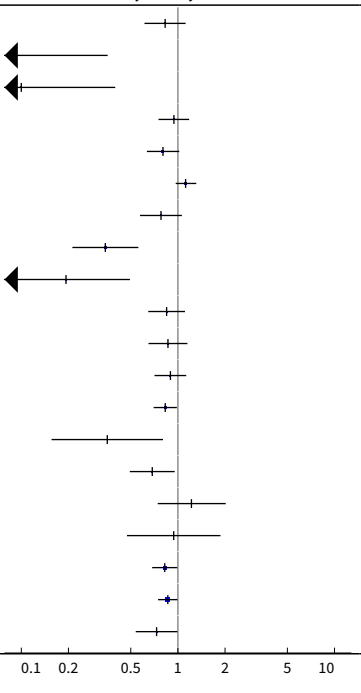
Favours placebo — Favours paracetamol

Study or subgroup	Paracetamol, all doses n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pinto 1984	24/29	10/29		1.96%	2.4[1.41,4.07]
Rubin 1984	86/123	52/109		10.81%	1.47[1.17,1.84]
Rubinstein 1986	22/30	8/30		1.57%	2.75[1.46,5.17]
Sakata 1986	17/30	3/27		0.62%	5.1[1.68,15.5]
Santos Pereira 1986	22/28	22/29		4.24%	1.04[0.78,1.37]
Schachtel 1989	20/37	13/38		2.51%	1.58[0.93,2.69]
Seymour 1996	21/41	5/21		1.3%	2.15[0.95,4.89]
Seymour 1996	19/41	5/20		1.32%	1.85[0.81,4.24]
Seymour 2003	13/62	3/32		0.78%	2.24[0.69,7.28]
Sunshine 1986	15/30	10/30		1.96%	1.5[0.81,2.79]
Sunshine 1989	22/75	0/50		0.12%	30.2[1.87,486.7]
Sunshine 1993	22/48	20/48		3.92%	1.1[0.7,1.73]
Winnem 1981	9/20	3/20		0.59%	3[0.95,9.48]
Winter 1979	34/49	22/51		4.23%	1.61[1.12,2.32]
Winter 1983	20/41	9/41		1.76%	2.22[1.15,4.29]
Young 1979	15/30	14/29		2.79%	1.04[0.62,1.74]
Total (95% CI)	**3277**	**2485**		**100%**	**2.42[2.21,2.64]**
Total events: 1497 (Paracetamol, all doses), 472 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=187.42, df=55(P<0.0001); I^2=70.65%					
Test for overall effect: Z=19.8(P<0.0001)					

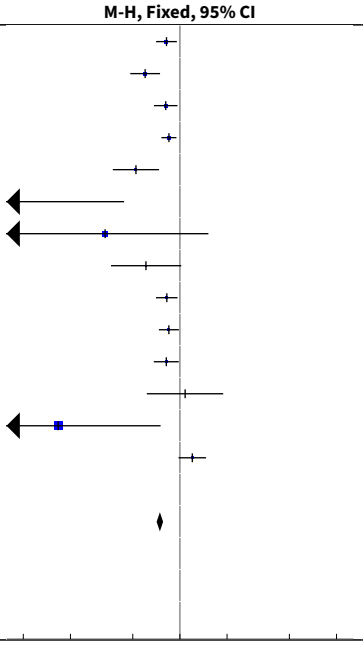


Analysis 1.2. Comparison 1 Paracetamol all doses versus placebo, Outcome 2 Participants using rescue medication over 4 to 6 hours.

Study or subgroup	Paracetamol, all doses n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	28/41	14/17		1.86%	0.83[0.61,1.12]
Berry 1975	2/76	23/76		2.17%	0.09[0.02,0.36]
Cooper 1981	2/37	20/37		1.88%	0.1[0.03,0.4]
Cooper 1988	28/36	33/40		2.94%	0.94[0.75,1.18]
Cooper 1989	37/59	50/64		4.52%	0.8[0.63,1.02]
Cooper 1991	35/37	37/44		3.18%	1.12[0.97,1.31]
Cooper 1998	30/50	20/26		2.48%	0.78[0.57,1.06]
Dolci 1994	15/72	46/76		4.21%	0.34[0.21,0.56]
Fassolt 1983	4/29	20/28		1.92%	0.19[0.08,0.49]
Forbes 1982	24/34	25/30		2.5%	0.85[0.65,1.11]
Forbes 1983	19/26	22/26		2.07%	0.86[0.65,1.15]
Forbes 1989	18/22	21/23		1.93%	0.9[0.71,1.13]
Forbes 1990a	29/36	33/34		3.2%	0.83[0.7,0.98]
Haglund 2006	5/20	12/17		1.22%	0.35[0.16,0.8]
Hersh 2000	32/63	20/27		2.64%	0.69[0.49,0.95]
Honig 1984	16/28	14/30		1.27%	1.22[0.74,2.02]
Jain 1986	10/29	11/30		1.02%	0.94[0.47,1.87]
Kiersch 1994	64/92	38/45		4.81%	0.82[0.69,0.99]
Kubitzek 2003	60/78	75/84		6.8%	0.86[0.75,0.99]
McQuay 1988	19/30	26/30		2.45%	0.73[0.54,0.99]

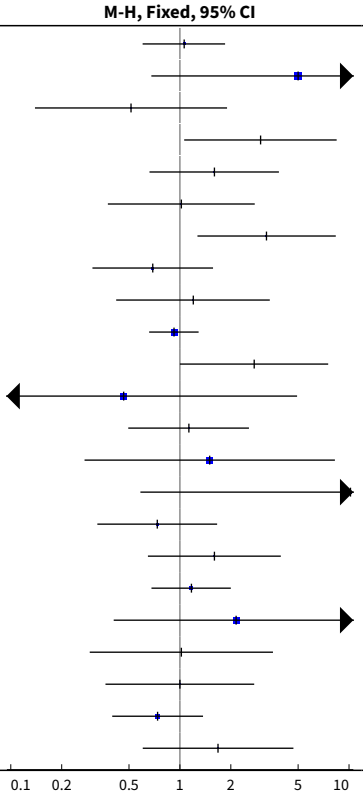


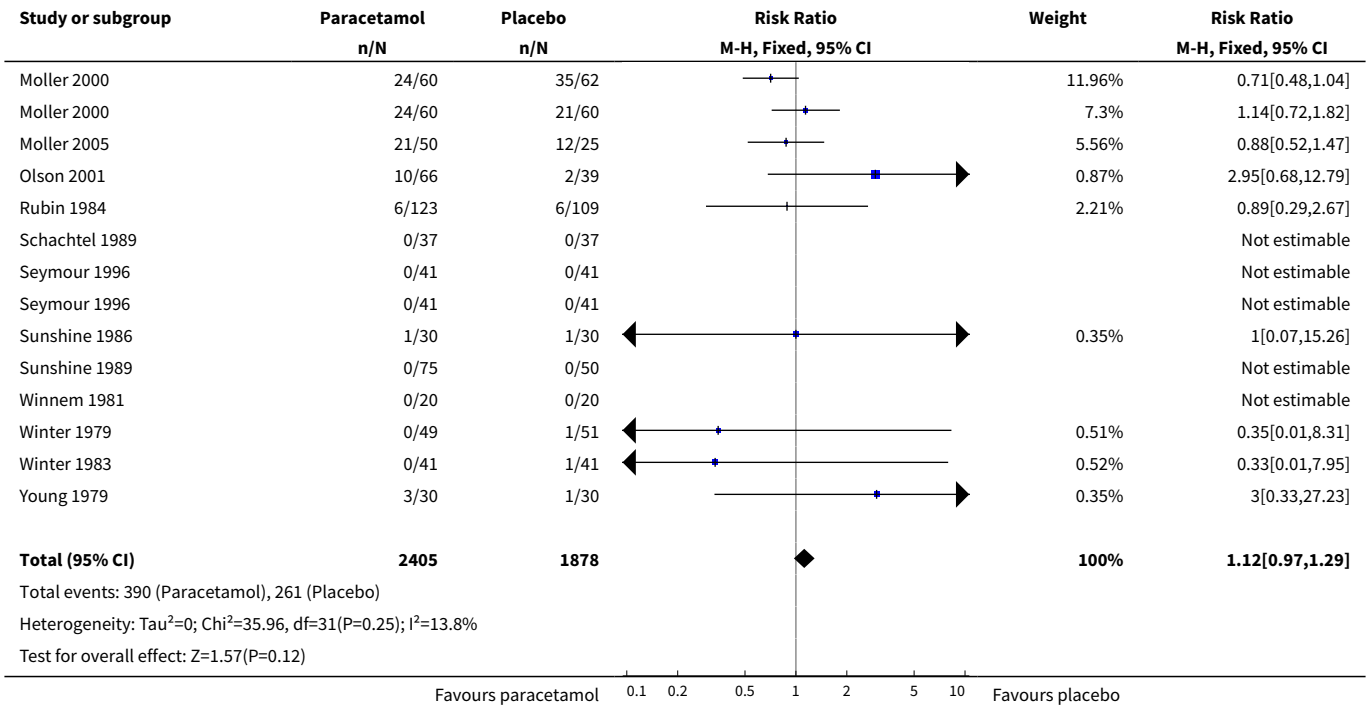
Study or subgroup	Paracetamol, all doses n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehlisch 1984	45/58	52/55		5.03%	0.82[0.7,0.96]
Mehlisch 1995	53/101	35/40		4.72%	0.6[0.48,0.75]
Moller 2000	44/60	56/62		5.19%	0.81[0.68,0.97]
Moller 2000	51/60	62/62		5.79%	0.85[0.76,0.95]
Olson 2001	25/60	31/39		3.54%	0.52[0.37,0.74]
Rubin 1984	1/123	15/109		1.5%	0.06[0.01,0.44]
Rubinstein 1986	2/30	6/30		0.56%	0.33[0.07,1.52]
Schachtel 1989	13/37	22/38		2.04%	0.61[0.36,1.02]
Seymour 1996	33/41	40/41		3.77%	0.83[0.7,0.97]
Seymour 1996	34/41	40/41		3.77%	0.85[0.73,0.98]
Seymour 2003	46/62	29/32		3.6%	0.82[0.68,0.98]
Sunshine 1986	14/30	13/30		1.22%	1.08[0.62,1.89]
Sunshine 1989	2/75	8/50		0.9%	0.17[0.04,0.75]
Sunshine 1993	42/48	35/48		3.3%	1.2[0.98,1.47]
Total (95% CI)	**1721**	**1461**		**100%**	**0.74[0.71,0.78]**
Total events: 882 (Paracetamol, all doses), 1004 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=143.98, df=33(P<0.0001); I^2=77.08%					
Test for overall effect: Z=12(P<0.0001)					



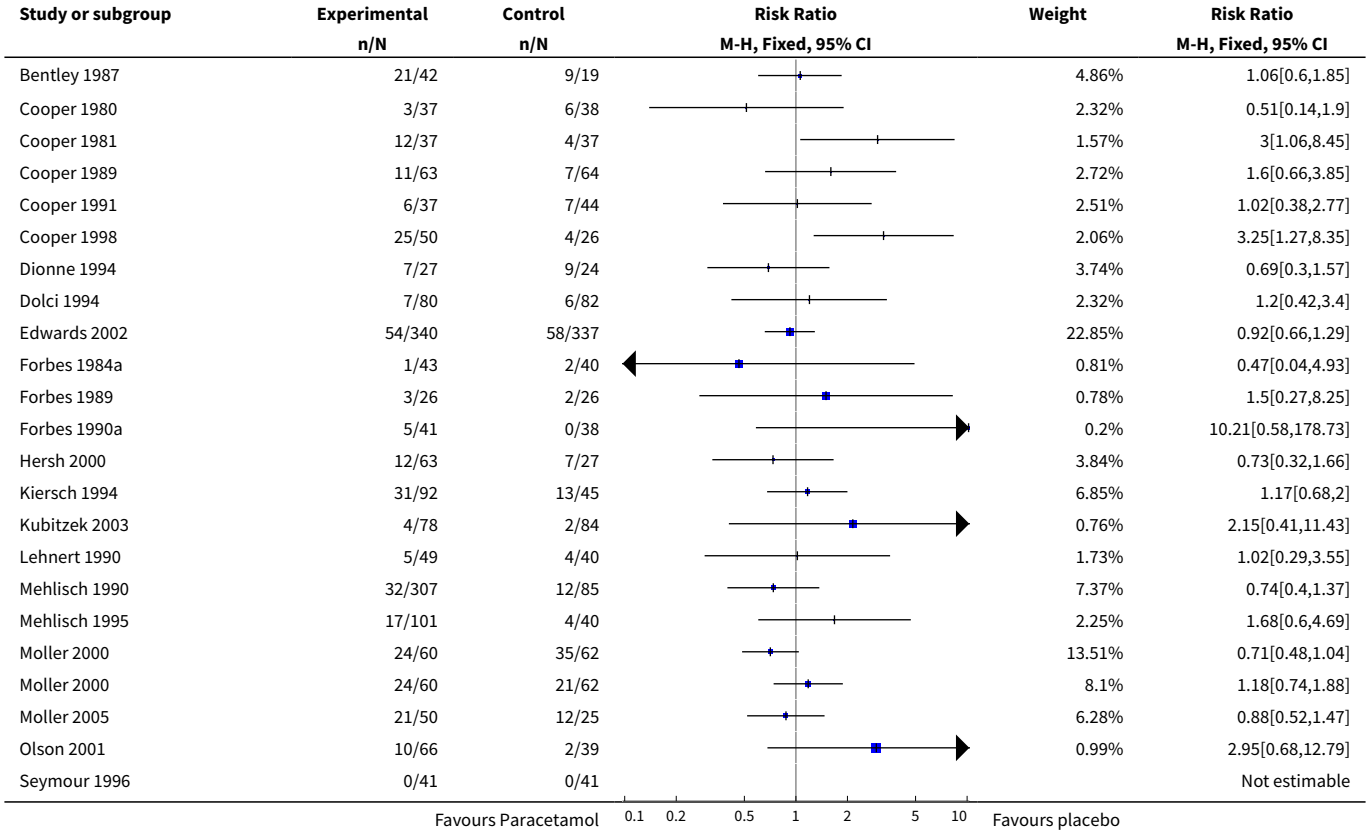
Analysis 1.3. Comparison 1 Paracetamol all doses versus placebo, Outcome 3 Participants with any adverse event.

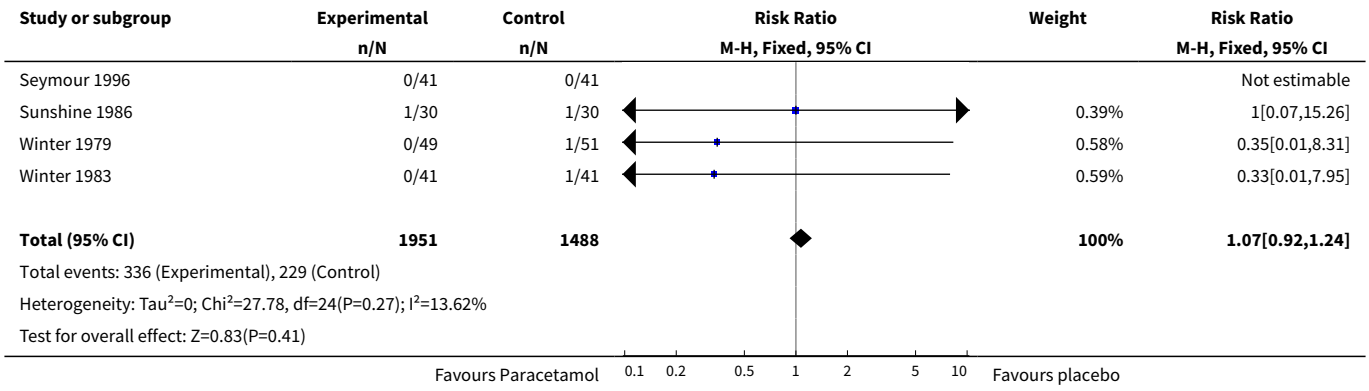
Study or subgroup	Paracetamol n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	21/42	9/19		4.31%	1.06[0.6,1.85]
Bjune 1996	10/50	1/25		0.46%	5[0.68,36.9]
Cooper 1980	3/37	6/38		2.06%	0.51[0.14,1.9]
Cooper 1981	12/37	4/37		1.39%	3[1.06,8.45]
Cooper 1989	11/63	7/64		2.41%	1.6[0.66,3.85]
Cooper 1991	6/37	7/44		2.22%	1.02[0.38,2.77]
Cooper 1998	25/50	4/26		1.83%	3.25[1.27,8.35]
Dionne 1994	7/27	9/24		3.31%	0.69[0.3,1.57]
Dolci 1994	7/80	6/82		2.06%	1.2[0.42,3.4]
Edwards 2002	54/340	58/337		20.25%	0.92[0.66,1.29]
Forbes 1983	11/26	4/26		1.39%	2.75[1,7.53]
Forbes 1984a	1/43	2/40		0.72%	0.47[0.04,4.93]
Forbes 1984b	9/33	8/33		2.78%	1.13[0.49,2.56]
Forbes 1989	3/26	2/26		0.7%	1.5[0.27,8.25]
Forbes 1990a	5/41	0/38		0.18%	10.21[0.58,178.73]
Hersh 2000	12/63	7/27		3.41%	0.73[0.32,1.66]
Jain 1986	9/30	6/32		2.02%	1.6[0.65,3.95]
Kiersch 1994	31/92	13/45		6.07%	1.17[0.68,2]
Kubitzek 2003	4/78	2/84		0.67%	2.15[0.41,11.43]
Lehnert 1990	5/49	4/40		1.53%	1.02[0.29,3.55]
McQuay 1988	6/30	6/30		2.09%	1[0.36,2.75]
Mehlisch 1990	32/307	12/85		6.53%	0.74[0.4,1.37]
Mehlisch 1995	17/101	4/40		1.99%	1.68[0.6,4.69]



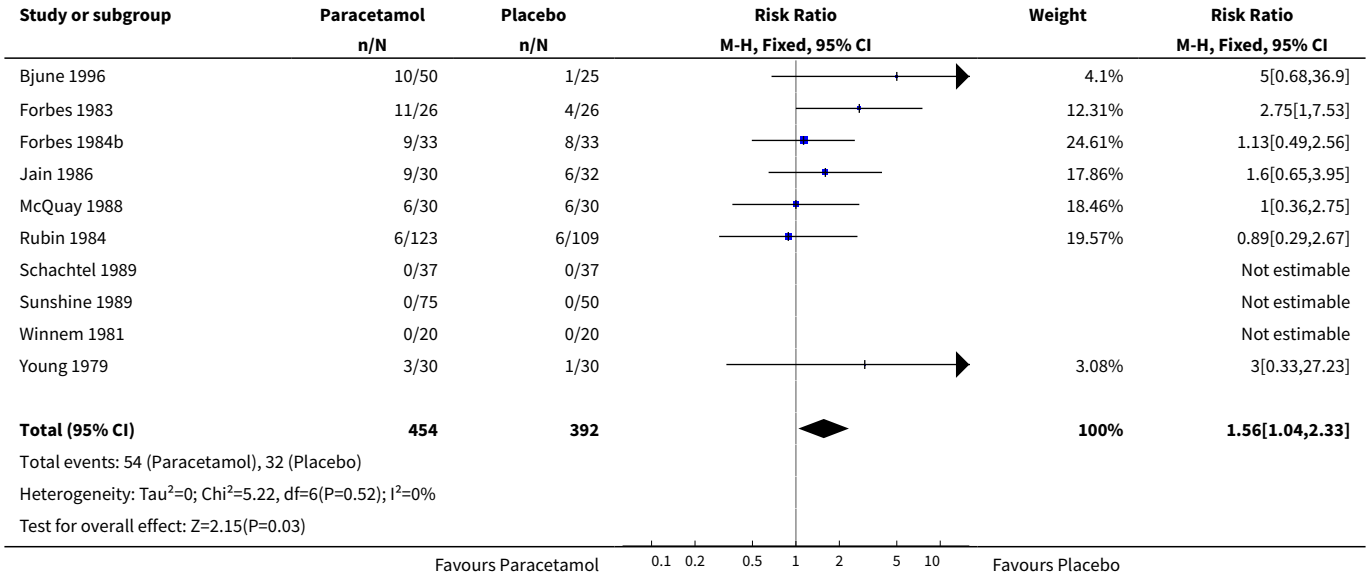


Analysis 1.4. Comparison 1 Paracetamol all doses versus placebo, Outcome 4 Participants with any adverse event, dental.





Analysis 1.5. Comparison 1 Paracetamol all doses versus placebo, Outcome 5 Participants with any adverse event, surgical.

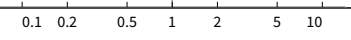


Comparison 2. Paracetamol 325 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Paracetamol 325 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or subgroup	Paracetamol 325 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Winter 1979	34/49	22/51		1.61[1.12,2.32]



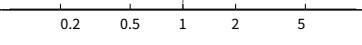
Favours placebo — Favours paracetamol

Comparison 3. Paracetamol 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 over 4 to 6 hours	6	561	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.57, 2.32]
2 Participants with at least 50% pain relief over 4 to 6 hours, dental	3	305	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.44, 2.50]
3 Participants with at least 50% pain relief over 4 to 6 hours, surgical	3	256	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.46, 2.52]
4 Participants using rescue medication over 4 to 6 hours	3	290	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.45, 0.69]
5 Participants with any adverse event	3	319	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.90]

Analysis 3.1. Comparison 3 Paracetamol 500 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

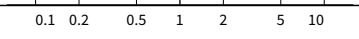
Study or subgroup	Paracet 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1980	11/37	11/38		12.19%	1.03[0.51,2.07]
Dolci 1994	54/72	25/76		27.33%	2.28[1.61,3.23]
Laska 1983 (Study 3)	46/81	22/57		29.02%	1.47[1.01,2.15]
Pinto 1984	24/29	10/29		11.24%	2.4[1.41,4.07]
Rubinstein 1986	22/30	8/30		8.99%	2.75[1.46,5.17]
Seymour 1996	19/41	10/41		11.24%	1.9[1.01,3.57]
Total (95% CI)	**290**	**271**		**100%**	**1.91[1.57,2.32]**
Total events: 176 (Paracet 500 mg), 86 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.82, df=5(P=0.17); I^2=36.04%					
Test for overall effect: Z=6.47(P<0.0001)					



Favours placebo — Favours paracetamol

Analysis 3.2. Comparison 3 Paracetamol 500 mg versus placebo, Outcome 2 Participants with at least 50% pain relief over 4 to 6 hours, dental.

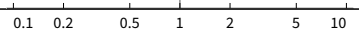
Study or subgroup	Paracetamol 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1980	11/37	11/38		24.02%	1.03[0.51,2.07]
Dolci 1994	54/72	25/76		53.84%	2.28[1.61,3.23]
Seymour 1996	19/41	10/41		22.13%	1.9[1.01,3.57]
Total (95% CI)	**150**	**155**		**100%**	**1.89[1.44,2.5]**
Total events: 84 (Paracetamol 500 mg), 46 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.01, df=2(P=0.13); I^2=50.1%					
Test for overall effect: Z=4.51(P<0.0001)					



Favours placebo — Favours paracetamol

Analysis 3.3. Comparison 3 Paracetamol 500 mg versus placebo, Outcome 3 Participants with at least 50% pain relief over 4 to 6 hours, surgical.

Study or subgroup	Paracetamol 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Laska 1983 (Study 3)	46/81	22/57		58.93%	1.47[1.01,2.15]
Pinto 1984	24/29	10/29		22.82%	2.4[1.41,4.07]
Rubinstein 1986	22/30	8/30		18.25%	2.75[1.46,5.17]
Total (95% CI)	**140**	**116**		**100%**	**1.92[1.46,2.52]**
Total events: 92 (Paracetamol 500 mg), 40 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.83, df=2(P=0.15); I^2=47.71%					
Test for overall effect: Z=4.64(P<0.0001)					



Favours placebo — Favours paracetamol

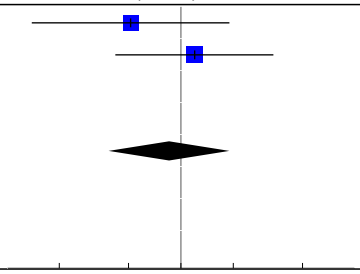
Analysis 3.4. Comparison 3 Paracetamol 500 mg versus placebo, Outcome 4 Participants using rescue medication over 4 to 6 hours.

Study or subgroup	Paracet 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dolci 1994	15/72	46/76		49.32%	0.34[0.21,0.56]
Rubinstein 1986	2/30	6/30		6.61%	0.33[0.07,1.52]
Seymour 1996	33/41	40/41		44.07%	0.83[0.7,0.97]
Total (95% CI)	**143**	**147**		**100%**	**0.56[0.45,0.69]**
Total events: 50 (Paracet 500 mg), 92 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.17, df=2(P<0.0001); I^2=92.9%					
Test for overall effect: Z=5.22(P<0.0001)					

Favours paracetamol — Favours placebo

Analysis 3.5. Comparison 3 Paracetamol 500 mg versus placebo, Outcome 5 Participants with any adverse event.

Study or subgroup	Paracet 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1980	3/37	6/38		49.97%	0.51[0.14,1.9]
Dolci 1994	7/80	6/82		50.03%	1.2[0.42,3.4]
Seymour 1996	0/41	0/41			Not estimable
Total (95% CI)	**158**	**161**		**100%**	**0.85[0.38,1.9]**
Total events: 10 (Paracet 500 mg), 12 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.38(P=0.7)					

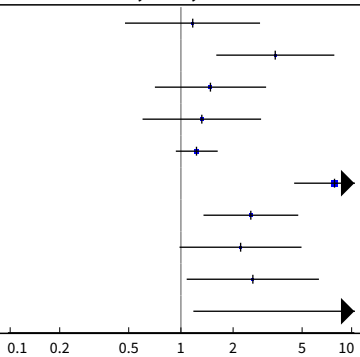


Comparison 4. Paracetamol 600-650 mg versus placebo

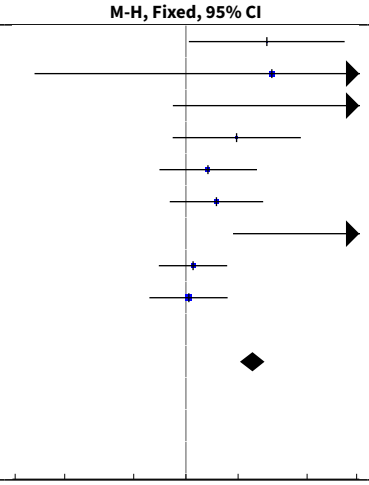
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	19	1886	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [2.05, 2.84]
2 Participants with at least 50% pain relief over 4 to 6 hours, dental	10	1276	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [2.42, 3.83]
3 Participants with at least 50% pain relief over 4 to 6 hours, surgical	9	610	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.41, 2.26]
4 Participants using rescue medication over 4 to 6 hours	13	917	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.77, 0.93]
5 Participants with any adverse event	13	1522	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.93, 1.50]

Analysis 4.1. Comparison 4 Paracetamol 600-650 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or subgroup	Paracet 600-650 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhounsule 1990	7/20	6/20		4.09%	1.17[0.48,2.86]
Cooper 1981	21/37	6/37		4.09%	3.5[1.6,7.67]
Cooper 1988	12/36	9/40		5.81%	1.48[0.71,3.1]
Cooper 1991	10/37	9/44		5.6%	1.32[0.6,2.9]
Dionne 1994	24/27	18/25		12.73%	1.23[0.93,1.63]
Edwards 2002	108/340	14/339		9.55%	7.69[4.5,13.15]
Fassolt 1983	21/29	8/28		5.54%	2.53[1.35,4.75]
Forbes 1982	15/34	6/30		4.34%	2.21[0.98,4.96]
Forbes 1983	13/26	5/26		3.41%	2.6[1.08,6.25]
Forbes 1984a	10/39	0/36		0.35%	19.43[1.18,319.95]

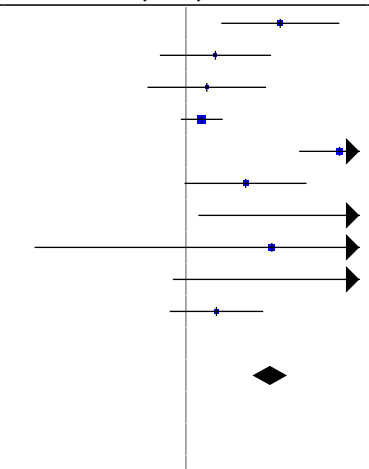


Study or subgroup	Paracet 600-650 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1984b	11/31	4/33		2.64%	2.93[1.04,8.23]
Forbes 1989	1/22	0/23		0.33%	3.13[0.13,72.99]
Forbes 1990a	7/36	0/34		0.35%	14.19[0.84,239.28]
Honig 1984	11/28	6/30		3.95%	1.96[0.84,4.6]
Jain 1986	13/29	10/30		6.69%	1.34[0.7,2.57]
Sunshine 1986	15/30	10/30		6.81%	1.5[0.81,2.79]
Sunshine 1989	22/75	0/50		0.41%	30.2[1.87,486.7]
Sunshine 1993	22/48	20/48		13.62%	1.1[0.7,1.73]
Young 1979	15/30	14/29		9.7%	1.04[0.62,1.74]
Total (95% CI)	**954**	**932**		**100%**	**2.42[2.05,2.84]**
Total events: 358 (Paracet 600-650 mg), 145 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=82.03, df=18(P<0.0001); I^2=78.06%					
Test for overall effect: Z=10.61(P<0.0001)					



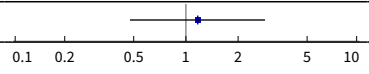
Analysis 4.2. Comparison 4 Paracetamol 600-650 mg versus placebo, Outcome 2 Participants with at least 50% pain relief over 4 to 6 hours, dental.

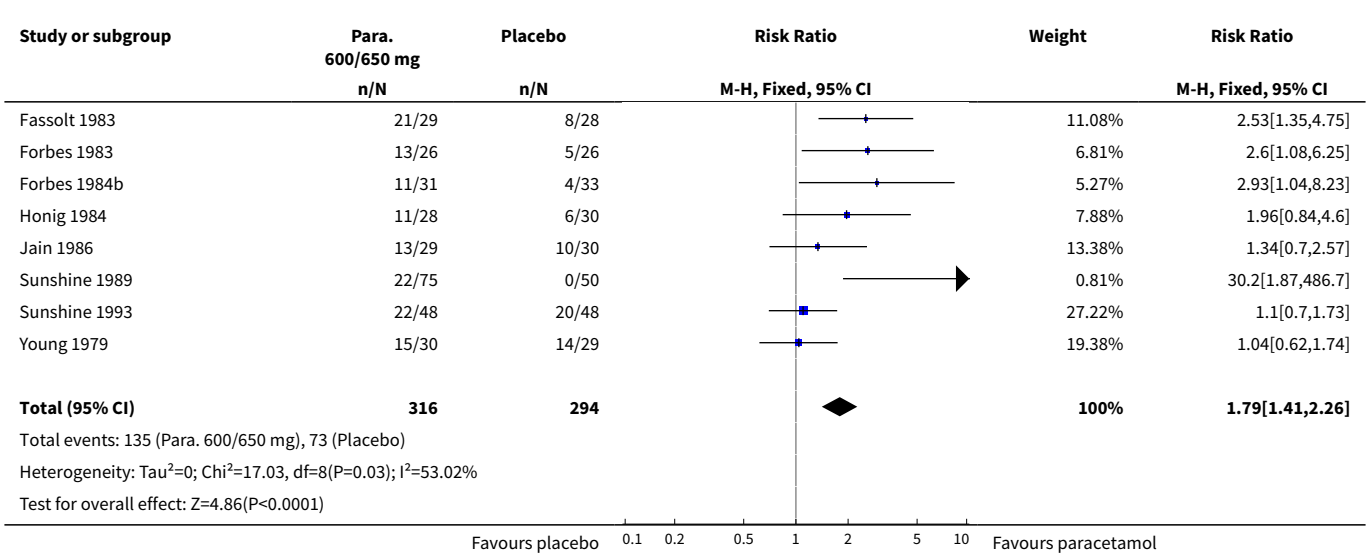
Study or subgroup	Para. 600/650 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1981	21/37	6/37		8.18%	3.5[1.6,7.67]
Cooper 1988	12/36	9/40		11.62%	1.48[0.71,3.1]
Cooper 1991	10/37	9/44		11.21%	1.32[0.6,2.9]
Dionne 1994	24/27	18/25		25.48%	1.23[0.93,1.63]
Edwards 2002	108/340	14/339		19.11%	7.69[4.5,13.15]
Forbes 1982	15/34	6/30		8.69%	2.21[0.98,4.96]
Forbes 1984a	10/39	0/36		0.71%	19.43[1.18,319.95]
Forbes 1989	1/22	0/23		0.67%	3.13[0.13,72.99]
Forbes 1990a	7/36	0/34		0.7%	14.19[0.84,239.28]
Sunshine 1986	15/30	10/30		13.63%	1.5[0.81,2.79]
Total (95% CI)	**638**	**638**		**100%**	**3.05[2.42,3.83]**
Total events: 223 (Para. 600/650 mg), 72 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=68.41, df=9(P<0.0001); I^2=86.84%					
Test for overall effect: Z=9.56(P<0.0001)					



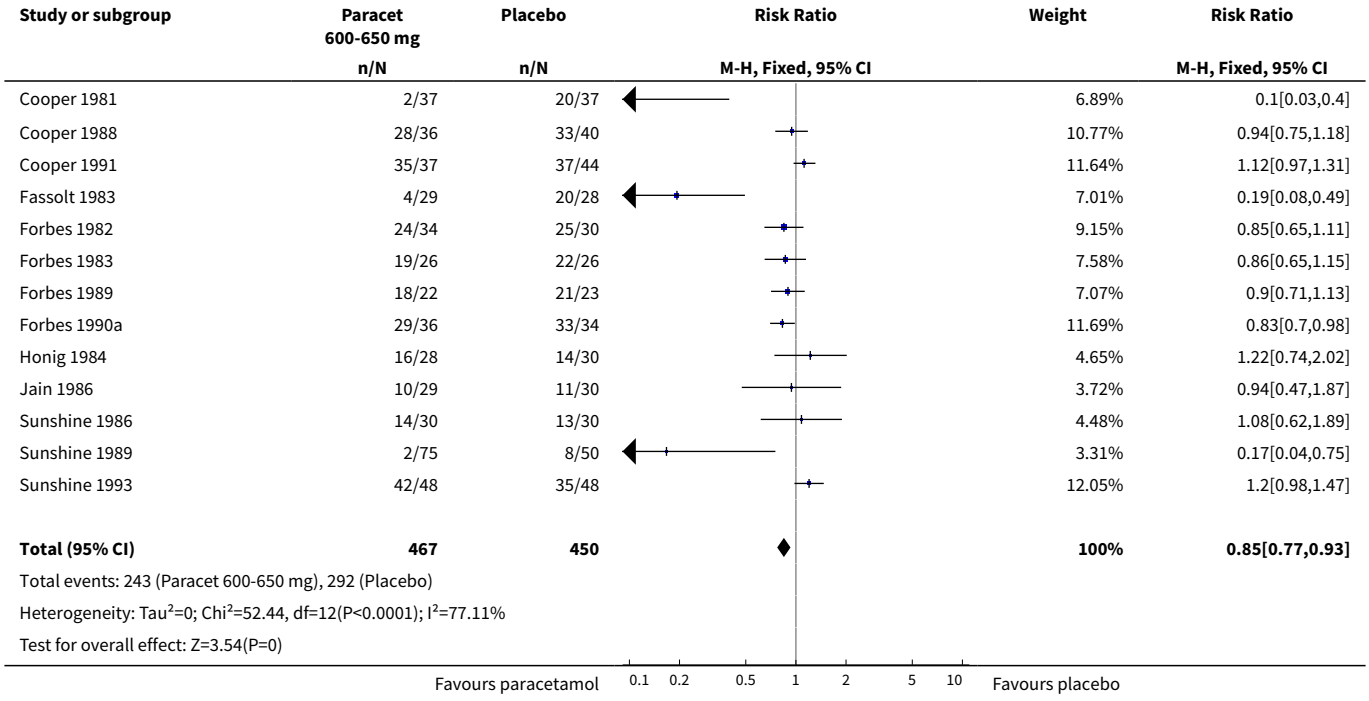
Analysis 4.3. Comparison 4 Paracetamol 600-650 mg versus placebo, Outcome 3 Participants with at least 50% pain relief over 4 to 6 hours, surgical.

Study or subgroup	Para. 600/650 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhounsule 1990	7/20	6/20		8.17%	1.17[0.48,2.86]



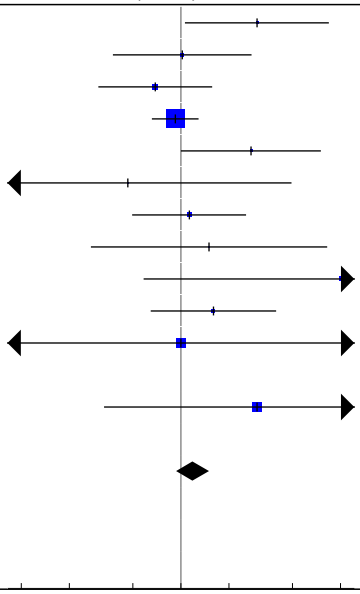


Analysis 4.4. Comparison 4 Paracetamol 600-650 mg versus placebo, Outcome 4 Participants using rescue medication over 4 to 6 hours.



Analysis 4.5. Comparison 4 Paracetamol 600-650 mg versus placebo, Outcome 5 Participants with any adverse event.

Study or subgroup	Paracet 600-650 n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cooper 1981	12/37	4/37		3.9%	3[1.06,8.45]
Cooper 1991	6/37	7/44		6.23%	1.02[0.38,2.77]
Dionne 1994	7/27	9/24		9.29%	0.69[0.3,1.57]
Edwards 2002	54/340	58/337		56.79%	0.92[0.66,1.29]
Forbes 1983	11/26	4/26		3.9%	2.75[1,7.53]
Forbes 1984a	1/43	2/40		2.02%	0.47[0.04,4.93]
Forbes 1984b	9/33	8/33		7.8%	1.13[0.49,2.56]
Forbes 1989	3/26	2/26		1.95%	1.5[0.27,8.25]
Forbes 1990a	5/41	0/38		0.51%	10.21[0.58,178.73]
Jain 1986	9/30	6/32		5.66%	1.6[0.65,3.95]
Sunshine 1986	1/30	1/30		0.97%	1[0.07,15.26]
Sunshine 1989	0/75	0/50			Not estimable
Young 1979	3/30	1/30		0.97%	3[0.33,27.23]
Total (95% CI)	**775**	**747**		**100%**	**1.18[0.93,1.5]**
Total events: 121 (Paracet 600-650), 102 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.59, df=11(P=0.26); I^2=19.07%					
Test for overall effect: Z=1.39(P=0.16)					

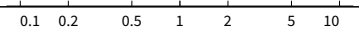


Comparison 5. Paracetamol 975-1000 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	28	3232	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [2.36, 3.02]
2 Participants with at least 50% pain relief over 4 to 6 hours, dental	18	2171	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [3.32, 5.17]
3 Participants with at least 50% pain relief over 4 to 6 hours, surgical	10	1075	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.49, 1.95]
4 Participants using rescue medication over 4 to 6 hours	17	1980	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.68, 0.77]
5 Participants with any adverse event	19	2342	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.93, 1.32]

Analysis 5.1. Comparison 5 Paracetamol 975-1000 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

Study or subgroup	Paracet 975-1000 n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	19/41	4/17		2.13%	1.97[0.79,4.93]
Berry 1975	63/76	18/76		6.78%	3.5[2.31,5.31]
Bjune 1996	12/43	0/21		0.25%	12.5[0.78,201.48]
Cooper 1986	20/38	3/22		1.43%	3.86[1.29,11.53]
Cooper 1989	27/59	9/64		3.25%	3.25[1.67,6.34]
Cooper 1998	17/50	3/26		1.49%	2.95[0.95,9.14]
Edwards 2002	45/100	25/100		9.41%	1.8[1.2,2.69]
Haglund 2006	10/20	0/17		0.2%	18[1.13,286.2]
Hersh 2000	35/63	5/27		2.63%	3[1.32,6.82]
Kiersch 1994	21/92	3/45		1.52%	3.42[1.08,10.88]
Kubitzek 2003	45/78	7/84		2.54%	6.92[3.32,14.43]
Laska 1983 (Study 3)	49/81	22/57		9.72%	1.57[1.08,2.27]
Lehnert 1990	24/49	5/40		2.07%	3.92[1.64,9.34]
McQuay 1988	10/30	3/30		1.13%	3.33[1.02,10.92]
Mehlisch 1984	16/58	0/55		0.19%	31.32[1.92,509.77]
Mehlisch 1990	131/306	9/85		5.3%	4.04[2.15,7.6]
Mehlisch 1995	35/101	1/40		0.54%	13.86[1.96,97.79]
Moller 2000	12/60	0/62		0.19%	25.82[1.56,426.59]
Moller 2000	15/60	0/60		0.19%	31[1.9,506.59]
Moller 2005	21/50	4/25		2.01%	2.63[1.01,6.82]
Olson 2001	41/66	5/39		2.37%	4.85[2.09,11.22]
Rubin 1984	86/123	52/109		20.75%	1.47[1.17,1.84]
Sakata 1986	17/30	3/27		1.19%	5.1[1.68,15.5]
Santos Pereira 1986	22/28	22/29		8.14%	1.04[0.78,1.37]
Schachtel 1989	20/37	13/38		4.83%	1.58[0.93,2.69]
Seymour 1996	21/41	10/41		3.76%	2.1[1.13,3.89]
Seymour 2003	13/62	3/32		1.49%	2.24[0.69,7.28]
Winnem 1981	9/20	3/20		1.13%	3[0.95,9.48]
Winter 1979	20/41	9/41		3.39%	2.22[1.15,4.29]
Total (95% CI)	**1903**	**1329**		**100%**	**2.67[2.36,3.02]**
Total events: 876 (Paracet 975-1000), 241 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=115.64, df=28(P<0.0001); I^2=75.79%					
Test for overall effect: Z=15.72(P<0.0001)					



Favours placebo — Favours paracetamol

Analysis 5.2. Comparison 5 Paracetamol 975-1000 mg versus placebo, Outcome 2 Participants with at least 50% pain relief over 4 to 6 hours, dental.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	19/41	4/17		6.12%	1.97[0.79,4.93]
Cooper 1986	20/38	3/22		4.11%	3.86[1.29,11.53]
Cooper 1989	27/59	9/64		9.34%	3.25[1.67,6.34]
Cooper 1998	17/50	3/26		4.27%	2.95[0.95,9.14]
Haglund 2006	10/20	0/17		0.58%	18[1.13,286.2]

Favours placebo — Favours paracetamol

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hersh 2000	35/63	5/27		7.58%	3[1.32,6.82]
Kiersch 1994	21/92	3/45		4.36%	3.42[1.08,10.88]
Kubitzek 2003	45/78	7/84		7.3%	6.92[3.32,14.43]
Lehnert 1990	24/49	5/40		5.96%	3.92[1.64,9.34]
Mehlisch 1984	16/58	0/55		0.56%	31.32[1.92,509.77]
Mehlisch 1990	131/306	9/85		15.25%	4.04[2.15,7.6]
Mehlisch 1995	35/101	1/40		1.55%	13.86[1.96,97.79]
Moller 2000	12/60	0/62		0.53%	25.82[1.56,426.59]
Moller 2000	15/60	0/62		0.53%	32.02[1.96,523.38]
Moller 2005	21/50	4/25		5.77%	2.63[1.01,6.82]
Olson 2001	41/66	5/39		6.8%	4.85[2.09,11.22]
Seymour 1996	21/41	10/41		10.82%	2.1[1.13,3.89]
Seymour 2003	13/62	3/32		4.28%	2.24[0.69,7.28]
Winter 1983	13/62	3/32		4.28%	2.24[0.69,7.28]
Total (95% CI)	**1356**	**815**		**100%**	**4.14[3.32,5.17]**
Total events: 536 (Experimental), 74 (Control)					
Heterogeneity: Tau^2=0; Chi^2=22.02, df=18(P=0.23); I^2=18.26%					
Test for overall effect: Z=12.55(P<0.0001)					

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours paracetamol

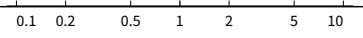
Analysis 5.3. Comparison 5 Paracetamol 975-1000 mg versus placebo, Outcome 3 Participants with at least 50% pain relief over 4 to 6 hours, surgical.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Berry 1975	63/76	18/76		9.73%	3.5[2.31,5.31]
Bjune 1996	12/43	0/21		0.36%	12.5[0.78,201.48]
Edwards 2002	45/100	25/100		13.51%	1.8[1.2,2.69]
Laska 1983 (Study 3)	49/81	22/57		13.96%	1.57[1.08,2.27]
McQuay 1988	10/30	3/30		1.62%	3.33[1.02,10.92]
Rubin 1984	86/123	52/109		29.8%	1.47[1.17,1.84]
Sakata 1986	17/30	3/27		1.71%	5.1[1.68,15.5]
Santos Pereira 1986	22/28	22/29		11.68%	1.04[0.78,1.37]
Schachtel 1989	20/37	30/38		16%	0.68[0.49,0.96]
Winnem 1981	9/20	3/20		1.62%	3[0.95,9.48]
Total (95% CI)	**568**	**507**		**100%**	**1.7[1.49,1.95]**
Total events: 333 (Experimental), 178 (Control)					
Heterogeneity: Tau^2=0; Chi^2=61.02, df=9(P<0.0001); I^2=85.25%					
Test for overall effect: Z=7.8(P<0.0001)					

Favours control 0.1 0.2 0.5 1 2 5 10 Favours paracetamol

Analysis 5.4. Comparison 5 Paracetamol 975-1000 mg versus placebo, Outcome 4 Participants using rescue medication over 4 to 6 hours.

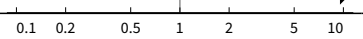
Study or subgroup	Paracetamol 975-1000 n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	28/41	14/17		2.9%	0.83[0.61,1.12]
Berry 1975	2/76	23/76		3.37%	0.09[0.02,0.36]
Cooper 1989	37/59	50/63		7.08%	0.79[0.63,1]
Cooper 1998	30/50	20/26		3.86%	0.78[0.57,1.06]
Haglund 2006	5/20	12/17		1.9%	0.35[0.16,0.8]
Hersh 2000	32/63	20/27		4.1%	0.69[0.49,0.95]
Kiersch 1994	64/92	38/45		7.48%	0.82[0.69,0.99]
Kubitzek 2003	60/78	75/84		10.58%	0.86[0.75,0.99]
McQuay 1988	19/30	26/30		3.81%	0.73[0.54,0.99]
Mehlisch 1984	45/58	52/55		7.82%	0.82[0.7,0.96]
Mehlisch 1995	53/101	35/40		7.35%	0.6[0.48,0.75]
Moller 2000	44/60	56/62		8.07%	0.81[0.68,0.97]
Moller 2000	51/60	62/62		9.01%	0.85[0.76,0.95]
Olson 2001	25/66	31/39		5.71%	0.48[0.34,0.67]
Rubin 1984	1/123	15/109		2.33%	0.06[0.01,0.44]
Schachtel 1989	13/37	22/38		3.18%	0.61[0.36,1.02]
Seymour 1996	34/41	40/41		5.86%	0.85[0.73,0.98]
Seymour 2003	46/62	29/32		5.6%	0.82[0.68,0.98]
Total (95% CI)	**1117**	**863**		**100%**	**0.72[0.68,0.77]**
Total events: 589 (Paracetamol 975-1000), 620 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=55.22, df=17(P<0.0001); I^2=69.21%					
Test for overall effect: Z=11.07(P<0.0001)					



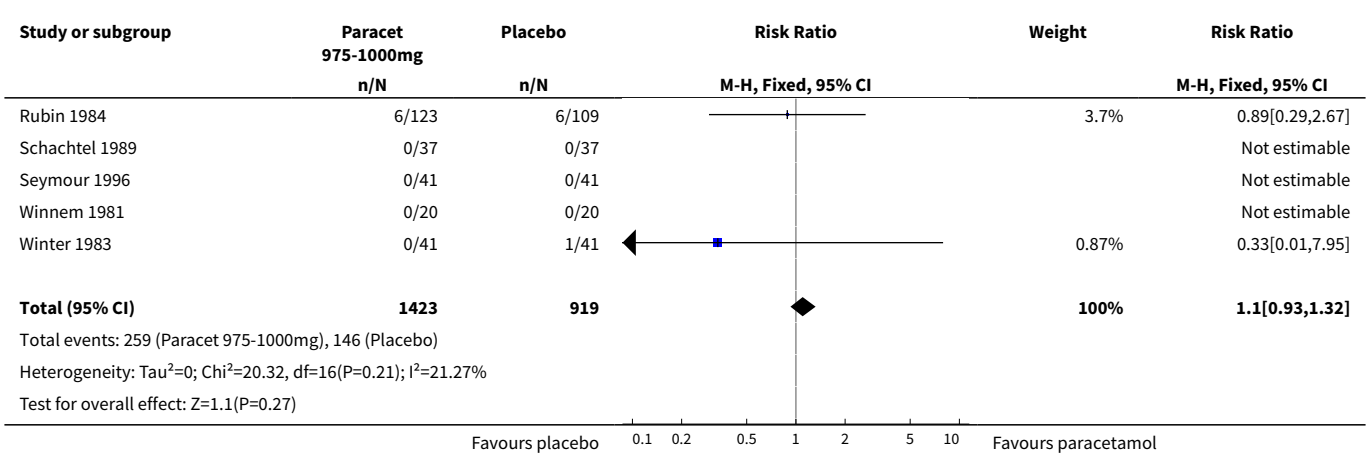
Favours paracetamol — Favours placebo

Analysis 5.5. Comparison 5 Paracetamol 975-1000 mg versus placebo, Outcome 5 Participants with any adverse event.

Study or subgroup	Paracet 975-1000mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	21/42	9/19		7.21%	1.06[0.6,1.85]
Bjune 1996	10/50	1/25		0.78%	5[0.68,36.9]
Cooper 1989	11/63	7/64		4.04%	1.6[0.66,3.85]
Cooper 1998	25/50	4/26		3.06%	3.25[1.27,8.35]
Hersh 2000	12/63	7/27		5.7%	0.73[0.32,1.66]
Kiersch 1994	31/92	13/45		10.16%	1.17[0.68,2]
Kubitzek 2003	4/78	2/84		1.12%	2.15[0.41,11.43]
Lehnert 1990	5/49	4/40		2.56%	1.02[0.29,3.55]
McQuay 1988	6/30	6/30		3.49%	1[0.36,2.75]
Mehlisch 1984	32/307	12/85		10.94%	0.74[0.4,1.37]
Mehlisch 1990	17/101	4/40		3.33%	1.68[0.6,4.69]
Moller 2000	24/60	35/62		20.03%	0.71[0.48,1.04]
Moller 2000	24/60	21/60		12.22%	1.14[0.72,1.82]
Moller 2005	21/50	12/25		9.31%	0.88[0.52,1.47]
Olson 2001	10/66	2/39		1.46%	2.95[0.68,12.79]



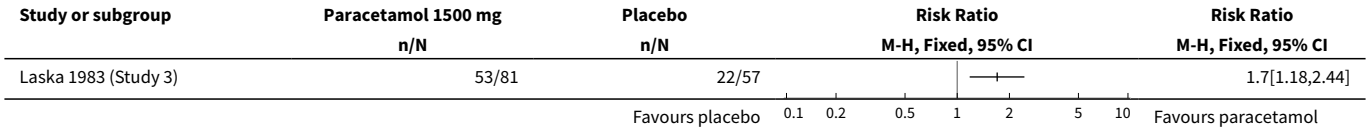
Favours placebo — Favours paracetamol



Comparison 6. Paracetamol 1500 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Paracetamol 1500 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours.

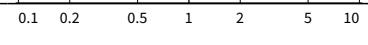


Comparison 7. Paracetamol versus placebo, sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality score of 3 or more	48	5549	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [2.27, 2.72]
2 Quality of 2	3	214	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.59, 2.97]
3 More than 40 patients in each arm, 975/1000mg paracetamol vs placebo, quality score of three of more, dental	11	1562	Risk Ratio (M-H, Fixed, 95% CI)	4.47 [3.41, 5.85]
4 Less than 40 patients in each arm, 975/1000mg paracetamol vs placebo, quality score of three of more, dental	2	97	Risk Ratio (M-H, Fixed, 95% CI)	5.61 [2.06, 15.33]

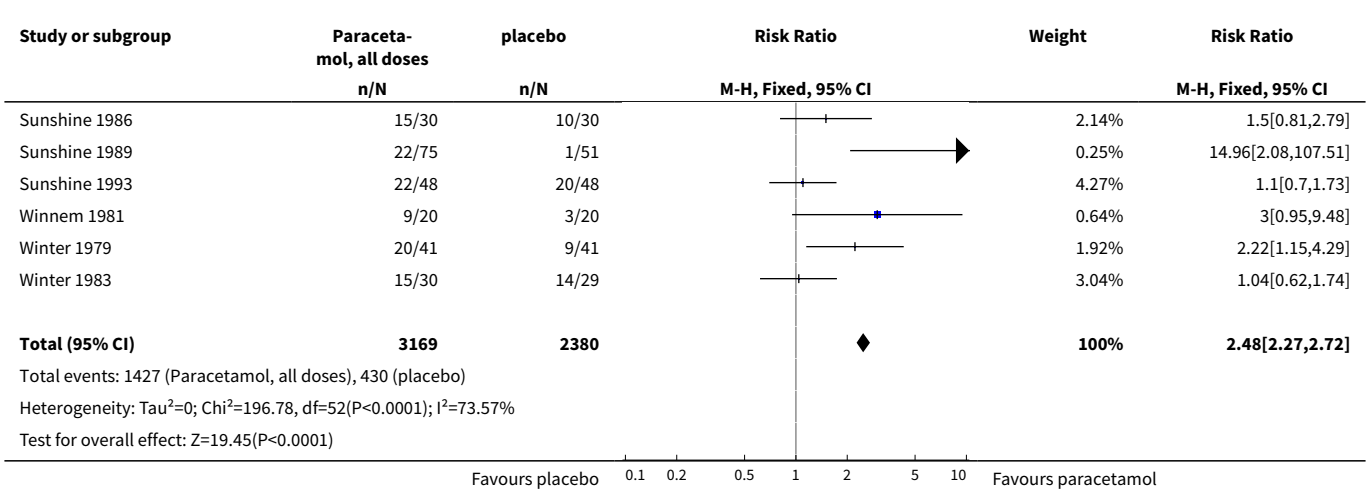
Analysis 7.1. Comparison 7 Paracetamol versus placebo, sensitivity analysis, Outcome 1 Quality score of 3 or more.

Study or subgroup	Paracetamol, all doses n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bentley 1987	19/41	4/17		1.21%	1.97[0.79,4.93]
Berry 1975	63/76	18/76		3.85%	3.5[2.31,5.31]
Bhounsule 1990	7/20	6/20		1.28%	1.17[0.48,2.86]
Bjune 1996	12/43	0/21		0.14%	12.5[0.78,201.48]
Cooper 1980	11/37	11/38		2.32%	1.03[0.51,2.07]
Cooper 1981	21/37	6/37		1.28%	3.5[1.6,7.67]
Cooper 1986	20/38	3/22		0.81%	3.86[1.29,11.53]
Cooper 1988	12/36	9/40		1.82%	1.48[0.71,3.1]
Cooper 1989	27/59	9/64		1.84%	3.25[1.67,6.34]
Cooper 1991	10/37	9/44		1.76%	1.32[0.6,2.9]
Cooper 1998	17/50	3/26		0.84%	2.95[0.95,9.14]
Dionne 1994	24/27	18/25		3.99%	1.23[0.93,1.63]
Dolci 1994	54/72	25/76		5.2%	2.28[1.61,3.23]
Edwards 2002	108/340	14/339		2.99%	7.69[4.5,13.15]
Edwards 2002	45/100	25/100		5.34%	1.8[1.2,2.69]
Forbes 1982	15/34	6/30		1.36%	2.21[0.98,4.96]
Forbes 1983	13/26	5/26		1.07%	2.6[1.08,6.25]
Forbes 1984a	11/39	0/36		0.11%	21.28[1.3,348.43]
Forbes 1984b	11/31	4/33		0.83%	2.93[1.04,8.23]
Forbes 1989	2/22	0/23		0.1%	5.22[0.26,102.93]
Forbes 1990a	7/36	0/34		0.11%	14.19[0.84,239.28]
Haglund 2006	10/20	0/17		0.12%	18[1.13,286.2]
Hersh 2000	35/63	5/27		1.5%	3[1.32,6.82]
Honig 1984	11/28	6/30		1.24%	1.96[0.84,4.6]
Jain 1986	13/29	10/30		2.1%	1.34[0.7,2.57]
Kiersch 1994	21/92	3/45		0.86%	3.42[1.08,10.88]
Kubitzek 2003	45/78	7/84		1.44%	6.92[3.32,14.43]
Laska 1983 (Study 3)	46/81	8/19		2.77%	1.35[0.77,2.36]
Laska 1983 (Study 3)	53/81	7/19		2.42%	1.78[0.97,3.27]
Laska 1983 (Study 3)	49/81	7/19		2.42%	1.64[0.89,3.04]
Lehnert 1990	24/49	5/40		1.18%	3.92[1.64,9.34]
McQuay 1988	10/30	3/30		0.64%	3.33[1.02,10.92]
Mehlisch 1984	16/58	0/55		0.11%	31.32[1.92,509.77]
Mehlisch 1990	131/306	9/85		3.01%	4.04[2.15,7.6]
Mehlisch 1995	35/101	1/40		0.31%	13.86[1.96,97.79]
Moller 2000	15/60	0/60		0.11%	31[1.9,506.59]
Moller 2000	12/60	0/62		0.11%	25.82[1.56,426.59]
Moller 2005	21/50	4/25		1.14%	2.63[1.01,6.82]
Olson 2001	41/66	5/39		1.34%	4.85[2.09,11.22]
Pinto 1984	24/29	10/29		2.14%	2.4[1.41,4.07]
Rubin 1984	86/123	52/109		11.78%	1.47[1.17,1.84]
Rubinstein 1986	22/30	8/30		1.71%	2.75[1.46,5.17]
Santos Pereira 1986	22/28	22/29		4.62%	1.04[0.78,1.37]
Schachtel 1989	20/37	13/38		2.74%	1.58[0.93,2.69]
Seymour 1996	19/41	5/21		1.41%	1.95[0.85,4.48]
Seymour 1996	21/41	5/20		1.44%	2.05[0.91,4.63]
Seymour 2003	13/62	3/32		0.85%	2.24[0.69,7.28]

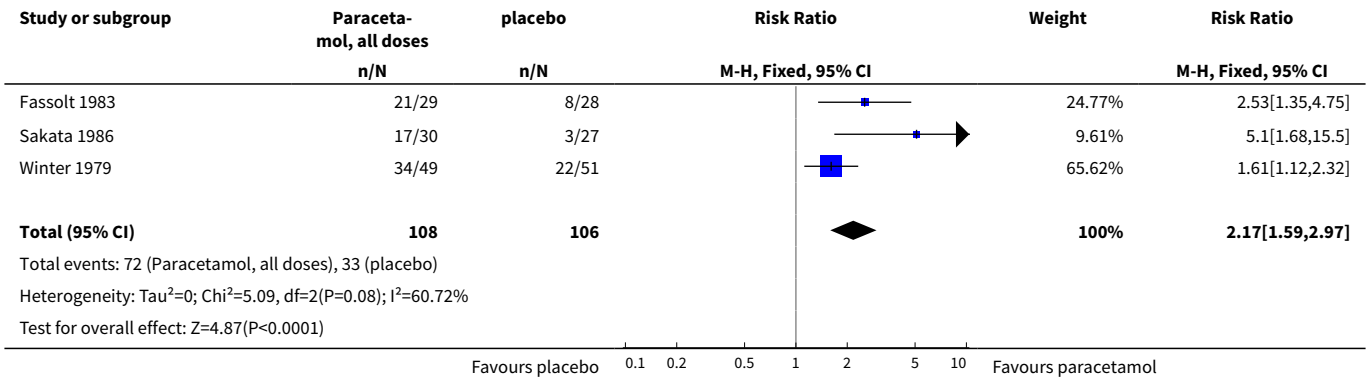


Favours placebo

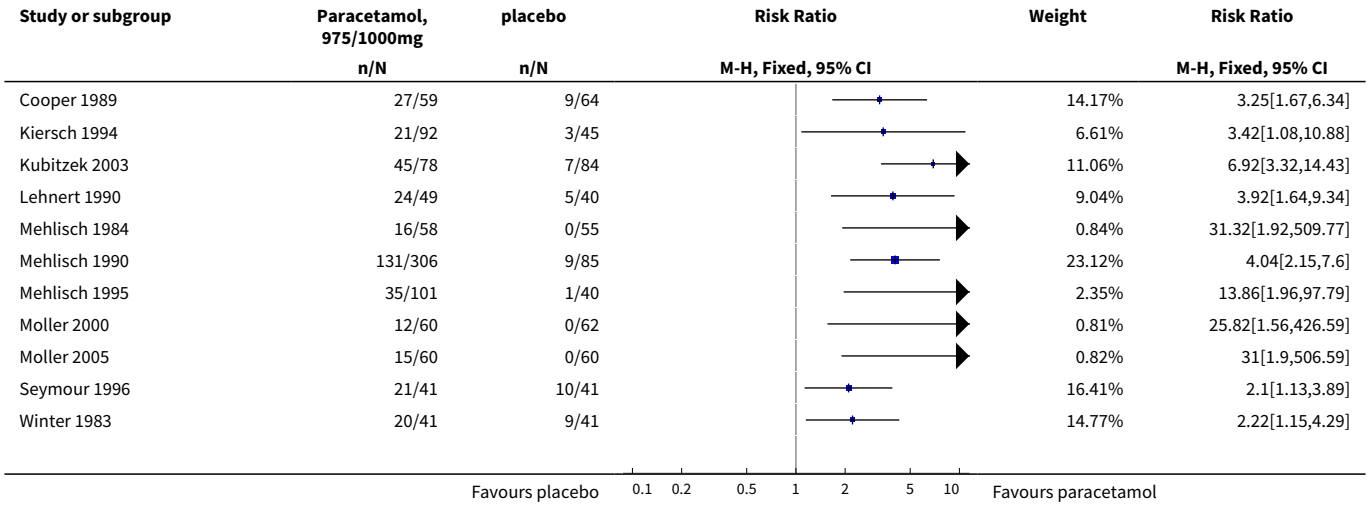
Favours paracetamol

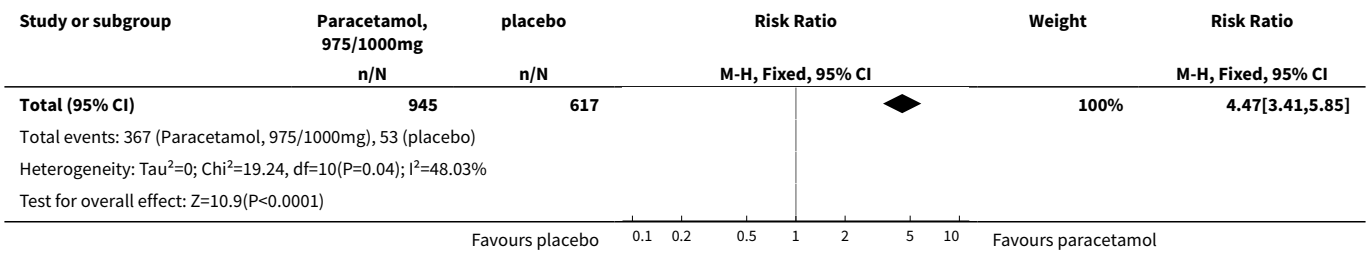


Analysis 7.2. Comparison 7 Paracetamol versus placebo, sensitivity analysis, Outcome 2 Quality of 2.

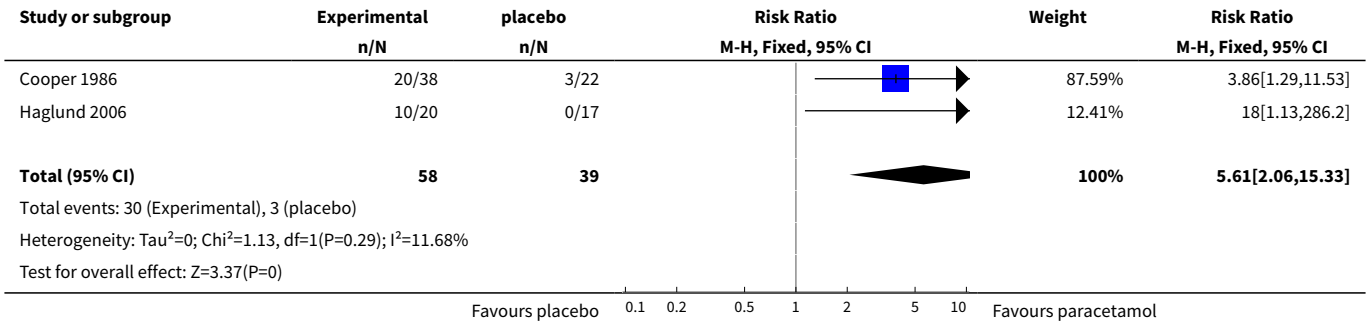


Analysis 7.3. Comparison 7 Paracetamol versus placebo, sensitivity analysis, Outcome 3 More than 40 patients in each arm, 975/1000mg paracetamol vs placebo, quality score of three of more, dental.





Analysis 7.4. Comparison 7 Paracetamol versus placebo, sensitivity analysis, Outcome 4 Less than 40 patients in each arm, 975/1000mg paracetamol vs placebo, quality score of three of more, dental.



ADDITIONAL TABLES

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

		Analgesia			Rescue medication	
Study ID	**Treatment**	**PI or PR**	**Number with 50% PR**	**PGE: very good or excellent**	**Time to use (hr)**	**% using**
Bentley 1987	(1) Paracetamol 1000 mg, n=41 (2) Paracetamol+codeine 1000/60 mg, n=41 (3) Codeine 60 mg, n=21 (4) Placebo, n=17	TOTPAR 5: (1) 8.7 (4) 4.9	(1) 19/41 (4) 4/17	No data	Median: (1) 3.3 (4) 1.4	at 4 hrs: (1) 68 (4) 81
Berry 1975	(1) Paracetamol 1000 mg, n=76 (2) Propoxyphene, 65 mg, n=73 (3) Placebo, n=76	non standard scales	(1) 63/76 (3) 18/76	Global rating > good: (1) 63/76 (3) 18/76	No data	at 4 hrs: (1) 2 (3) 17
Bhounsule 1990	(1) Paracetamol 1000 mg, n=20 (2) Ibuprofen 400 mg, n=20 (3) Aspirin 600 mg, n=20	SPID 6: (1) 5.4 (5) 4.4	(1) 7/20 (5) 6/20	No data	No data	No data

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

	(4) Analgin 500 mg, n=20 (5) Placebo, n=20					
Bjune 1996	(1) Paracetamol 1000 mg, n=50 (2) Paracetamol+codeine 800/60 mg, n=50 (3) Placebo, n=25	TOTPAR 6: severe pain (1) 6.4 (3) 0 moderate pain (1) 8.0 (3) 1.5	(1) 12/43 (3) 0/21	No data	No data	No data
Cooper 1980	(1) Paracetamol 500 mg, n=37 (2) Oxycodone 5 mg, n=42 (3) Paracetamol+oxycodone 500/5 mg, n=45 (4) Paracetamol+oxycodone 1000/5 mg, n=40 (5) Paracetamol+oxycodone 1000/10 mg, n=45 (6) Placebo, n=38	TOTPAR 4: (1) 5.1 (6) 4.8	(1) 11/37 (6) 11/38	No data	Mean: (1) 2.8 (6) 2.5	No data
Cooper 1981	(1) Paracetamol 650 mg, n=37 (2) Paracetamol+codeine 650/60 mg, n=42 (3) Paracetamol+d-propoxyphene 650/100 mg, n=42 (4) Ibuprofen 200 mg, n=42 (5) Placebo, n=37	TOTPAR 4: (1) 8.2 (3) 3.4	(1) 21/37 (5) 6/37	No usable data	Mean: (1) 3.5 (5) 2.9	at 4 hrs: (1) 5 (5) 54
Cooper 1986	(1) Paracetamol 1000 mg, n=38 (2) Paracetamol+codeine+caffeine 1000/16/30 mg, n=39 (3) Placebo, n=22	TOTPAR 6: (1) 11.6 (3) 4.3	(1) 20/38 (3) 3/22	No data	Mean: (1) 4.7 (3) 3.5	No data
Cooper 1988	(1) Paracetamol 600 mg, n=36 (2) Paracetamol+codeine 600+60 mg, n=31 (3) Placebo, n=40	TOTPAR 6: (1) 8.0 (3) 6.3	(1) 12/36 (3) 9/40	(1) 12/36 (3) 8/40	No data	at 6 hrs: (1) 78 (3) 82
Cooper 1989	(1) Paracetamol 1000 mg, n=59 (2) Ibuprofen 400 mg, n=61 (3) Placebo, n=64	TOTPAR 6: (1) 10.2 (3) 4.7	(1) 27/59 (3) 9/64	(1) 16/59 (3) 4/64	Median: (1) 3.7 (3) 2.3 Mean:	at 6 hrs: (1) 63 (3) 78

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

					(1) 4.1 (3) 3.3	
Cooper 1991	(1) Paracetamol 650 mg, n=37 (2) Paracetamol+codeine 650/60 mg, n=39 (3) Zomepirac 100 mg, n=23 (4) Flurbiprofen 50 mg, n=42 (5) Flurbiprofen 100 mg, n=41 (6) Placebo, n=44	TOTPAR 6: (1) 6.8 (6) 5.7	(1) 10/37 (6) 9/44	(1) 3/37 (6) 2/44	Mean: (1) 3.2 (6) 3.1	at 6 hrs: (1) 95 (6) 84
Cooper 1998	(1) Paracetamol 1000 mg n=50 (2) Ketoprofen 100 mg, n=51 (3) Ketoprofen 1000 mg, n=50 (4) Placebo, n=26	TOTPAR 6: (1) 8.2 (4) 4.5	(1) 17/50 (4) 3/26	No data	median: (1) 3.3 (4) 1.7	at 6 hrs: (1) 60 (4) 78
Dionne 1994	(1) Paracetamol 650 mg, n=27 (2) Paracetamol+codeine 650/60 mg, n=24 (3) Flurbiprofen 50 mg, n=25 (4) Flurbiprofen 100 mg, n=22 (5) Placebo, n=25	TOTPAR 6: (1) 18.4 (5) 14.9	(1) 24/27 (5) 18/25	No usable data	no data	no data
Dolci 1994	(1) Paracetamol 500 mg, n=72 (2) Piroxicam 20 mg, n=76 (3) Piroxicam cyclodextrin =20 mg, n=74 (4) Placebo, n=76	TOTPAR 4: (1) 10.5 (6) 5.4	(1) 54/72 (4) 25/76	No usable data	no data	at 4 hrs: (1) 15/72 (4) 46/76
Edwards 2002	(1) Paracetamol 650 mg, n=340 (2) Placebo, n=339 5 dental studies included in meta-analysis	TOTPAR 6: values not given	(1) 108/340 (2) 14/339	(1) 110/340 (2) 34/337	No data	1) 9 2) 36
Edwards 2002	(1) Paracetamol 975 mg, n=100 (2) Placebo, n=100 2 gynae or ortho studies in meta-analysis	TOTPAR 6: values not given	(1) 45/100 (2) 25/100	(1) 37/100 (2) 22/100	No data	1) 3 2) 1
Fassolt 1983	(1) Paracetamol 650 mg, n=29 (2) Suprofen 200 mg, n=32 (3) Suprofen 400 mg, n=28 (4) Paracetamol+suprofen 650/100 mg, n=29 (5) Placebo, n=28	TOTPAR 6: (1) 15.1 (5) 7.5	(1) 21/29 (5) 8/28	(1) 21/29 (5) 5/27	No data	at 6 hrs: (1) 4/29 (5) 19/28

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

Forbes 1982	(1) Paracetamol 600 mg, n=34 (2) Paracetamol+codeine 600/60 mg, n=31 (3) Diflusinal 500 mg, n=32 (4) Diflusinal 1000 mg, n=32 (5) Placebo, n=30	TOTPAR 4: (1) 8.9 (5) 3.8	(1) 15/34 (5) 6/30	No usable data	Median: (1) 3.5 (5) 2.4	at 6 hrs: (1) 70 (5) 82
Forbes 1983	(1) Paracetamol 600 mg, n=26 (2) Paracetamol+codeine 600/60 mg, n=26 (3) Diflusinal 500 mg, n=26 (4) Diflusinal 1000 mg, n=28 (5) Placebo, n=26	TOTPAR 6: (1) 11.2 (5) 5.4	(1) 13/26 (5) 5/26	No usable data	Median: (1) 4.0 (5) 1.9	at 6 hrs: (1) 73 (5) 86
Forbes 1984a	(1) Paracetamol 650 mg, n=39 (2) Phenyltoloxamine 60 mg, n=33 (3) Patacetamol+phenyltoxolamine 650/60 mg, n=40 (4) Placebo, n=36	TOTPAR 6: (1) 6.7 (4) 2.1	(1) 10/39 (4) 0/36	No usable data	Mean: (1) 4.3 (4) 2.7	at 6 hrs: (1) 74 (4) 97
Forbes 1984b	(1) Paracetamol 650 mg, n=31 (2) Nalbuphine 30 mg, n=32 (3) Paracetamol+nalbuphine 650/30 mg, n=33 (4) Placebo, n=33	TOTPAR 6: (1) 8.5 (4) 4.5	(1) 11/31 (4) 4/33	No usable data	No data	No data
Forbes 1989	(1) Paracetamol 600 mg, n=22 (2) Paracetamol+codeine 600/60 mg, n=17 (3) Flurbiprofen 100 mg, n=26 (4) Placebo, n=23	(1) 4.6 (4) 2.0	(1) 1/22 (4) 0/23	No usable data	Median: (1) 2.8 (4) 1.7	at 4 hrs: (1) 82 (4) 91
Forbes 1990	(1) Paracetamol 600 mg, n=36 (2) Paracetamol+codeine 600/60 mg, n=38 (3) Ketorolac 10 mg, n=31 (4) Ketorolac 20 mg, n=35 (5) Ibuprofen 400 mg, n=32 (6) Placebo, n=34	TOTPAR 6: (1) 5.8 (6) 1.9	(1) 7/3 (6) 0/34	No usable data	Median: (1) 3.0 (6) 1.8 Mean: (1) 3.9 (6) 2.9	at 6 hrs: (1) 81 (6) 97
Haglund 2006	(1) Paracetamol 1000 mg, n=20 (2) Rofecoxib+paracetamol 50/1000 mg, n=34 (3) Rofecoxib 50 mg, n=36	TOTPAR 6: (1) 11.5 (4) 0.25	(1) 10/20 (4) 0/17	No usable data	Median: (1) >8 (4) 1.5	At 8 hrs: (1) 40.0 (4) 71 At 6 hrs:

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

	(4) Placebo n=17					(1) 24 (4) 70
Hersch 2000	(1) Paracetamol capsule 1000 mg, n=63 (2) Ibuprofen liquigel 200 mg, n=61 (3) Ibuprofen liquigel, 400 mg n=59 (4) Placebo, n=27	TOTPAR 6: (1) 11.99 (4) 5.25		at 6 hrs: (1) 52% (4) 14%	Median: (1) 6 (4) 1.63	at 6 hrs: (1) 50 (4) 75
Honig 1984	(1) Paracetamol 600 mg, n = 28 (2) Paracetamol+codeine 600/60 mg, n=28 (3) Codeine 60 mg, n=28 (4) Placebo, n = 25	TOTPAR 6: (1) value not given (4) 8.9	(1) 11/28 (4) 6/30	at 6 hrs: (1) 8/28 (4) 4/25	No data	at 6 hrs: (1) 16/28 (4) 114/30
Jain 1986	(1) Paracetamol 650 mg, n=30 (2) Nalbuphine 30 mg, n=34 (3) Paracetamol+nalbuphine 650/30 mg, n=32 (4) Placebo, n=32	TOTPAR 6: (1) 10.4 (4) 7.9	(1) 13/29 (4) 10/30	No data	No data	at 6 hrs: (1) 10/30 (4) 11/32
Kiersch 1994	(1) Paracetamol 1000 mg, n=92 (2) Naproxen Na 440 mg, n=89 (3) Placebo, n=45	TOTPAR 6: (1) 6.2 (3) 3.1	(1) 21/92 (3) 3/45	No usable data	Median: (1) 3.1 (3) 2.0	at 6 hrs: (1) 69 (3) 85
Kubitzek 2003	(1) Paracetamol 1000 mg, n=78 (2) Diclofenac K 25 mg, n=83 (3) Placebo, n=84	TOTPAR 6: values not given	At 6 hrs: (1) 45/78 (3) 7/84	at 6 hrs: (1) 17/78 (3) 1/84	Median: (1) 4.2 (3) 1.5	at 6h: (1) 76 (3) 89
Laska 1983 (Study 3)	(1) Paracetamol 500 mg, n=81 (2) Paracetamol 1000 mg, n=81 (3) Paracetamol 1500 mg, n=81 (4) Placebo, n=57	%max SPID: (1) 43 (2) 46.4 (3) 49.8 (4) 29.9	(1) 46/81 (2) 49/81 (3) 53/81 (4) 22/57	No data	not estimable	at 4 hrs: None
Lenhert 1990	(1) Paracetamol 1000 mg, n=49 (2) Aspirin 1000 mg, n=45 (3) Placebo, n=40	SPID 6: (1) 5.8 (3) 1.5	(1) 24/49 (3) 5/40	No usable data	No data	No data
McQuay 1988	(1) Paracetamol 1000 mg, n=30 (2) Bromfenac 5 mg, n=30 (3) Bromfenac 10 mg, n=30	TOTPAR 6: (1) 7.9 (5) 4.1	(1) 10/30 (5) 3/30	No usable data	Median: (1) 3.7 (5) 3.0	at 6 hrs: (1) 63 (5) 87

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

	(4) Bromfenac 25 mg, n=30 (5) Placebo, n=30					
Mehlisch 1984	(1) Paracetamol 1000 mg, n=58 (2) Aspirin 650 mg, n=49 (3) Placebo, n=55	TOTPAR 6: (1) 7.0 (3) 1.8	(1) 16/58 (3) 0/55	No usable data	No data	at 6hrs: (1) 45/58 (3) 52/55
Mehlisch 1990	(1) Paracetamol 1000 mg, n=306 (2) Ibuprofen 400 mg, n=306 (3) Placebo, n=85	(1) 4.1 (3) 1.2	(1) 131/306 (3) 9/85	No data	No data	No data
Mehlisch 1995	(1) Paracetamol 1000 mg, n=101 (2) Ibuprofen 400 mg, n=98 (3) Placebo, n=40	(1) 8.4 (3) 2.6	(1) 35/101 (3) 1/40	(1) 31/101 (3) 1/40	Median: (1) 4.2 (3) 1.4	at 6 hrs: (1) 60 (3) 88
Moller 2000	(1) Paracetamol tablet 1000 mg, n=60 (2) Placebo tablet, n=60 (3) Paracetamol effervescent 1000 mg, n = 60 (4) Placebo effervescent, n=62	TOTPAR 6: (1) 4.4 (2) 0.8 (3) 3.7 (4) 0.8	(1) 15/60 (2) 0/60 (3) 12/60 (4) 0/62	No usable data	Median: (1) 2.7 (2) 1.0 (3) 2.1 (4) 1.0	(1) 73 (2) 93 (3) 85 (4) 100
Moller 2005	(1) Paracetamol tablet 1000 mg, n=50 (2) Propacetamol 2000 mg iv bolus, n=50 (3) Propacetamol 2000 mg 15 min infusion, n=50 (4) Placebo, n=25	TOTPAR 6: (1) 9.4 (4) 5.0	(1) 22/50 (4) 4/25	No data	Median: (1) 4.6 (4) 1.1	No data
Olson 2001	(1) Paracetamol 1000 mg, n=66 (2) Ibuprofen liquigel 400 mg, n=67 (3) Ketoprofen 25 mg, n=67 (4) Placebo, n=39	TOTPAR 6: (1) 13.3 (4) 4.3	(1) 41/66 (4) 5/39	at 6 hrs: (1) 57% (4) 11%	Median: (1) >6 (4) 1.3	at 6 hrs: (1) 25/66 (4) 31/39
Pinto 1984	(1) Paracetamol 500 mg, n = 29 (2) Dipyrone 500 mg, n=29 (3) Placebo, n = 29	TOTPAR 4: (1) 11.4 (3) 5.6	(1) 24/29 (3) 10/29	No usable data	No data	at 4 hrs: (1) 0 (3) 28
Rubin 1984	(1) Paracetamol 1000 mg, n=123 (2) Paracetamol+aspirin 648/648 mg, n=123 (3) Aspirin+caffeine 800/6.5 mg, n=121 (4) Placebo, n=109	%max SPID: (1) 53.3 (4) 36.6	(1) 86/123 (4) 52/109	no data	no data	at 4 hrs: (1) 1/123 (4) 15/109

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

Rubinstein 1986	(1) Paracetamol 500 mg, n=30 (2) Dypyrone 500 mg, n=30 (3) Placebo, n=30	TOTPAR 4: (1) 10.1 (3) 4.7	(1) 22/30 (3) 8/30	No usable data	No data	at 4 hrs: (1) 7 (3) 20
Sakata 1986	(1) Paracetamol 1000 mg, n=30 (2) Dipyrone 1000 mg, n=30 (3) Placebo, n=27	TOTPAR 4: (1) 8.4 (3) 2.8	(1) 17/30 (3) 3/27	No usable data	No data	No data
Santos Pereira 1986	(1) Paracetamol 1000 mg, n=28 (2) Dipyrone 1000 mg, n=28 (3) Placebo, n=29	SPID 4: (1) 6.4 (3) 2.1	(1) 22/28 (3) 7/29	No usable data	No data	(1) 0 (3) 38
Schachtel 1989	(1) Paracetamol 1000 mg, n=37 (2) Ibuprofen 400 mg, n=36 (3) Placebo, n=38	TOTPAR 6: (1) 7.9 (3) 5.5	(1) 20/37 (3) 13/38	No usable data	No data	at 6 hrs: (1) 35 (3) 58
Seymour 1996	(1) Paracetamol 500 mg n=41 (2) Paracetamol 1000 mg n=41 (3) Ketoprofen 12.5 mg n=42 (4) ketoprofen 25 mg n=41 (5) Placebo, n=41	VAS SPID 6: (1) 135.4 (2) 150.0 (5) 75	(1) 19/41 (2) 21/41 (5) 10/41	at 6 hr: (1) 15/41 (2) 23/41 (5) 8/41	Median: (1) 2.8 (2) 4.1 (5) 1.8	(1) 32/40 (2) 33/40 (5) 38/39
Seymour 2003	(1) Paracetamol 1000 mg, n=62 (2) Aspirin (soluble) 900 mg, n=59 (3) Placebo, n=32	SPID 4 (VAS): (1) 40.7 (3) 22.6	(1) 13/62 (3) 3/32	at 4 hrs: (1) 53% (3) 10%	Median: (1) 1.6 (3) 1.1	At 4 hrs: (1) 74% (3) 91%
Sunshine 1986	(1) Paracetamol 650 mg, n=30 (2) Paracetamol+codeine 650/60 mg, n=31 (3) Flurbiprofen 50 mg, n=31 (4) Flurbiprofen 100 mg, n=29 (5) Zomepirac 100 mg, n=31 (6) Placebo, n=30	TOTPAR 6: (1) 11.1 (6) 8.3	(1) 15/30 (6) 10/30	No usable data	No data	at 6 hrs: (1) 47 (6) 43
Sunshine 1989	(1) Paracetamol 650 mg, n=75 (2) Paracetamol+phenyltoloxamine 650/60 mg, n=75 (3) Placebo, n=50	TOTPAR 6: (1) 7.3 (3) 2.2	(1) 22/75 (3) 0/50	No usable data	No data	at 6 hrs: (1) 3 (3) 16
Sunshine 1993	(1) Paracetamol 650mg, n=48 (2) Paracetamol+oxycodone 650/10 mg, n=48	TOTPAR 6: (1) 10.4	(1) 22/48 (5) 20/48	No usable data	Of pts with onset: Median:	at 8 hrs: (1) 88

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

	(3) Ketoprofen 50 mg, n=48 (4) Ketoprofen 100 mg, n=48 (5) Placebo, n=48	(5) 9.7			(1) 7 .0 (5) 6.0 No usable data	(5) 73
Winnem 1981	(1) Paracetamol 1000 mg, n=20 (2) Tiaramide 100 mg, n=20 (3) Tiaramide 200 mg, n=19 (4) Placebo, n=20	SPID 6: (1) 4.3 (4) 1.7	(1) 9/20 (4) 3/20	No data	No usable data	at 6 hrs: (1) 24 (4) 45
Winter 1979	(1) Paracetamol 325 mg, n=49 (2) Orphenadrine 25 mg, n=50 (3) Paracetamol+orphenadrine 325/25 mg, n=50 (4) Placebo, n=51	SPID 6: (1) 9.5 (4) 5.9	(1) 34/49 (4) 22/51	No data	Mean: (1) 3.1 (4) 2.9	at 6 hrs: (1) 67 (4) 75
Winter 1983	(1) Paracetamol 1000 mg, n=41 (2) Paracetamol+caffeine 1000/130 mg, n=40 (3) Caffeine 130 mg, n=42 (4) Placebo, n=41	TOTPAR 4: (1) 7.4 (4) 4.0	(1) 20/41 (4) 9/41	No data	No data	at 4 hrs: (1) 2 (4) 2
Young 1979	Study 1: (1) Paracetamol 650 mg, n=30 (2 Paracetamol+butorphanol 650/4 mg, n=30 (3) Butorphanol 4 mg, n=30 (4) Placebo, n=29	TOTPAR 4: (1) 7.3 (4) 7.2	(1) 15/30 (4) 14/29	No usable data	No data	No data

Table 2. Summary of Outcomes: adverse events and withdrawals

		Adverse events		Withdrawals	
Study ID	**Treatment**	**Any**	**Serious**	**Adverse event**	**Other**
Bentley 1987	(1) Paracetamol 1000 mg, n=41 (2) Paracetamol+codeine 1000/60 mg, n=41 (3) Codeine 60 mg, n=21 (4) Placebo, n=17	(1) 21/42 (4) 9/19	None reported	None reported	7 excluded form efficacy analysis due to invalid data, 1 did not return forms

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

Berry 1975	(1) Paracetamol 1000 mg, n=76 (2) Propoxyphene 65 mg, n=73 (3) Placebo, n=76	None related to medication	None reported	None reported	None reported
Bhounsule 1990	(1) Paracetamol 1000 mg, n=20 (2) Ibuprofen 400 mg, n=20 (3) Aspirin 600 mg, n=20 (4) Analgin 500 mg, n=20 (5) Placebo, n=20	None related to medication	None reported	None reported	None
Bjune 1996	(1) Paracetamol 1000 mg, n=50 (2) Paracetamol+codeine 800/60 mg, n=50 (3) Placebo, n=25	(1) 10/50 (3) 1/25	None	None	7 paracetamol, 4 placebo pts excluded due to invalid data
Cooper 1980	(1) Paracetamol 500 mg, n=37 (2) Oxycodone 5 mg, n=42 (3) Paracetamol+oxycodone 500/5 mg, n=5 (4) Paracetamol+oxycodone 1000/5 mg, n=40 (5) Paracetamol+oxycodone 1000/10 mg, n=45 (6) Placebo, n=38	(1) 3/37 (6) 6/38	None reported	None reported	Exclusions due to invalid data, numbers not given per group
Cooper 1981	(1) Paracetamol 650 mg, n=37 (2) Paracetamol+codeine 650/60 mg, n=42 (3) Paracetamol+d-propoxyphene 650/100 mg, n=42 (4) Ibuprofen 200 mg, n=42 (5) Placebo, n=37	(1) 12/37 (5) 4/37	None	None	Exclusions due to invalid data, numbers not given per group
Cooper 1986	(1) Paracetamol 1000 mg, n=38 (2) Paracetamol+codeine+caffeine 1000/16/30 mg, n=39 (3) Placebo, n=22	No data	None	None	6 paracetamol, 1 placebo excluded due to invalid data
Cooper 1988	(1) Paracetamol 600 mg, n=36 (2) Paracetamol+codeine 600+60 mg, n=31 (3) Placebo, n=40	No data	No data	None	Exclusions due to invalid data, numbers not given per group

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

Cooper 1989	(1) Paracetamol 1000 mg, n=59 (2) Ibuprofen 400 mg, n=61 (3) Placebo, n=64	(1) 11/63 (3) 7/64	None	None	Exclusions due to invalid data, numbers not given per group
Cooper 1991a	(1) Paracetamol 650 mg, n=37 (2) Paracetamol+codeine 650/60 mg, n=39 (3) Zomepirac 100 mg, n=23 (4) Flurbiprofen 50 mg, n=42 (5) Flurbiprofen 100 mg, n=41 (6) Placebo, n=44	(1) 6/37 (6) 7/44	None reported	None reported	Exclusions due to invalid data, numbers not given per group
Cooper 1998	(1) Paracetamol 1000mg n=50 (2) Ketoprofen 100 mg, n=51 (3) Ketoprofen 1000 mg, n=50 (4) Placebo n=26	(1) 25/50 (4) 4/26	None	None	None
Dionne 1994	(1) Paracetamol 650 mg, n=27 (2) Paracetamol+codeine 650/60 mg, n=24 (3) Flurbiprofen 50 mg, n=25 (4) Flurbiprofen 100 mg, n=22 (5) Placebo, n=25	(1) 7/27 (5) 9/24	None reported	None reported	11 excluded from analysis: enrolled twice, early rescue medication, asleep during observations, lost to follow up
Dolci 1994	(1) Paracetamol 500 mg, n=72 (2) Piroxicam 20 mg, n=76 (3) Piroxicam cyclodextrin =20 mg, n=74 (4) Placebo, n=76	(1) 7/80 (4) 6/82	None reported	(1) 2/80 (4) 1/82	Exclusions due to invalid data, numbers not given per group
Edwards 2002	(1) Paracetamol 650 mg, n=340 (2) Placebo, n=339 5 dental studies included in meta-analysis	(1) 54/340 (2) 58/337	None reported	(1) 1/340 (2)2/337	No data
Edwards 2002	(1) Paracetamol 975 mg, n=100 (2) Placebo, n=100 2 gynae or ortho studies in meta-analysis	No data	No data	No data	No data
Fassolt 1983	(1) Paracetamol 650 mg, n=29 (2) Suprofen 200 mg, n=32 (3) Suprofen 400 mg, n=28	No data	None reported	No data	No data

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

	(4) Paracetamol+suprofen 650/100 mg, n=29				
Forbes 1982	(1) Paracetamol 600 mg, n=34 (2) Paracetamol+codeine 600/60 mg, n=31 (3) Diflusinal 500 mg, n=32 (4) Diflusinal 1000 mg, n=32 (5) Placebo, n=30	No usable data	None	None	None reported
Forbes 1983	(1) Paracetamol 600 mg, n=26 (2) Paracetamol+codeine 600/60 mg, n=26 (3) Diflusinal 500 mg, n=26 (4) Diflusinal 1000 mg, n=28 (5) Placebo, n=26	(1) 11/26 (5) 4/26	None reported	None	None
Forbes 1984a	(1) Paracetamol 650 mg, n=39 (2) Phenyltoloxamine 60 mg, n=33 (3) Patacetamol+phenyltoxolamine 650/60 mg, n=40 (4) Placebo, n=36	(1) 1/423 (4) 2/40	None	None	Exclusions due to invalid data, numbers not given per group
Forbes 1984b	(1) Paracetamol 650 mg, n=31 (2) Nalbuphine 30 mg, n=32 (3) Paracetamol+nalbuphine 650/30 mg, n=33 (4) Placebo, n=33	(1) 9/33 (4) 8/33	None	None	Three pts excl from efficacy analysis due to invalid data
Forbes 1989	(1) Paracetamol 600 mg, n=22 (2) Paracetamol+codeine 600/60 mg, n=17 (3) Flurbiprofen 100 mg, n=26 (4) Placebo, n=23	(1) 3/26 (4) 4/26	None	None	10 pts excl from efficacy analysis due to invalid data
Forbes 1990	(1) Paracetamol 600 mg, n=36 (2) Paracetamol+codeine 600/60 mg, n=38 (3) Ketorolac 10 mg, n=31 (4) Ketorolac 20 mg, n=35 (5) Ibuprofen 400 mg, n=32 (6) Placebo, n=34	(1) 5/41 (6) 0/38	None	None	37 pts excl from efficacy analysis due to invalid data

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

Haglund 2006	(1) Paracetamol 1000 mg, n=20 (2) Rofecoxib/paracetamol 50/1000mg, n=34 (3) Rofecoxib 50 mg, n=36 (4) Placebo, n=17	No usable data	None	None reported	5 - inadequately filled in questionnaires. Not included in final analysis
Hersch 2000	(1) Paracetamol capsule 1000 mg, n=63 (2) Ibuprofen liquigel 200 mg, n=61 (3) Ibuprofen liquigel 400 mg n=59 (4) Placebo, n=27	(1) 12/63 (4) 7/27	None	None	None
Honig 1984	(1) Paracetamol 600 mg, n = 28 (2) Paracetamol+codeine 600/60 mg, n=28 (3) Codeine 60 mg, n=28 (4) Placebo, n=25	No data	none	None reported	None reported
Jain 1986	(1) Paracetamol 650 mg, n=30 (2) Nalbuphine 30 mg, n=34 (3) Paracetamol+nalbuphine 650/30 mg, n=32 (4) Placebo, n=32	(1) 9/30 (4) 6/32	None reported	None reported	6 pts excl from efficacy analysis due to invalid data
Kiersch 1994	(1) Paracetamol 1000 mg, n=92 (2) Naproxen Na 440 mg, n=89 (3) Placebo, n=45	(1) 31/94 (3) 13/45	None	(1) 2/94 (vomiting within 10 mins) (3) 0/45	None
Kubitzek 2003	(1) Paracetamol 1000 mg, n=78 (2) Diclofenac K 25 mg, n= 83 (3) Placebo, n=84	48 hrs: (1) 4/78 (3) 2/84	None	None	1 in placebo group due to dosing protocol violation
Laska 1983 (Study 3)	(1) Paracetamol 500 mg, n=81 (2) Paracetamol 1000 mg, n=81 (3) Paracetamol 1500 mg, n=81 (4) Placebo, n=57	No data	No data	None reported	Various protocol violations - groups not given
Lenhert 1990	(1) Paracetamol 1000 mg, n=49 (2) Aspirin 1000 mg, n=45 (3) Placebo, n=40	(1) 5/49 (2) 4/40	None reported	None reported	11 did not take the medication, 3 were lost to follow up and 3 for various protocol violations.

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

McQuay 1988	(1) Paracetamol 1000 mg, n=30 (2) Bromfenac 5 mg, n=30 (3) Bromfenac 10 mg, n=30 (4) Bromfenac 25 mg, n=30 (5) Placebo, n=30	(1) 6/30 (2) 6/30	None	None reported	8 excluded from analysis due to invalid data
Mehlisch 1984	(1) Paracetamol 1000 mg, n=58 (2) Aspirin 650 mg, n=49 (3) Placebo, n=55	No usable data	No data	None	162 analysed. Exclusions: 9 failed to comply with protocol & 3 were lost to follow up.
Mehlisch 1990	(1) Paracetamol 1000 mg, n=306 (2) Ibuprofen 400 mg, n=306 (3) Placebo, n=85	(1) 32/307 (3) 12/85	None reported	None reported	2 Paracetamol lost to follow up, 1 Paracetamol entered in trial twice (invalid data)
Mehlisch 1995	(1) Paracetamol 1000 mg, n=101 (2) Ibuprofen 400 mg, n=98 (3) Placebo, n=40	(1) 17/101 (3) 4/40	None	None	None
Moller 2000	(1) Paracetamol tablet 1000 mg, n=60 (2) Placebo tablet, n=60 (3) Paraceamol effervescent 1000 mg, n=60 (4) Placebo effervescent, n=62	(1) 24/60 (2) 21/60 (3) 24/60 (4) 35/60	None	None reported	None
Moller 2005	(1) Paracetamol tablet 1000 mg, n=50 (2) Propacetamol 2000 mg iv bolus, n=50 (3) Propacetamol 2000 mg 15 min infusion, n=50 (4) Placebo, n=25	At 7 days: (1) 21/50 (4) 12/25	1 in propacetamol iv bolus group	None	None
Olson 2001	(1) Paracetamol 1000 mg, n=66 (2) Ibuprofen liquigel 400 mg, n=67 (3) Ketoprofen 25 mg, n=67 (4) Placebo, n=39	At 6 hrs: (1) 10/66 (4) 2/39	None	None	None
Pinto 1984	(1) Paracetamol 500 mg, n=29 (2) Dipyrone 500 mg, n=29	(1) 0/29 (3) 0/29	None reported	No data	No data

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

	(3) Placebo, n=29				
Rubin 1984	(1) Paracetamol 1000 mg, n=123 (2) Paracetamol+aspirin 648/648 mg, n=123 (3) Aspirin+caffeine 800/6.5 mg, n=121 (4) Placebo, n=109	(1) 6/123 (4) 6/109	None	None	None
Rubinstein 1986	1) Paracetamol 500 mg, n=30 2) Dypyrone 500 mg, n=30 3) Placebo, n=30	(1) 1/30 (3) 0/30	None reported	None	None
Sakata 1986	(1) Paracetamol 1000 mg, n=30 (2) Dipyrone 1000 mg, n=30 (3) Placebo, n=27	No data	No data	No data	No data
Santos Pereira 1986	(1) Paracetamol 1000 mg, n=28 (2) Dipyrone 1000 mg, n=28 (3) Placebo, n = 29	No data	No data	No data	No data
Schachtel 1989	(1) Paracetamol 1000 mg, n=37 (2) Ibuprofen 400 mg, n=36 (3) Placebo, n=38	None	None	None	None
Seymour 1996	(1) Paracetamol 500 mg, n=41 (2) Paracetamol 1000 mg, n=41 (3) Ketoprofen 12.5 mg, n= 42 (4) ketoprofen 25 mg, n=41 (5) Placebo, n=41	No patients reported any AE	None	None	2 placebo, 1 from each paracetamol group excl from efficacy analysis due to early rescue medication
Seymour 2003	(1) Paracetamol 1000 mg, n=62 (2) Aspirin (soluble) 900 mg, n=59 (3) Placebo, n=32	At 4 hrs: (1) 39/62 (3) 28/32	None reported	None reported	None
Sunshine 1986	(1) Paracetamol 650 mg, n=30 (2) Paracetamol+codeine 650/60 mg, n=31 (3) Flurbiprofen 50 mg, n=31 (4) Flurbiprofen 100 mg, n=29 (5) Zomepirac 100 mg, n=31	(1) 1/30 (6) 1/30	None	None	None

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

	(6) Placebo, n=30				
Sunshine 1989	(1) Paracetamol 650 mg, n=75 (2) Paracetamol+phenyltoloxamine 650/60 mg, n=75 (3) Placebo, n=50	(1) 0/75 (3) 0/50	None	None	None
Sunshine 1993	(1) Paracetamol 650 mg, n=48 (2) Paracetamol+oxycodone 650/10 mg, n=48 (3) Ketoprofen 50 mg, n=48 (4) Ketoprofen 100 mg, n=48 (5) Placebo, n=48	No details for single dose phase	No cases of possible clinical concern	None reported	None
Winnem 1981	(1) Paracetamol 1000 mg, n=20 (2) Tiaramide 100 mg, n=20 (3) Tiaramide 200 mg, n=19 (4) Placebo, n=20	None	None	None	1 excl from analysis for vomiting medication within 30 mins.
Winter 1979	(1) Paracetamol 325 mg, n=49 (2) Orphenadrine 25 mg, n=50 (3) Paracetamol+orphenadrine 325/25 mg, n=50 (4) Placebo, n=51	(1) 0/49 (4) 1/51	None	None	None reported
Winter 1983	(1) Paracetamol 1000 mg, n=41 (2) Paracetamol+caffeine 1000/130 mg, n=40 (3) Caffeine 130 mg, n=42 (4) Placebo, n=41	(1) 0/41 (4) 1/41	None	None	None reported

APPENDICES

Appendix 1. MEDLINE search strategy

1. acetaminophen [single term MESH]

2. acetaminophen OR paracetamol

3. OR/1-2

4. PAIN, POSTOPERATIVE [single term MeSH]

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$) or ("post-operative analgesi$")) [in title, abstract or keywords]

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$))[in title, abstract or keywords]

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")) [in title, abstract or keywords]

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)) [in title, abstract or keywords]

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$"))[in title, abstract or keywords]

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$"))

11. OR/4-10

12. randomized controlled trial.pt.

13. controlled clinical trial.pt.

14. randomized controlled trials.sh.

15. random allocation.sh.

16. double-blind method.sh.

17. clinical trial.pt.

18. exp clinical trials/

19. (clin$ adj25 trial$) [in title, abstract or keywords]

20. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)) [in title, abstract or keywords]

21. placebos.sh.

22. placebo$ [in title, abstract or keywords]

23. random$ [in title, abstract or keywords]

24. research design.sh.

25. OR/12-24

26. 3 AND 11 AND 25

Appendix 2. EMBASE search strategy

1. acetaminophen [single term MESH]

2. acetaminophen OR paracetamol

3. OR/1-2

4. PAIN, POSTOPERATIVE [single term MeSH]

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$) or ("post-operative analgesi$"))

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$))

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after"))

8. (("post surg$" or post-surg$) AND (pain$ or discomfort))

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$"))

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $"))

11. OR/4-10

12. clinical trials [exp MESH term]

13. controlled clinical trials [exp MESH term]

14. randomized controlled trial [exp MESH term]

15. double-blind procedure [single term MESH]

16. (clin$ adj25 trial$)

17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$))

18. placebo$

19. random$

20. OR/12-19

21. 3 AND 11 AND 20

Appendix 3. Cochrane CENTRAL search strategy

1. acetaminophen [single term MESH]

2. (acetaminophen OR paracetamol) [ti, ab, kw]

3. OR/1-2

4. PAIN, POSTOPERATIVE [single term MeSH]

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 [exp MESH term]

13. controlled clinical trials [exp MESH term]

14. randomized controlled trial [exp MESH term]

15. double-blind procedure [single term MESH]

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

Appendix 4. Glossary

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

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

TOTPAR: Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule.

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.

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 1, 2004

Date	Event	Description
25 April 2012	Review declared as stable	The authors have checked the data on this topic and though there may be new studies, they are very unlikely to change the review's current conclusions. Therefore this review has been made 'stable' for at least five years.
31 July 2008	New search has been performed	New studies identified and included in analysis. All studies checked for additional data on use of rescue medication.
31 July 2008	New citation required but conclusions have not changed	Efficacy estimates only moderately changed
30 November 2003	New search has been performed	New studies found and included or excluded: 9/25/03

Date	Event	Description
25 October 1999	Amended	This review is an update of 'Single dose paracetamol (acetaminophen) with and without codeine for postoperative pain' published in 1998. The review was split into two reviews: paracetamol alone, and paracetamol plus codeine. The ID followed the first published review, paracetamol alone.

CONTRIBUTIONS OF AUTHORS

For the updated review (2008): LT and SD identified studies for inclusion, carried out data extraction, analysis and writing. RAM was involved with analysis and writing. HJM acted as arbitrator and was involved with writing.

DECLARATIONS OF INTEREST

RAM & HJM have consulted for various pharmaceutical companies. RAM & HJM have received lecture fees from pharmaceutical companies that market analgesics and other healthcare interventions. RAM, HJM and SD have received research support from charities, government and industry sources at various times, but no such support was received for this work.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Funds, UK.

External sources

- NHS Cochrane Collaboration Grant Scheme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update includes outcomes that were not considered for the protocol in the original review. This reflects increased understanding of the clinical trial data over the past 10 years or more, in part because of the results of systematic reviews. Use of individual patient data, rather than averages, has also helped shape different attitudes to outcomes, as has the input from professionals and consumers.

NOTES

This review was first published as a Cochrane systematic review by Moore et al entitled: 'Single dose paracetamol (acetaminophen) with and without codeine for postoperative pain' , published in 1998. The original review has been split into two reviews: paracetamol alone, and paracetamol plus codeine. Paracetamol alone was updated and published as a Cochrane review by Barden et al in 2004. This review is an update of the 2004 review on 'Single dose oral paracetamol (acetaminophen) for postoperative pain in adults'.

October 2017

A restricted search in September 2017 did not identify any potentially relevant studies. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Humans