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Paracetamol for pain relief after surgical removal of lower wisdom teeth (Review)

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[Intervention Review]

Paracetamol for pain relief after surgical removal of lower wisdom teeth

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ABSTRACT

Background

Paracetamol has been commonly used for the relief of postoperative pain following oral surgery. In this review we investigated the optimal dose of paracetamol and the optimal time for drug administration to provide pain relief, taking into account the side effects of different doses of the drug. This will inform dentists and their patients of the best strategy for pain relief after the surgical removal of wisdom teeth.

Objectives

To assess the beneficial and harmful effects of paracetamol for pain relief after surgical removal of lower wisdom teeth, compared to placebo, at different doses and administered postoperatively.

Search methods

We searched the Cochrane Oral Health Group's Trials Register; the Cochrane Pain, Palliative and Supportive Care Group's Trials Register; CENTRAL; MEDLINE; EMBASE and the Current Controlled Trials Register. Handsearching included several dental journals. We checked the bibliographies of relevant clinical trials and review articles for studies outside the handsearched journals. We wrote to authors of the identified randomised controlled trials (RCTs), to manufacturers of analgesic pharmaceuticals, we searched personal references in an attempt to identify unpublished or ongoing RCTs. No language restriction was applied. The last electronic search was conducted on 24th August 2006.

Selection criteria

Randomised, parallel group, placebo controlled, double blind clinical trials of paracetamol for acute pain, following third molar surgery.

Data collection and analysis

All trials identified were scanned independently and in duplicate by two review authors, any disagreements were resolved by discussion, or if necessary a third review author was consulted. The proportion of patients with at least 50% pain relief was calculated for both paracetamol and placebo. The number of patients experiencing adverse events, and/or the total number of adverse events reported were analysed.

Main results

Twenty-one trials met the inclusion criteria. A total of 2048 patients were initially enrolled in the trials (1148 received paracetamol, and 892 the placebo) and of these 1968 (96%) were included in the meta-analysis (1133 received paracetamol, and 835 the placebo). Paracetamol

provided a statistically significant benefit when compared with placebo for pain relief and pain intensity at both 4 and 6 hours. Most studies were found to have moderate risk of bias, with poorly reported allocation concealment being the main problem. Risk ratio values for pain relief at 4 hours 2.85 (95% confidence interval (CI) 1.89 to 4.29), and at 6 hours 3.32 (95% CI 1.88 to 5.87). A statistically significant benefit was also found between up to 1000 mg and 1000 mg doses, the higher the dose giving greater benefit for each measure at both time points. There was no statistically significant difference between the number of patients who reported adverse events, overall this being 19% in the paracetamol group and 16% in the placebo group.

Authors' conclusions

Paracetamol is a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth.

PLAIN LANGUAGE SUMMARY

Paracetamol for pain relief after surgical removal of lower wisdom teeth

The surgical removal of wisdom teeth (third molars) is the most commonly performed surgical procedure undertaken in oral surgery practice. Postoperative complications may include swelling, bruising and limited mouth opening but patients are most often concerned about postoperative pain, which may be severe. Paracetamol is effective in relieving pain with a low incidence of adverse effects. It is one of the most commonly used analgesics and is widely available without prescription around the world. In this review we investigated the optimal dose of paracetamol and the optimal time for drug administration to provide pain relief after the surgical removal of wisdom teeth. The side effects of different doses of the drug were also explored.

Twenty-one trials (with over 2000 participants) were included. Paracetamol provided a statistically significant benefit when compared with placebo for pain relief at both 4 and 6 hours after taking the drug. It is most effective at 1000 mg dose, and can be taken at six hourly intervals without compromising safety. There was no statistically significant difference between the number of patients who reported adverse events, overall this being 19% in the paracetamol group and 16% in the placebo group. It should be noted that most of the studies were found to have some limitations mainly due to poor reporting of information. However the review concludes that paracetamol is a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth.

BACKGROUND

The surgical removal of wisdom teeth is the most commonly performed surgical procedure undertaken in oral surgery practice. Postoperative complications may include swelling, bruising and limited mouth opening but patients are most often concerned about postoperative pain, which may be severe. The pain experienced after oral surgery is a validated and widely used pain model for the clinical evaluation of analgesic efficacy (Cooper 1976). Tissue damage produced during surgery releases chemicals that initiate inflammatory pain by activating and sensitising nerve fibre receptors (Loeser 1999). Chemicals include bradykinin, prostaglandins, serotonin and histamine (Dray 1997).

Paracetamol (acetaminophen) is a nonopioid analgesic possessing antipyretic activity and is effective in relieving pain with a low incidence of adverse effects (Moore 1998). It is one of the most commonly used analgesics and is widely available without prescription around the world. Paracetamol is often grouped with the nonsteroidal anti-inflammatory drug (NSAID) family, however, it is considered only to have relatively weak anti-inflammatory activity (Rang 2003). NSAIDs are assumed largely to produce their analgesia as a result of the inhibition of prostaglandin production by the enzyme cyclo-oxygenase (Malmberg 1992). The mechanism of action has not been fully understood. Among several theories it has been suggested that paracetamol is a selective inhibitor of the newly described COX-3 enzyme, a cyclo-oxygenase-1 variant, in the central nervous system. This inhibition could represent a primary central mechanism by which paracetamol decreases pain and possibly fever (Chandrasekharan 2002). Major evidence has been accumulated showing that paracetamol inhibits cyclo-oxygenase by reducing the higher oxidative state of the cyclo-oxygenase enzyme, by reducing oxygen radical co-substrates (Aronoff 2006). Paracetamol has been shown to be an effective analgesic in the control of postoperative dental pain in a number of clinical trials (Bentley 1987; Kiersch 1994; Mehlisch 1990). Pain intensity following third molar surgery has been suggested to reach its maximum between 3 to 5 hours following surgery (Fisher 1988; Seymour 1985) and therefore this pain model is used to test the efficacy of a single analgesic dose.

A recent systematic review (Barden J 2004) has looked at the efficacy and safety of paracetamol for postoperative pain management and has included the findings of studies involving a wide variety of types of surgery such as gynaecology surgery, abdominal surgery, orthopaedic surgery amongst others including the removal of wisdom teeth. There is some debate as to whether dental pain is different from other pain. It has been suggested that the effect of some analgesics including tramadol were worse for dental pain than for other types of postsurgical pain (Moore 1997).

In this review we investigated the optimal dose of paracetamol and the optimal time for drug administration to provide pain relief, taking into account the side effects of different doses of the drug. This will inform dentists and their patients of the best strategy for best pain relief after the surgical removal of wisdom teeth.

OBJECTIVES

To assess the beneficial and harmful effects of paracetamol for pain relief after surgical removal of lower wisdom teeth, compared to placebo, at different doses and administered preoperatively or postoperatively.

Primary

- To test the null hypothesis of no difference in the beneficial and harmful effects between paracetamol and placebo for pain relief in patients requiring surgical removal of a lower wisdom tooth or teeth, against the alternative hypothesis of a difference.

Secondary

- To test the null hypothesis of no difference in the beneficial and harmful effects between different doses of paracetamol for pain relief in patients requiring surgical removal of a lower wisdom tooth or teeth, against the alternative hypothesis of a difference.
- To test the null hypothesis of no difference in the beneficial and harmful effects between different times of administration of paracetamol for pain relief in patients requiring surgical removal of a lower wisdom tooth or teeth, against the alternative hypothesis of a difference.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled double blind clinical trials.

Types of participants

Patients of all health states who required the surgical removal of a lower wisdom tooth and who had at least had a baseline pain intensity of moderate to severe pain. Patients who also required removal of an additional tooth or teeth were included. Surgery was undertaken under local anaesthesia, intravenous sedation or general anaesthesia. Patients taking concurrent analgesia were excluded.

Types of interventions

Efficacy

- Paracetamol given as a single dose by mouth in any dose and in any formulation (for example, immediate or slow release) regardless of when the single dose was given (for example, preoperatively or postoperatively).

Side effects

In order to investigate side effects more thoroughly, we included both single and multiple dose studies.

- Paracetamol given up to 7 days by mouth in any dose and in any formulation (for example, immediate or slow release) regardless of when the first dose was given (for example, preoperatively or postoperatively).

Types of outcome measures

- Pain intensity (visual analogue scale (VAS), categorical verbal rating, verbal numerical scale, global subjective efficacy ratings and other categorical rating scales).
- Pain relief (VAS, categorical verbal rating, verbal numerical scale, global subjective efficacy ratings and other categorical rating scales) and derived pain relief outcomes extracted will be total pain relief (TOTPAR), summed pain intensity difference (SPID) over 4 and 6 hours.
- Side effects (for example, hepatic and renal) (binary).

Search methods for identification of studies

To identify studies for inclusion or consideration in this review a detailed search strategy was developed for each database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database. The search strategy combined a sensitive search strategy for randomised controlled trials (RCTs) revised from phases 1 and 2 of the Cochrane Sensitive Search Strategy for RCTs (as published in Appendix 5b in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6 (updated September 2006)). The subject search used a combination of controlled vocabulary and free text terms based on the search strategy for searching CENTRAL (*see* Appendix 1).

Databases to be searched

The Cochrane Oral Health Group's Trials Register (to 24th August 2006)
The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 3)
The Cochrane Pain, Palliative and Supportive Care Group's Trials Register (to 24th August 2006)
MEDLINE (1966 to 24th August 2006)
EMBASE (1980 to 25th August 2006)
Current Controlled Trials Register (www.controlled-trials.com) (to 24th August 2006).

The bibliographies of papers and review articles were checked for studies outside the handsearched journals. Personal references were also searched.

Language

There were no language restrictions and where necessary, translation into the English language of relevant studies was conducted.

Unpublished studies

Authors of RCTs identified were written to in order to obtain further information about the trial and to attempt to identify unpublished or ongoing studies. We also wrote to manufacturers of analgesic pharmaceuticals.

Handsearching

Several journals relevant to this review were handsearched as part of the Cochrane Oral Health Group's ongoing journal handsearching programme. The list of the dental journals handsearched by The Cochrane Collaboration can be found at http://www.ohg.cochrane.org/.

Data collection and analysis

The titles and abstracts (when available) of all reports identified were scanned independently and in duplicate by two review authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained and assessed independently and in duplicate by two review authors to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. All studies meeting the inclusion criteria then underwent quality assessment and data extracted. Studies rejected at this or subsequent stages were recorded in the Characteristics of excluded studies table, and reasons for exclusion were recorded.

Quality assessment

The quality assessment of the included trials was undertaken independently and in duplicate by two review authors based on what is written in the articles.
Only double blind trials were included in the review so blinding was not included in the quality assessment.

Two main quality criteria were examined.
(1) Allocation concealment, recorded as:
(A) Adequate -2 points
(B) Unclear - 1 point
(C) Inadequate - 0 points.

(2) Completeness of follow up (is there a clear explanation for withdrawals and drop outs in each treatment group?) assessed as:
(A) Yes - 1 point
(B) No - 0 points.

The agreement for the quality criteria between assessors was determined by Kappa statistics.
After taking into account the additional information provided by the authors of the trials, studies were grouped into the following categories.
(A) Low risk of bias - 3 points (plausible bias unlikely to seriously alter the results) if all criteria were met.
(B) Moderate or high risk of bias - 0 to 2 points. Moderate risk of bias - plausible bias that raises some doubt about the results if one or more criteria are partly met (for example, when authors responded that they had made some attempts to conceal the allocation of patients, to give an explanation for withdrawals, but these attempts were not judged to be ideal, these criteria were categorised as 'partly'). High risk of bias - plausible bias that seriously weakens confidence in the results if one or more criteria were not met as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6.

We also reported whether the authors of included trials have conducted a sample size calculation.

Data extraction

Data were extracted by two review authors independently and in duplicate using specially designed data extraction forms. Any disagreement was discussed and a third review author consulted where necessary. Authors were contacted for clarification of missing information. Data were excluded until further clarification was available if agreement could not be reached.
For each trial the following data were recorded.

- Year of publication, country of origin, setting and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the study design (parallel group or cross-over design).
- Details on the type of intervention.
- Details of the outcomes reported, including method of assessment and time intervals.

Data synthesis

From the mean total pain relief (TOTPAR) or summed pain intensity difference (SPID) pain indices reported we computed a dichotomous outcome variable for the number of patients with at least 50% pain relief according to the methods outlined in a Cochrane review (Collins 1999). For each of the three objectives we examined the appropriateness of different continuous outcome measurements, and these were meta-analysed and reported in the final review.

For dichotomous outcomes, the estimate of an intervention was expressed as risk ratios together with 95% confidence intervals. For continuous outcomes, mean differences and 95% confidence intervals were used to summarise the data for each trial.

Clinical heterogeneity was assessed by examining the types of participants, interventions and outcomes in each study. Meta-analyses were conducted only with studies of similar comparisons reporting the same outcome measures. Risk ratios were used to combine dichotomous data, and mean differences for continuous data, using random-effects models. The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and any heterogeneity investigated.
Where both visual analogue scale (VAS) and categorical scales were used to measure pain intensity or pain relief or both, the categorical data were used in the meta-analysis as this was the most frequently used scale.

Subgroup analyses

Subgroup analyses were planned for studies.

- Where patients underwent surgery with local anaesthesia alone, local anaesthesia and intravenous sedation, general anaesthesia alone and general anaesthesia with local anaesthetic.
- Where different types of formulation of paracetamol were used: for instance, immediate release versus slow release.
- Where different doses of paracetamol were used (1000 mg or more, and less than 1000 mg).
- Where time of administration of paracetamol differs: preoperative versus postoperative.
- Where TOTPAR was calculated using pain relief measures and pain intensity measures.

The difference between studies comparing up to 1000 mg doses with studies comparing 1000 mg or more, was examined by performing random-effects metaregression analyses in Stata version 9.0 (Stata Corporation, USA) using the program Metareg.

The results of the metaregressions for comparing the two dose levels, up to 1000 mg and 1000 mg or more are presented in Additional Table 1.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Characteristics of the trial setting and investigators

Of the 67 eligible trials, 46 were excluded as shown in the excluded studies section. Of the 21 included studies, one was conducted in Denmark (Moller 2000), two in Germany (Kubitzek 2003; Lehnert 1990), one in Italy (Dolci 1994), one in Norway (Skoglund 1991), two in Puerto Rico (Olson 2001; Sunshine 1986), one in Thailand (Vattaraphudej 1986), two in the United Kingdom (Seymour 1996; Seymour 2003), and 11 in the United States of America (Cooper 1980; Cooper 1981; Cooper 1988; Cooper 1998; Dionne 1994; Forbes 1984b; Forbes 1989; Forbes 1990; Hersh 2000; Kiersch 1994; Mehlisch 1995). Six trials were conducted at university clinics (Cooper 1998; Hersh 2000; Moller 2000; Olson 2001; Sunshine 1986; Vattaraphudej 1986), five at private practices (Dionne 1994; Forbes 1984b; Forbes 1989; Forbes 1990; Kubitzek 2003), seven did not state a setting (Cooper 1981; Dolci 1994; Kiersch 1994; Mehlisch 1995; Seymour 1996; Seymour 2003; Skoglund 1991). One reported a single site (Cooper 1988), two reported two sites (Forbes 1989; Seymour 2003) and six specifically stated outpatients (Cooper 1980; Cooper 1988; Forbes 1989; Forbes 1990; Hersh 2000; Lehnert 1990). Seventeen trials were sponsored by industry (Cooper 1981; Cooper 1988; Cooper 1998; Dionne 1994; Forbes 1984b; Forbes 1989; Forbes 1990; Hersh 2000; Kiersch 1994; Kubitzek 2003; Lehnert 1990; Mehlisch 1995; Moller 2000; Olson 2001; Seymour 2003; Skoglund 1991; Sunshine 1986), one by a university grant (Vattaraphudej 1986), and it was unclear as whether the remaining three trials (Cooper 1980; Dolci 1994; Seymour 1996) were sponsored, but it is likely that they were from correspondence with some of the authors.

Characteristics of interventions

All included interventions were randomised, parallel group, and double blind. Eleven trials used doses of paracetamol of less than 1000 mg (Cooper 1980; Cooper 1981; Cooper 1988; Dionne 1994; Dolci 1994; Forbes 1984b; Forbes 1989; Forbes 1990; Seymour 1996; Sunshine 1986; Vattaraphudej 1986). Eleven trials used doses of 1000 mg (Cooper 1998; Hersh 2000; Kiersch 1994; Kubitzek 2003; Lehnert 1990; Mehlisch 1995; Moller 2000; Olson 2001; Seymour 1996; Seymour 2003; Skoglund 1991). One study (Seymour 1996) used both doses. Seven trials used paracetamol in tablet form (Dolci 1994; Forbes 1989; Kubitzek 2003; Mehlisch 1995; Moller 2000; Seymour 2003; Skoglund 1991). Seven trials used capsules (Forbes 1984b; Forbes 1989; Forbes 1990; Kiersch 1994; Lehnert 1990; Sunshine 1986; Vattaraphudej 1986). Two trials used caplets (Hersh 2000; Olson 2001) and one trial used effervescent tablets (Moller 2000). Five trials did not state what formulation was used (Cooper 1980; Cooper 1981; Cooper 1988; Cooper 1998; Dionne 1994). All trials used placebos in the same formulation as the intervention.

Characteristics of outcome measures

For all trials it was possible to calculate the number of patients with at least 50% total pain relief (TOTPAR) at either 4 hours, 6 hours or both. Pain intensity was measured in all but one trial (Kubitzek 2003), pain relief was measured in all but two trials (Kubitzek 2003; Seymour 2003). Kubitzek 2003 gave a figure for TOTPAR at six hours, and Seymour 2003 measured pain intensity only. Fifteen trials measured pain intensity at 4 hours using a 4-point categorical scale of 0 to 3, where 0 was no pain at all and 3 was severe pain. Five trials measured pain intensity using a visual analogue scale (VAS) of 0 to 100 mm where 0 was no pain and 100 was the worst pain imaginable. Twelve trials measured pain intensity at 6 hours using

a 4-point categorical scale, where 0 was no pain and 3 was severe pain, and three trials measured pain intensity at 6 hours using a VAS of 0 to 100 mm, where 0 was no pain and 100 mm was the worst pain imaginable. Sixteen trials measured pain relief at 4 hours using a 5-point categorical scale of 0 to 4, where 0 was none and 4 was complete pain relief, two trials measured pain relief at 4 hours using a VAS of 0 to 100 mm, in one trial 0 was none and 100 was complete relief, and in the other trial 0 was complete relief and 100 was no relief (these data were reversed for statistical purposes). Twelve trials measured pain relief at 6 hours using a 5-point categorical scale of 0 to 4, where 0 was none and 4 was complete pain relief, two trials measured pain relief at 6 hours using a VAS of 0 to 100 mm, in one trial 0 was none and 100 was complete relief, and in the other trial 0 was complete relief and 100 was no relief (these data were reversed for statistical purposes).

Adverse events and global assessments were recorded in most of the trials. Nineteen trials reported the number of patients with side effects, eight for doses of 1000 mg or more, and 15 for doses of less than 1000 mg. Fifteen trials reported the number of adverse events, seven for doses of 1000 mg or more, and eight for doses of less than 1000 mg. Fourteen trials recorded global assessment using a 5-point categorical scale of either 0 to 4, or 1 to 5, where 0 or 1 was poor and 4 or 5 was excellent, and four trials used a 4-point categorical scale of 0 to 3, where 0 was poor and 3 was excellent. (Additional Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11; Table 12; Table 13; Table 14; Table 15; Table 16; Table 17).

Risk of bias in included studies

Details of the quality assessment are presented in Additional Table 18; Table 19; Table 20. Seven out of the 21 studies reported adequate concealed allocation, for the remaining studies it was unclear. Over half of the studies (11/21) gave clear explanation of withdrawals or drop outs. Taking these two factors into account only three trials were assessed as being at low risk of bias.

Effects of interventions

Comparison 1: Paracetamol versus placebo using pain relief measurements

(Comparison 1, Outcome 1.1 & Comparison 1, Outcome 1.2) (Analysis 1.1; Analysis 1.2)

There are 16 studies providing pain relief measurements for comparing paracetamol versus placebo at 4 hours, 11 at doses up to 1000 mg and 5 at doses of 1000 mg. Overall there was a highly statistically significant benefit with the paracetamol, with risk ratio (RR) values for achieving 50% pain relief for all doses of paracetamol for 4 hours RR 2.85 (95% confidence interval (CI) 1.89 to 4.29), Chi^2 = 62.94, degrees of freedom (df) = 15, P < 0.001, I^2 = 76%, number needed to treat (to benefit) (NNT) 4 (95% CI 3 to 4). The statistically significant benefit was apparent for both subgroups with RR for up to 1000 mg 1.96 (95% CI 1.34 to 2.86), Chi^2 = 26.44, df = 9, P = 0.002, I^2 = 66.0%, NNT 4 (95% CI 3 to 5), and RR for 1000 mg 4.56 (95% CI 2.86 to 7.27), Chi^2 = 5.44, df = 5, P = 0.36, I^2 = 8.2%, NNT 3 (95% CI 3 to 4). Although both had a statistically significant benefit over placebo there was a statistically significant difference between the two subgroups with an enhanced benefit for the higher doses (metaregression P < 0.001, Additional Table 1). This subgroup analysis explained some of the heterogeneity in the overall comparison however, there is still some unexplained heterogeneity between the trials in the up to 1000 mg dose comparison.

There are 13 studies providing pain relief measurements for comparing paracetamol versus placebo at 6 hours, 6 doses up to 1000 mg paracetamol, and 7 doses of 1000 mg paracetamol. Overall there was a highly statistically significant benefit with the paracetamol, with RR values for 50% pain relief at 6 hours RR 3.32 (95% CI 1.88 to 5.87), Chi^2 = 63.35, df = 12, P < 0.00001, I^2 = 81.1%, NNT 3 (95% CI 3 to 4). The statistically significant benefit was apparent in both subgroups with RR for up to 1000 mg 1.89 (95% CI 0.98 to 3.67), Chi^2 = 14.45, df = 5, P = 0.01, I^2 = 65.4%, NNT 6 (95% CI 4 to 10), and RR for 1000 mg 4.21 (95% CI 2.97 to 5.98), Chi^2 = 5.09, df = 6, P = 0.53, I^2 = 0%, NNT 3 (95% CI 2 to 3). Although both had a statistically significant benefit over placebo there was a statistically significant difference between the two subgroups with an enhanced benefit for the higher doses (metaregression P < 0.001, Additional Table 1). This subgroup analysis explained some of the heterogeneity in the overall comparison however, there is still some unexplained heterogeneity between the trials in the up to 1000 mg dose comparison.

Comparison 2: Paracetamol versus placebo using pain intensity difference measurements

(Comparison 2, Outcome 2.1 & Comparison 2, Outcome 2.2) (Analysis 2.1; Analysis 2.2)

There are 18 studies providing pain intensity measurements for comparing paracetamol versus placebo at 4 hours, 10 at doses up to 1000 mg and 8 at doses of 1000 mg. Overall there was a highly statistically significant benefit with paracetamol, with RR values for 50% pain relief at 4 hours RR 4.87 (95% CI 2.83 to 8.37), Chi^2 = 49.73, df = 17, P < 0.0001, I^2 = 65.8%, NNT 3 (95% CI 3 to 5). The statistically significant benefit was apparent in both subgroups with RR up to 1000 mg 4.33 (95% CI 2.19 to 8.58), Chi^2 = 26.22, df = 9, P = 0.002, I^2 = 65.7%, NNT 3 (95% CI 3 to 4), and RR for 1000 mg 6.46 (95% CI 2.34 to 17.85), Chi^2 = 23.47, df = 7, P = 0.001, I^2 = 70.2%, NNT 4 (95% CI 3 to 5). Both had a statistically significant benefit over placebo, but there was no statistically significant difference between the two subgroups (metaregression P = 0.67, Additional Table 1).

There are 14 studies providing pain intensity measurements for comparing paracetamol versus placebo at 6 hours, 6 at doses up to 1000 mg and 8 at doses of 1000 mg. Overall there was a highly statistically significant benefit with paracetamol, with RR values for 50% pain relief RR 3.41 (95% CI 2.34 to 4.97), Chi^2 = 18.23, df = 13, P = 0.15, I^2 = 28.7%, NNT 4 (95% CI 3 to 4). The statistically significant benefit was apparent in both groups with RR up to 1000 mg 2.67 (95% CI 1.46 to 4.90), Chi^2 = 7.05, df = 5, P = 0.22, I^2 = 29.1%, NNT 5 (95% CI 3 to 7), and RR for 1000 mg 3.96 (95% CI 2.52 to 6.23), Chi^2 = 8.63, df = 7, P = 0.28, I^2 = 18.9%, NNT 3 (95% CI 3 to 4). Both had a statistically significant benefit over placebo, but there was no statistically significant difference between the two subgroups (metaregression P = 0.15, Additional Table 1).

Comparison 3: Number of patients with adverse events for paracetamol versus placebo

(Comparison 3, Outcome 3.1) (Analysis 3.1)

There are 17 studies that reported the number of patients with adverse events for paracetamol versus placebo, 9 studies used less

than 1000 mg and 8 studies used 1000 mg. There was no statistically significant difference in any group. For all doses of paracetamol the RR for an adverse event RR 1.19 (95% CI 0.90 to 1.57), Chi^2 = 20.73, df = 15, P = 0.15, I^2 = 27.6%, number needed to treat to harm (NNTH) 33 (95% CI 14.3 to infinity). For doses of less than 1000 mg RR 1.25 (95% CI 0.69 to 2.25), Chi^2 = 9.06, df = 7, P = 0.25, I^2 = 22.8%, NNTH 33 (95% CI 14.3 to infinity). For 1000 mg paracetamol RR 1.16 (95% CI 0.84 to 1.60), Chi^2 = 10.96, df = 7, P = 0.14, I^2 = 36.2%, NNTH 33 (95% CI 12.5 to infinity).

Subgroup analyses

Where patients underwent surgery with local anaesthesia alone, local anaesthesia and intravenous sedation, general anaesthesia alone and general anaesthesia with local anaesthetic

When the data were reviewed it was not possible to do a meta-analysis. Of the 21 included studies, 7 did not state what anaesthesia was used, 7 used combinations of anaesthesia, but were unclear in reporting which patients received which anaesthesia, 4 used local anaesthetic only and 3 used general anaesthetic only.

Where different types of formulation of paracetamol were used (immediate release versus slow release)

Most included studies did not report on the formulation, other than to say whether it was tablets, capsules or caplets. Only one paper indicated that their study used effervescent tablets (Moller 2000) and their results showed that effervescent tablets gave a faster onset of pain relief. Median value for time to onset of analgesia was 20 minutes in the effervescent group and 45 minutes in the tablet group, and time to meaningful pain relief was 45 minutes in the effervescent group and 1 hour in the tablet group. However at the end of a 4-hour period pain relief was better in the tablet group (4.4) than the effervescent group (3.7).

Where different doses of paracetamol were used (1000 mg or more, and less than 1000 mg)

This meta-analysis was conducted. 11 studies used doses of 1000 mg or more, and 11 studies used doses of less than 1000 mg (Seymour 1996, used both doses).

NNT for < 1000 mg of paracetamol is 4 (95% CI 3 to 5) at 4 hours and 6 (95% CI 4 to 10) at 6 hours (using pain relief measurements).

NNT for < 1000 mg of paracetamol is 3 (95% CI 3 to 4) at 4 hours and 5 (95% CI 3 to 7) at 6 hours (using intesity measurements).

NNT for 1000 mg of paracetamol is 3 (95% CI 3 to 4) at 4 hours and 3 (95% CI 2 to 3) at 6 hours (using pain relief measurements).

NNT for 1000 mg of paracetamol is 4 (95% CI 3 to 5) at 4 hours, and 3 (95% CI 3 to 4) at 6 hours (using intensity measurements).

Where time of administration of paracetamol differs: preoperative versus postoperative

No included study used a preoperative dose, as the patients did not reach moderate or severe pain before the intervention.

Where total pain relief (TOTPAR) was calculated using pain relief measures and pain intensity measures

This meta-analysis was undertaken where the relevant data were available. 16 studies had pain relief data and 17 studies had pain intensity data.
NNT using pain relief scales for < 1000 mg of paracetamol is 4 (95% CI 3 to 5) at 4 hours, and 6 (95% CI 4 to 10) at 6 hours.
NNT using pain intensity scales for < 1000 mg of paracetamol is 3 (95% CI 3 to 4) at 4 hours, and 5 (95% CI 3 to 7) at 6 hours.
NNT using pain relief scales for 1000 mg of paracetamol is 3 (95% CI 3 to 4) at 4 hours, and 3 (95% CI 2 to 3) at 6 hours.
NNT using pain intensity scales for 1000 mg of paracetamol is 4 (95% CI 3 to 5) at 4 hours, and 3 (95% CI 3 to 4) at 6 hours.

DISCUSSION

The results show paracetamol to be an effective analgesia for use following third molar surgery. The number needed to treat (to benefit) (NNTs) and number needed to treat to harm (NNTHs) support the use of 1000 mg as an optimal dose. It is effective over both 4 and 6 hours. In considering the use of pain relief, or pain intensity difference as a measure of efficacy it was of interest that metaregression showed that pain relief scales showed a statistically significant difference for increased dose, and pain intensity did not. It is acknowledged that this review only considered single dose studies when considering efficacy, multidosed studies may be considered when updating the review. The NNTs and NNTHs found in this review are similar to those recorded by a systematic review (Barden J 2004) where they investigated paracetamol for pain involving various types of surgery. This would confirm yet again the value of the third molar pain model, showing that dental pain is comparable with pain from other sources. The implementation of NICE (National Institute for Health and Clinical Excellence) Guidelines for removal of third molars has led to a decrease in the performance of this surgery, which may have an adverse effect on the number of trials able to use the third molar model. In the United States of America such guidelines have not yet been adopted. It is of interest that in striving to provide evidence based treatment the opportunity for research using the third molar pain model may be adversely affected.

The data available for adverse events show that NNTH for < 1000 mg of paracetamol is 33 (14.3 to infinity), for 1000 mg of paracetamol is 33 (12.5 to infinity) and for all doses 33 (14.3 to infinity), suggesting it is an extremely safe drug. Only one severe adverse event was recorded by any researchers, and that was a severe headache (Olson 2001), two other participants stopped taking paracetamol because of vomiting. However there was a high degree of inconsistency across the trials in the way that adverse events were recorded, raising the concern that only adverse events considered by the researchers to be attributable to paracetamol were recorded, with some trials recording many AEs and some reporting none. The diverse way in which adverse events were recorded led to there being over 20 categories of adverse events. The main categories are shown in Additional Table 21. Of interest are adverse events where placebo scored more highly than paracetamol, which could suggest that paracetamol may possibly have a beneficial effect eg dry socket, but this would require further investigation. As all patients had surgery, and various combinations of local anaesthesia, general anaesthesia, and sedation making it difficult to ascertain which effects are directly related to the

intervention. However the results strongly support the use of paracetamol in doses up to 1000 mg as a safe effective analgesia.

The efficacy of paracetamol decreases with times, and the recommended interval between doses is 8 hours, which would suggest there may be some benefit in a slow release formulation. None of the studies in this trial used a slow release formulation, but a trial (Coulthard 2001) compared sustained release and standard release formulations of paracetamol and found that the sustained release was statistically significantly more effective at 6 and 8 hours, with no loss of efficacy at 4 hours. Safety for both formulations was comparable, making sustained release paracetamol a safe and effective choice.

The methodology used in the included trials was generally good. This resulted in a large number of participants being included in this meta-analysis, while using only double blind randomised trials. The included trials gave a strong, consistent result. Many of the trials were done by researchers with extensive experience in the field of pain research, whose methods have been refined with experience. A large proportion of the trials were done in the United States, and were mostly funded by pharmaceutical companies. This seems to be reflected in the methodology. However, quality assessment showed, there were only three trials with a low risk of bias, and 18 with moderate/high risk. This was mainly the result of unreported allocation concealment methods. In speaking to some of the authors it is highly likely that the allocation concealment was good in all the trials, but that the details were not well reported. Most trials were sponsored by pharmaceutical companies who supplied paracetamol and placebo in identical appearance. The reporting of withdrawals and drop outs was sporadic, and even when numbers were cited it was not always clear to which treatment group the participant had been originally allocated.

Mean global assessments (Additional Table 14; Table 15; Table 16; Table 17) all showed higher scores for paracetamol than placebo. It is of interest that despite achieving 50% pain relief participants did not record 50% on a global assessment scale. This again raises the question of the value of the instruments used to measure the efficacy of an intervention. None of the trials relied on global assessments as their only measure of efficacy, but this information could be of value to other researchers. It raises interesting questions concerning patient's expectations and the difficulties associated with quantifying such a subjective experience.

A lot of valuable information was gathered, incidental to the main findings, in most of the trials. So though the topic was concerned with the use of paracetamol for pain, information collected in many of the trials shed valuable light on subjects such as side effects, measuring instruments, and methodology. Further appraisal of the multidisciplinary approach to research, a broader view of data collection, and a more accurate reporting of data already collected could be extremely valuable in the future. It would allow research to be more widely used in various meta-analyses. Data from areas seemingly unrelated to the original null hypothesis, eg comparison of pain relief and pain intensity as a measuring tool, adverse event reporting, the significance of global assessments etc. could be more readily available. If the third molar trial population does decrease it would be advantageous to collect as much data as possible from any trial being undertaken.

AUTHORS' CONCLUSIONS

Implications for practice

Paracetamol (acetaminophen) is an effective drug to use for postoperative pain following oral surgery, and the reporting of adverse events shows it to be a safe drug (number needed to treat (to benefit) (NNT) is 3 for 1000 mg of paracetamol at 6 hours, number needed to treat to harm (NNTH) 33). It is most effective at 1000 mg dose, and can be taken at six hourly intervals without compromising safety. It could be considered more readily by dentist and patients both as a first choice analgesic, or to be taken alternately with doses of other analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDS).

Implications for research

There is a large body of research in this area, and further research, other than as a comparison seems unnecessary. However, in one trial (Moller 2000) it was found that an effervescent formulation appeared to have a faster onset of pain relief, which would be beneficial to patients who are looking for a rapid onset of relief. It may be helpful to undertake some research to confirm these findings. The use of pain relief and pain intensity difference as a measure of pain relief may be another area for further investigation. It is valuable to have NNT/NNTH as a baseline for comparison with other analgesics. Maximizing the third molar pain model population by multidisciplinary research is another area of interest highlighted by this review.

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CHARACTERISTICS OF STUDIES

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

Cooper 1980

Methods	Randomised, parallel group, double blind study
Participants	298 participants randomised to 6 groups, withdrawals unclear (51 from all groups) Number randomised to intervention: male 13, female 24, mean age 22.5 Number randomised to placebo: male 11, female 27, mean age 23.5 Number of third molars removed: mean for intervention and placebo 1.9 Baseline pain intensity: mean for intervention 2.41 (moderate 22, severe 15), mean for placebo 2.42 (moderate 22, severe 16) Setting - outpatients (USA)
Interventions	Paracetamol 500 mg versus placebo Formulation not stated Anaesthesia: not stated
Outcomes	PI at 4 hours: categorical scale 0-3 (none - severe) PR at 4 hours: categorical scale 0-4 (none - complete) Global assessment: categorical scale 0-4 (poor - excellent) Adverse events table
Notes	Sponsored unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cooper 1981

Methods	Randomised, parallel group, double blind study
Participants	248 participants randomised to 5 groups, withdrawals unclear (48 from all groups) Number randomised to intervention: male 15, female 22, mean age 22.2 Number randomised to placebo: male 13, female 24, mean age 23.7 Number of third molars removed: not stated Baseline pain intensity: mean for intervention 2.2 (moderate 29, severe 9), mean for placebo 2.3 (moderate 26, severe 11) Setting not stated (USA)
Interventions	Paracetamol 650 mg versus placebo Formulation: not stated Anaesthesia: LA or GA
Outcomes	PI at 4 hours: categorical scale 0-3 (none - severe) PR at 4 hours: categorical scale 0-4 (none - complete) Global assessment: categorical scale 0-4 (poor - excellent) Total number of adverse events and number of people with adverse events reported
Notes	Sponsored by Adria Laboratories

Cooper 1981 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cooper 1988

Methods	Randomised, parallel group, double blind study
Participants	165 participants randomised to 4 groups, withdrawals unclear (22 from all groups) Number randomised to intervention: male 7, female 29, mean age 24.6 Number randomised to placebo: male 11, female 29, mean age 24.7 Number of third molars removed: mean for intervention 1.4, mean for placebo 1.5 Baseline pain intensity: mean for intervention 2.4 (moderate 21, severe 15), mean for placebo 2.4 (moderate 25, severe 15) Setting - outpatients - single site (USA)
Interventions	Paracetamol 600 mg versus placebo Formulation: not stated Anaesthesia: LA or LA and SED
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete) Global assessment: categorical scale 0-4 (poor - excellent) Total number of adverse events
Notes	Sponsored by Parke-Davis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cooper 1998

Methods	Randomised, parallel group, double blind study
Participants	177 participants randomised to 4 groups, no withdrawals Number randomised to intervention: male 23, female 27, mean age 23.6 Number randomised to placebo: male 12, female 14, mean age 22.7 Number of third molars removed: not stated Baseline pain intensity: mean for intervention: categorical 2.3, VAS 60.3, mean for placebo: categorical 2.2, VAS 62.8 Setting - Georgetown University Hospital (USA)
Interventions	Paracetamol 1000 mg versus placebo Formulation: not stated Anaesthesia: LA or LA and SED

Cooper 1998 *(Continued)*

Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe), VAS scale 0-100 mm (none - worst pain imaginable) PR at 4 hours and 6 hours: categorical scale 0-4 (no relief - complete relief) Global assessment: not stated Adverse effects table
Notes	Sponsored by Whitehall-Robins

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dionne 1994

Methods	Randomised, parallel group, double blind study
Participants	135 participants randomised to 5 groups, withdrawals unclear (11 from all groups) Number randomised to intervention: male 14, female 13, mean age 29.6 Number randomised to placebo: male 15, female 10, mean age 28.2 Number of third molars removed: not stated Baseline pain intensity for intervention and placebo: not stated Setting: private dental practice (USA)
Interventions	Paracetamol 650 mg versus placebo Formulation: not stated Anaesthesia: LA, or LA and SED, or GA
Outcomes	PI at 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete) Global assessment: categorical scale 1-5 (poor - excellent) Adverse effects table
Notes	Sponsored by Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dolci 1994

Methods	Randomised, parallel group, double blind study
Participants	338 participants enrolled in 4 groups, withdrawals unclear (40 from all groups) Number randomised to intervention: male 28, female 44, mean age 27.9, age range 18-49 Number randomised to placebo: male 28, female 48, mean age 27.2, age range 18-45 Number of third molars removed: not stated

Dolci 1994 *(Continued)*

	Baseline pain intensity: range for intervention and placebo given together as average 21.4 (2.08 - 2.19) Setting not stated (Italy)
Interventions	Paracetamol 500 mg versus placebo Formulation: tablets Anaesthesia: not stated
Outcomes	PI at 4 hours: categorical scale 0-3 (none - severe) PR at 4 hours: categorical scale 0-4 (none - complete) Global assessment: categorical 0-4 (negative - very good) Adverse effects table
Notes	Sponsored - unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Forbes 1984b

Methods	Randomised, parallel group, double blind study
Participants	191 participants randomised to 4 groups, withdrawals unclear (43 from all groups, 164 used in reporting of adverse events) Number randomised to intervention: male 19, female 20, mean age 21.95 Number of third molars removed: mean 2.44 Number randomised to placebo: male 21, female 15, mean age 15-32 Number of third molars removed: mean 2.78 Baseline pain intensity: mean for intervention 2.46 (moderate 21, severe 18), mean for placebo 2.47 (moderate 19, severe 17) Setting: private dental practice (USA)
Interventions	Paracetamol 650 mg versus placebo Formulation: capsules Anaesthesia: GA
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete) Global assessment: categorical scale 0-4 (poor - excellent) Adverse effects: reported as total number of adverse events, and number of patients with adverse events
Notes	Sponsored by McNeil Consumer Products

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Forbes 1989

Methods	Randomised, parallel group, double blind study
Participants	107 participants randomised to 5 groups, withdrawals unclear (19 from all groups, 98 participants used in reporting of adverse events) Number randomised to intervention: male 9, female 13, mean age 20.59, age range 17-31 Number randomised to placebo: male 12, female 11, mean age 23.74, age range 16-39 Number of third molars removed: mean for intervention 2.59, mean for placebo 2.09 Baseline pain intensity: mean for intervention 2.45, mean for placebo 2.39 Setting - 2 sites, private dental practice, outpatients (USA)
Interventions	Paracetamol 600 mg versus placebo Formulation - 1 tablet & 1 capsule Anaesthesia: LA and GA
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete) Global assessment : categorical 0-4 (poor - excellent) Adverse effects reported by number of patients with adverse events
Notes	Sponsored by Boots Company Ltd., G.H. Besselaar Associates

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Forbes 1990

Methods	Randomised, parallel group, double blind study
Participants	206 participants randomised to 6 groups Number randomised to intervention: male 20, female 16, (5 withdrawals), mean age 22.5, age range 16-46 Number randomised to placebo: male 18, female 16, (4 withdrawals), mean age 23.65, age range 16-45 Number of third molars removed: mean for intervention 2.58, mean for placebo 2.35 Baseline pain intensity: mean for intervention 2.39 (moderate 22, severe 14), mean for placebo 2.32 (moderate 23, severe 11) Setting - private dental practice outpatients (USA)
Interventions	Paracetamol 600 mg versus placebo Formulation: capsules Anaesthesia: LA and GA
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete) Global assessment: categorical 0-4 (poor - excellent) Adverse effects table
Notes	Sponsored by Syntex Research

Risk of bias

Forbes 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hersh 2000

Methods	Randomised, parallel group, double blind study
Participants	210 participants randomised to 4 groups, no withdrawals Number randomised to intervention: male 20, female 43, mean age 23.3 Number of third molars removed/patient: (1/1), (2/6), (3/5), (4/51) Number randomised to placebo: male 9, female 8, mean age 23.7 Number of wisdom teeth removed per patient: (1/1) (2/5) (3/3) (4/18) Baseline pain intensity: mean for intervention 2.3 (moderate 47, severe 16), mean for placebo 2.2 (moderate 22, severe 5) Setting - University of Pennsylvania School of Dental Medicine - outpatients (USA)
Interventions	Paracetamol 1000 mg versus placebo Formulation: caplets Anaesthesia: LA or LA and SED
Outcomes	PI at 4 hours and 6 hours: categorical 0-3 (none - severe) PR at 4 hours and 6 hours: categorical 0-4 (no relief - complete relief) Global assessment: categorical 0-4 (poor - excellent) Adverse effects by total number of adverse events, and number of patients with adverse events
Notes	Sponsored by Whitehall-Robins

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kiersch 1994

Methods	Randomised, parallel group, double blind study
Participants	232 participants enrolled in 3 groups Number randomised to intervention 91, withdrawals 4 (2 before and 2 after randomisation): male 72, female 17, mean age 23.1, age range 15-39 Number of third molars removed/patient: (1/0), (2/0), (3/31), (4/54) Number randomised to placebo 47, withdrawals 2: male 35, female 10, mean age 24.7, age range 15-39 Number of third molars removed/patient: (1/0), (2/0), (3/19), (4/26) Baseline pain intensity: mean for intervention and placebo categorical 2.12, VAS 58.35 Setting not stated (USA)
Interventions	Paracetamol 1000 mg versus placebo Formulation: capsules Anaesthesia: not stated

Kiersch 1994 *(Continued)*

Outcomes	PI at 4 hours and 6 hours: categorical 0-3 (none - severe) PR at 4 hours and 6 hours: categorical 0-4 (none - complete), VAS 0-100 mm (no pain - worst pain I can imagine) Global assessment: categorical 0-4 (poor - excellent) Adverse effects reported by total number of adverse events, and by number of patients with adverse events
Notes	Sponsored by Syntex Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kubitzek 2003

Methods	Randomised, parallel group, double blind study
Participants	245 participants randomised to 3 groups, no withdrawals Number randomised to intervention 78 Number randomised to placebo 84: male:female, 40% male over both groups Number of third molars removed: 1 or 2 for each patient Baseline pain intensity: moderate to severe 65-76% in both groups Setting: dental practice (Germany)
Interventions	Paracetamol 1000 mg versus placebo Formulation: tablets Anaesthesia: LA
Outcomes	PI: not stated PR given as TOTPAR at 6 hours Global assessment: categorical 1-5 (poor - excellent) Adverse effects not stated
Notes	Sponsored by Novartis Consumer Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Lehnert 1990

Methods	Randomised, parallel group, double blind study
Participants	150 participants randomised to 3 groups, 50 to each Number randomised to intervention, 1 withdrawal: male 23, female 26, mean age 25.3, age range 17-52 Number randomised to placebo, 2 withdrawals: male 24, female 18, mean age 25.1, age range 18-53

Lehnert 1990 *(Continued)*

	Number of hird molars removed: not stated Baseline pain intensity: mean for intervention 2.55 (moderate 22, severe 27), mean for placebo 2.5 (moderate 21, severe 21) Setting: outpatients (Germany)
Interventions	Paracetamol 1000 mg versus placebo Formulation: capsules Anaesthesia: not stated
Outcomes	PI at 6 hours, categorical scale 0-3 (no pain - severe) PR at 6 hours, categorical scale 0-3 (none - complete) Global assessment: categorical scale 0-3 (poor - excellent) Adverse effects by number of patients
Notes	Sponsored by GH Besselar Associates

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mehlisch 1995

Methods	Randomised, parallel group, double blind study
Participants	240 participants randomised to 3 groups, 1 withdrawal from the acetaminophen group Number randomised to intervention (1 withdrawal): male 30, female 71, mean age 25.3, age range 15-60 Number of third molars removed/patient: (1/0, 2/95, 3/3, 4/3) Number randomised to placebo: male 19, female 21, mean age 24.2, age range 15-48 Number of third molars removed/patient: (1/0, 2/39, 3/0, 4/1) Baseline pain intensity: mean for intervention 2.21 (moderate 80, severe 21), mean for placebo 2.20 (moderate 32, severe 8) Setting not stated (USA)
Interventions	Paracetamol 1000 mg versus placebo Formulation: 2 tablets Anaesthesia: not stated
Outcomes	PI at 4 hours and 6 hours, categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours, categorical scale 0-4 (none - complete) Global assessment: categorical scale 0-4 (poor - excellent) Adverse events reported by number of patients
Notes	Sponsored by Biomedical Research Group; and Merck Research Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Moller 2000

Methods	Randomised, parallel group, double blind study
Participants	242 participants randomised to 4 groups, no withdrawals Number randomised to Intervention A: male 27, female 33, mean age 24.5 Number randomised to Intervention B: male 26, female 34, mean age 26.2 Number randomised to Placebo A: male 21, female 41, mean age 25.0 Number randomised to Placebo B: male 24, female 36, mean age 24.6 Number of third molars removed per patient, in both groups: 1 Mean baseline intensity Intervention A: categorical 2.00 (moderate 60) VAS 49.4 Mean baseline intensity Intervention B: categorical 2.00 (moderate 60) VAS 47.3 Mean baseline intensity Placebo A: categorical 2.00 (moderate 61, severe 1) VAS: 50.5 Mean baseline intensity Placebo B: categorical 2.00 (moderate 61) VAS: 47.6 Setting: Department of Oral and Maxillofacial Surgery, Royal Dental College, Aarhus (Denmark)
Interventions	Intervention A: Paracetamol 1000 mg versus Placebo A Formulation: effervescent tablets Intervention B: Paracetamol 1000 mg versus Placebo B Formulation: tablets Anaesthesia: not stated
Outcomes	PI at 4 hours: categorical scale 0-3 (none - severe) VAS scale 0-100 mm (no pain - worst possible pain) PR at 4 hours: categorical 0-4 (none - complete) Global assessment: categorical 0-3 (poor - excellent) Adverse effects reported as total number of adverse events, and number of patients with adverse events
Notes	Sponsored by Bristol Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Olson 2001

Methods	Randomised, parallel group, double blind study
Participants	239 participants randomised to 4 groups, no withdrawals Number randomised to intervention: male 22, female 44, mean age 22.2 Number randomised to placebo: male 11, female 28, mean age 23.9 Number of third molars removed/patient: intervention - (1/1), (2/64), (3/1), (4/0), placebo - (1/1), (2/38), (3/0), (4/0) Baseline pain intensity: mean for intervention 2.86 (moderate 9, severe 57) mean for placebo 2.9 (moderate 4, severe 35) Setting: University of Puerto Rico School of Dentistry (Puerto Rico)
Interventions	Paracetamol 1000 mg versus placebo Formulation: caplets Anaesthesia: LA
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe)

Olson 2001 *(Continued)*

	PR at 4 hours and 6 hours: categorical scale 0-4 (none - complete relief) Global assessment: categorical scale 0-4 (poor - excellent) Adverse effects table
Notes	Sponsored by Whitehall Robins

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Seymour 1996

Methods	Randomised, parallel group, double blind study
Participants	206 participants randomised to 5 groups Number randomised to intervention A, 1 withdrawal: male 12, female 28, mean age 23.8 Number randomised to intervention B, 1 withdrawal: male 12, female 28 mean age 27.7, 1 withdrawal Number randomised to placebo, 2 withdrawals: male 15, female 24, mean age 24.6 Number of third molars removed/patient: not stated Baseline pain intensity: mean for intervention A, VAS 54.9, mean for intervention B, VAS 54.2, mean for placebo VAS 56.5 Setting: not stated (UK)
Interventions	Intervention A: paracetamol 500 mg versus placebo Intervention B: paracetamol 1000 mg versus placebo Formulation: not stated Anaesthesia: GA
Outcomes	PI at 6 hours: VAS scale 0-100 mm (no pain - unbearable pain) Global assessment: categorical 0 -3 (very good - very poor) but categories 1 & 2, and 4 & 5 not reported separately so unable to include data in tables Adverse effects - none reported by any participants in any group
Notes	Sponsored - unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Seymour 2003

Methods	Randomised, parallel group, double blind study
Participants	167 randomised to 3 groups, withdrawals unclear (14 from all groups) Number randomised to intervention: male 19, female 43, mean age 25.0 Number randomised to placebo: male 11, female 21, mean age 25.1

Seymour 2003 *(Continued)*

	Number of third molars removed/patient: intervention - (1/2), (2/14), (3/12), (4/34), placebo - (1/3), (2/5), (3/9), (4/15) Baseline pain intensity: mean for intervention 50.6, mean for placebo 54.1 Setting not clear (2 sites, Cardiff and Hexham, UK)
Interventions	Paracetamol 1000 mg versus placebo Formulation: tablets Anaesthesia: GA
Outcomes	PI at 4 hours: VAS scale 0-100 mm (none - worst pain imaginable) PR: not stated Global assessment: categorical scale 1-5 (very poor - very good) Adverse effects table
Notes	Sponsored by Reckitt Benckiser Healthcare

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Skoglund 1991

Methods	Randomised, parallel group, double blind study
Participants	147 participants randomised to 4 groups, withdrawals unclear (8 from all groups) Number randomised to intervention: male 16, female 16, mean age 24.7 Number randomised to placebo: male 16, female 17, mean age 24.4 Number of third molars removed: not stated Baseline pain intensity: mean for intervention approx 55, mean for placebo, approx 45 Setting not stated (Norway)
Interventions	Paracetamol 1000 mg versus placebo Formulation: tablets Anaesthesia: LA
Outcomes	PI at 4 hours and 6 hours: VAS scale 0-100 mm (none - pain cannot be worse) PR at 4 hours and 6 hours: VAS scale 0-100 mm (complete relief - no relief) reversed for statistical analysis Global assessment: not stated Adverse effects table
Notes	Sponsored by Apothekernes Laboratorium

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sunshine 1986

Methods	Randomised, parallel group, double blind study
Participants	182 participants randomised to 6 groups, no withdrawals (only patients with moderate to severe pain were randomised) Number randomised to intervention: male 6, female 24, mean age 21.9 Number randomised to placebo: male 14, female 16, mean age 23 Number of third molars removed: not stated Baseline pain intensity: mean for intervention 2.00, mean for placebo 2.00 Setting: University of Puerto Rico School of Dentistry Clinic
Interventions	Paracetamol 650 mg versus placebo Formulation: capsules Anaesthesia: LA
Outcomes	PI at 4 hours and 6 hours: categorical scale 0-3 (none - severe) PR at 4 hours and 6 hours: categorical scale 0-4 (none 0% - complete 100%) Global assessment: categorical 0-3 (poor - excellent) Overall improvement 1-7 (very much worse - very much better) Adverse effects reported by number of patients with adverse events
Notes	Sponsored by Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Vattaraphudej 1986

Methods	Randomised, parallel group, double blind study
Participants	83 enrolled to 4 groups, withdrawals unclear (16 from all groups) Number randomised to intervention: male 8, female 8 Number randomised to placebo: male 10, female 9 Number of third molars removed: mean for intervention 1.25, mean for placebo 1.32 Baseline pain intensity: mean for intervention 2.37, mean for placebo 2.26 Setting: Dept of Oral Surgery, Khon Kaen University, Thailand
Interventions	Paracetamol 650 mg versus placebo Formulation: capsules Anaesthesia not stated
Outcomes	PI at 4 hours: categorical scale 0-3 (none - severe) PR at 4 hours: categorical scale 0-4 (no relief - total relief) Global assessment: categorical scale 0-3 (poor - excellent) Adverse effects, none reported
Notes	Sponsored by Khon Kaen University, Thailand, Dr Sompong Thongpradith, Merck, and Russel

Risk of bias

Vattaraphudej 1986 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

GA - general anaesthetic, LA - local anaesthetic, PI - pain intensity, PR - pain relief, SED - sedation, TOTPAR - total pain relief, VAS - visual analogue scale

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

Study	Reason for exclusion
Adame 1979	Title not in journal quoted, unable to find paper.
Barden J 2004	Meta-analysis, dental papers included individually where appropriate.
Becker 1990	Not a third molar study.
Bentley 1987	Unable to extract data for third molars only, written to authors.
Breivik 1998	Dose given at 3 hours postoperatively regardless of baseline pain, unable to get 4-hour data. Study used for side effects only.
Cooper 1986	Unable to extract third molar data, written to authors.
Cooper 1989	Unable to extract third molar data, written to authors.
Cooper 1991	Unclear if third molars only, written to authors.
Dionne 1983 (1)	Not single dose, administered preoperatively.
Dionne 1983 (2)	Not placebo controlled, not single dose, administered preoperatively.
Dionne 1986	Not placebo controlled.
Dolci 1993	The data for the participants in this study are duplicated in Dolci 1994.
Edwards 2002	This was a meta-analysis. Need to identify source of data to clarify whether third molar studies, and exclude duplication. Written to authors.
Forbes 1982	Unable to extract third molar data, written to author.s
Forbes 1984a	Not third molar study.
Gallardo 1990	Not third molar study (periodontal surgery).
Gustafsson 1983	Patients given either paracetamol preoperatively and placebo postoperatively or vice versa, unable to extract relevant data.
Haanaes 1986	Not placebo controlled. Study used for side effects only.
Irvine 1982	Not placebo controlled.
Laska 1983	Not placebo controlled.

Study	Reason for exclusion
Lecointre 1991	Not placebo controlled.
Liashek 1987	Multiple doses, unable to extract single dose data.
Macleod 2002	Not placebo controlled.
Medve 2001	Only 8-hour SPID and TOTPAR available, need 4-hour and/or 6-hour to include in review, written to authors.
Mehlisch 1984	Unable to extract third molar data, written to authors.
Mehlisch 1990	Unable to extract third molar data.
Moore 1986	Multiple doses given, unable to extract single dose data.
Nystrom 1988	Not placebo controlled.
Petersen 1983	Unable to locate complete article.
Quiding 1981	Not placebo controlled.
Quiding 1982 (1)	Not placebo controlled.
Quiding 1982 (2)	Not placebo controlled.
Quiding 1984	No placebo used.
Ragot 1991	Not placebo controlled.
Reijntjes 1987	Not placebo controlled.
Rodrigo 1987	Mixed parallel and cross-over trial, multiple doses, unable to extract relevant data.
Rodrigo 1989	Not placebo controlled.
Rosen 1985	Not placebo controlled, multiple doses used, unable to extract single dose data.
Sakata 1989	Unable to obtain study.
Selcuk 1996	Not placebo controlled.
Seymour 1981	Cross-over trial, baseline pain not stated, unable to extract relevant data.
Seymour 1983	Acetaminophen administered intravenously.
Skjelbred 1979	Multiple doses, unable to extract single dose data.
Strom 1990	Not placebo controlled.
Van Aken 2004	Propacetamol administered intravenously.
Winter 1983	Unable to extract third molar data, written to authors.

SPID - summed pain intensity difference, TOTPAR - total pain relief

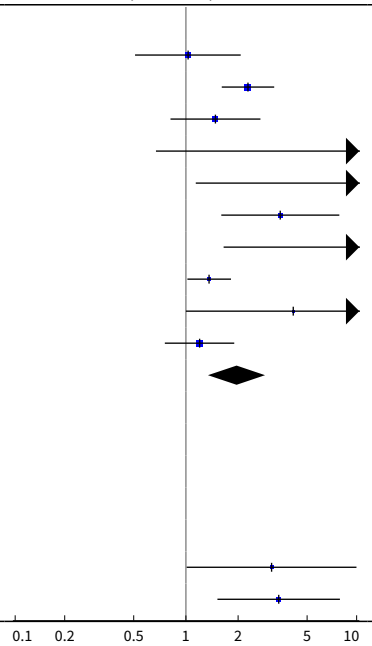
DATA AND ANALYSES

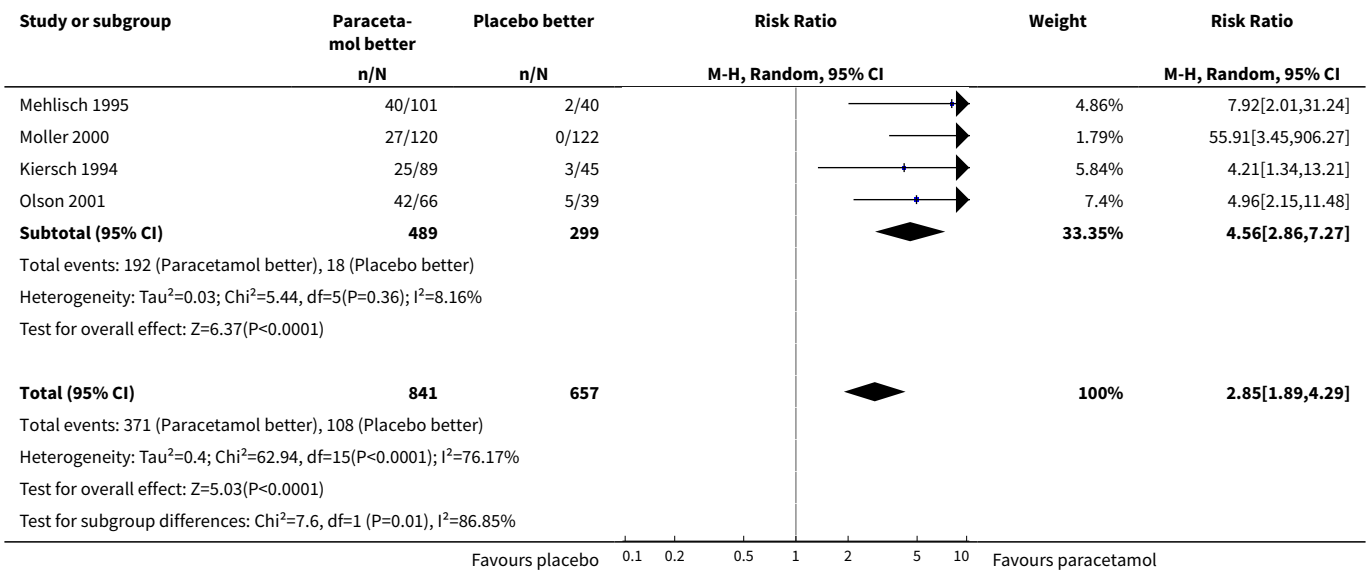
Comparison 1. 50% pain relief using pain relief measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paracetamol versus placebo: number of people with at least 50% pain relief at 4 hours	16	1498	Risk Ratio (M-H, Random, 95% CI)	2.85 [1.89, 4.29]
1.1 Up to 1000 mg of paracetamol	10	710	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.34, 2.86]
1.2 1000 mg or more	6	788	Risk Ratio (M-H, Random, 95% CI)	4.56 [2.86, 7.27]
2 Paracetamol versus placebo: number of people with at least 50% pain relief at 6 hours	13	1155	Risk Ratio (M-H, Random, 95% CI)	3.32 [1.88, 5.87]
2.1 Up to 1000 mg of paracetamol	6	378	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.98, 3.67]
2.2 1000 mg or more	7	777	Risk Ratio (M-H, Random, 95% CI)	4.21 [2.97, 5.98]

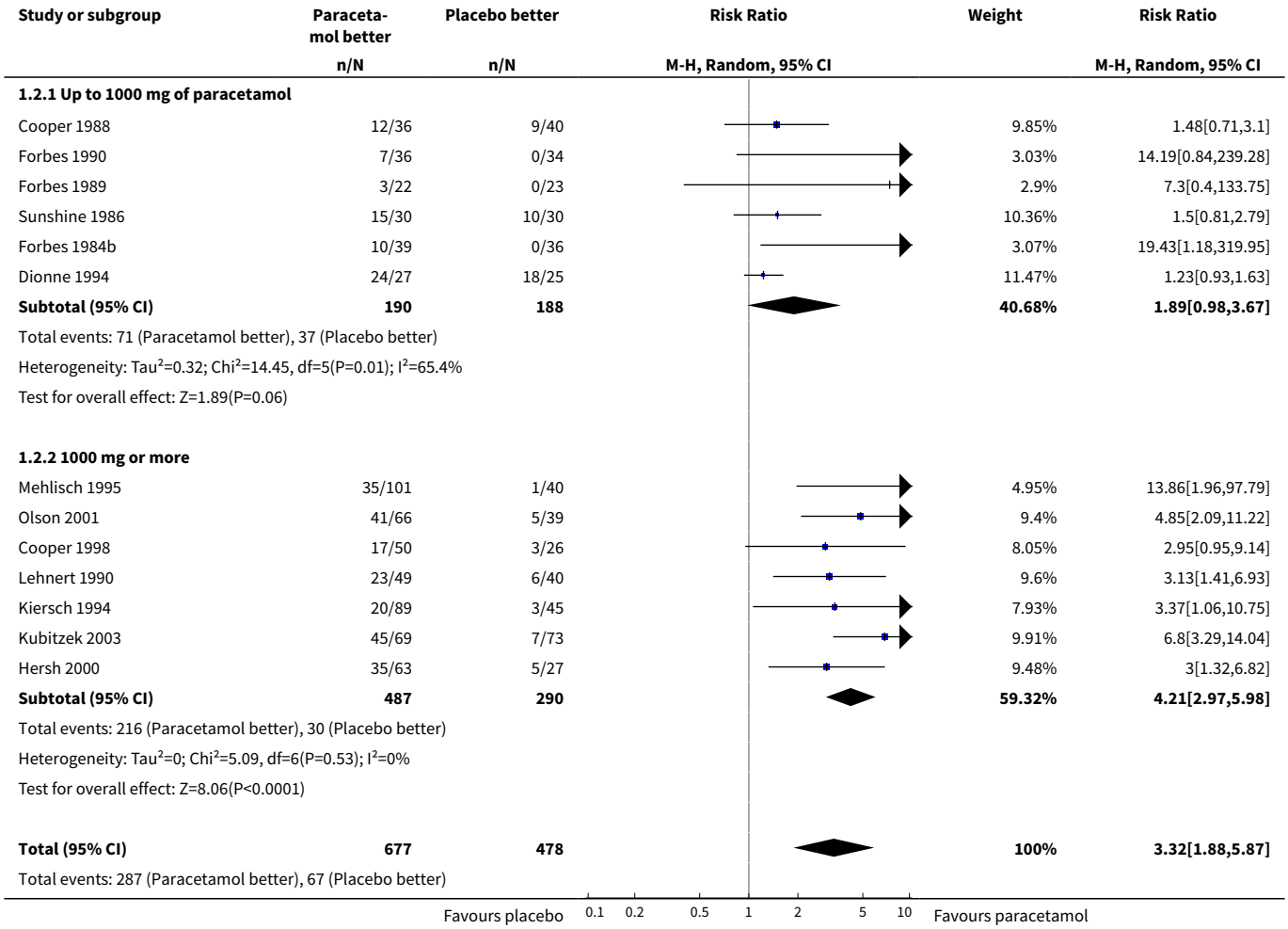
Analysis 1.1. Comparison 1 50% pain relief using pain relief measures, Outcome 1 Paracetamol versus placebo: number of people with at least 50% pain relief at 4 hours.

Study or subgroup	Paracetamol better n/N	Placebo better n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Up to 1000 mg of paracetamol					
Cooper 1980	11/37	11/38		8.16%	1.03[0.51,2.07]
Dolci 1994	54/72	25/76		9.97%	2.28[1.61,3.23]
Cooper 1988	16/36	12/40		8.74%	1.48[0.81,2.69]
Forbes 1989	5/22	0/23		1.74%	11.48[0.67,196.07]
Forbes 1990	9/36	1/34		2.98%	8.5[1.14,63.57]
Cooper 1981	21/37	6/37		7.7%	3.5[1.6,7.67]
Forbes 1984b	13/39	1/36		3.04%	12[1.65,87.16]
Dionne 1994	25/27	17/25		10.2%	1.36[1.02,1.82]
Vattaraphudej 1986	7/16	2/19		4.66%	4.16[1,17.26]
Sunshine 1986	18/30	15/30		9.45%	1.2[0.76,1.9]
Subtotal (95% CI)	**352**	**358**		**66.65%**	**1.96[1.34,2.86]**
Total events: 179 (Paracetamol better), 90 (Placebo better)					
Heterogeneity: Tau^2=0.18; Chi^2=26.44, df=9(P=0); I^2=65.97%					
Test for overall effect: Z=3.49(P=0)					
1.1.2 1000 mg or more					
Cooper 1998	18/50	3/26		5.92%	3.12[1.01,9.63]
Hersh 2000	40/63	5/27		7.54%	3.43[1.52,7.73]





Analysis 1.2. Comparison 1 50% pain relief using pain relief measures, Outcome 2 Paracetamol versus placebo: number of people with at least 50% pain relief at 6 hours.



Study or subgroup	Paracetamol better n/N	Placebo better n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.72; Chi²=63.35, df=12(P<0.0001); I²=81.06%					
Test for overall effect: Z=4.12(P<0.0001)					
Test for subgroup differences: Chi²=4.38, df=1 (P=0.04), I²=77.16%					

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours paracetamol

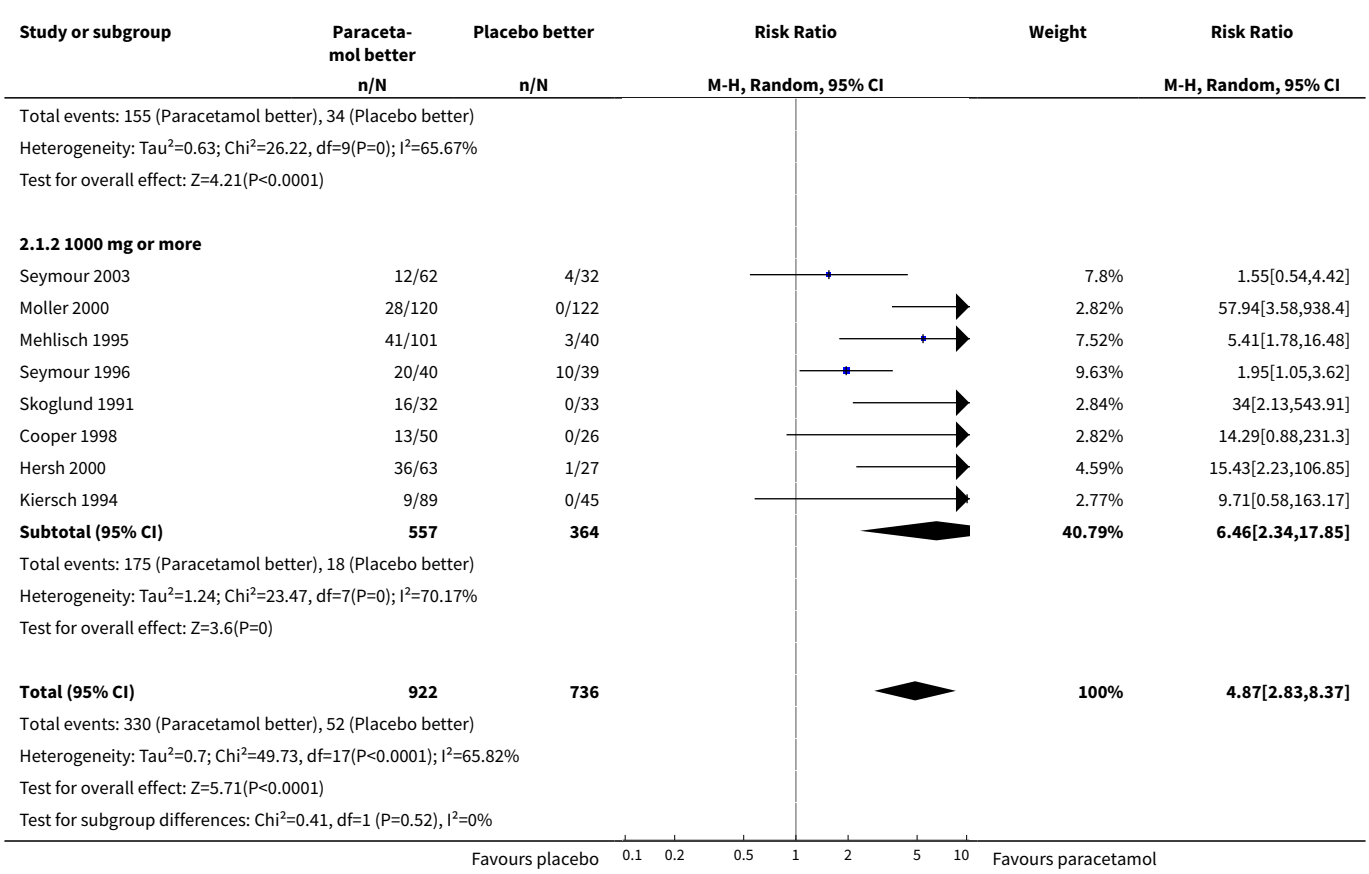
Comparison 2. 50% pain relief using pain intensity measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paracetamol versus placebo: number of people with at least 50% pain relief at 4 hours	17	1658	Risk Ratio (M-H, Random, 95% CI)	4.87 [2.83, 8.37]
1.1 Up to 1000 mg of paracetamol	10	737	Risk Ratio (M-H, Random, 95% CI)	4.33 [2.19, 8.58]
1.2 1000 mg or more	8	921	Risk Ratio (M-H, Random, 95% CI)	6.46 [2.34, 17.85]
2 Paracetamol versus placebo: number of people with at least 50% pain relief at 6 hours	13	1184	Risk Ratio (M-H, Random, 95% CI)	3.41 [2.34, 4.97]
2.1 Up to 1000 mg of paracetamol	6	403	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.46, 4.90]
2.2 1000 mg or more	8	781	Risk Ratio (M-H, Random, 95% CI)	3.96 [2.52, 6.23]

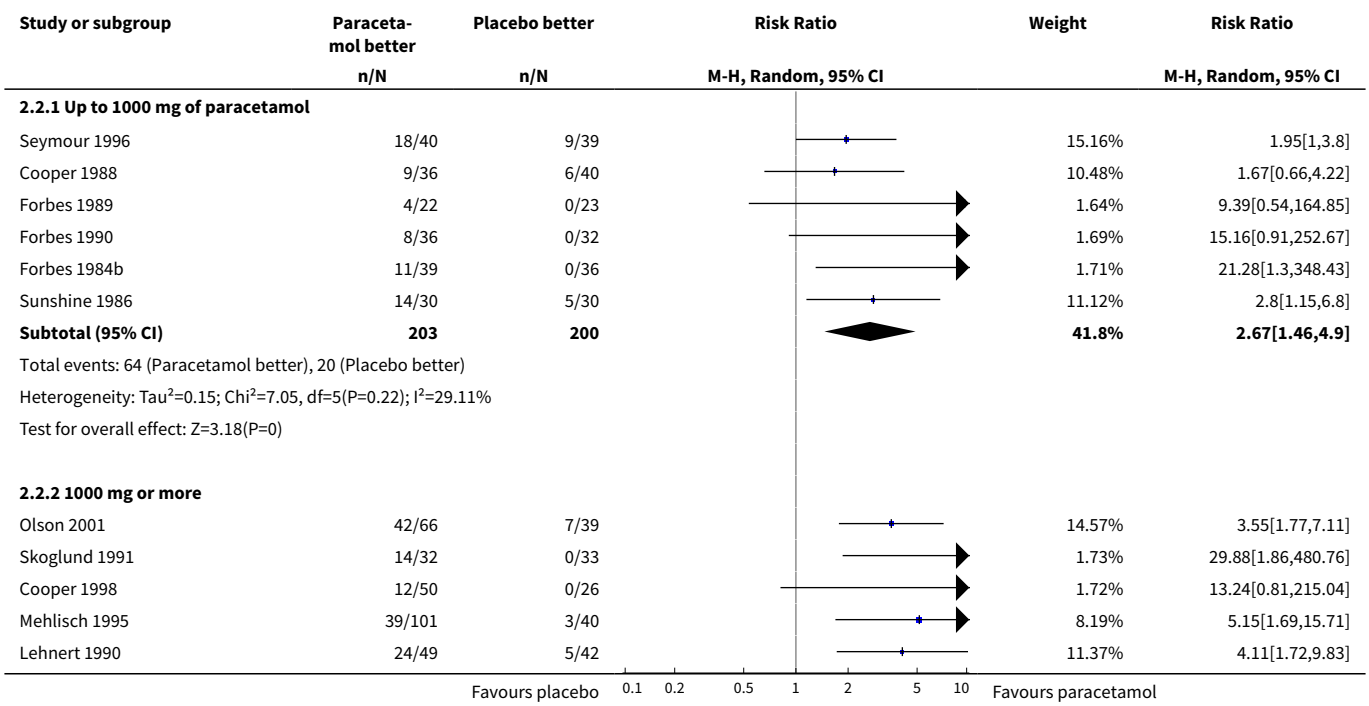
Analysis 2.1. Comparison 2 50% pain relief using pain intensity measures, Outcome 1 Paracetamol versus placebo: number of people with at least 50% pain relief at 4 hours.

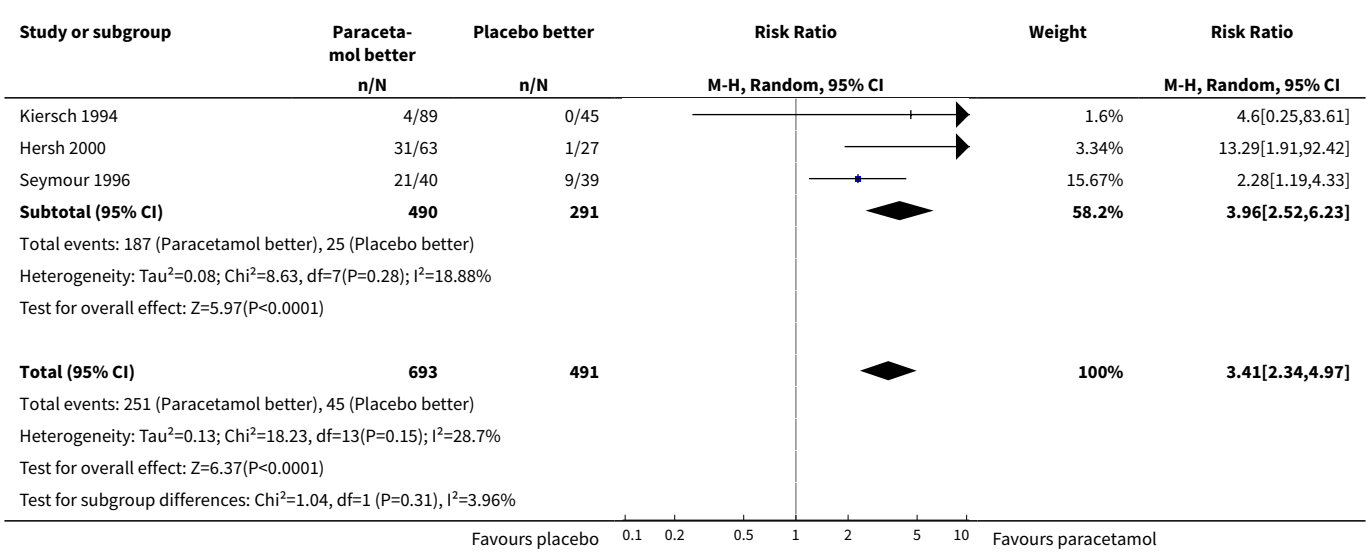
Study or subgroup	Paracetamol better n/N	Placebo better n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Up to 1000 mg of paracetamol					
Cooper 1980	7/37	4/38		7.4%	1.8[0.57,5.63]
Seymour 1996	19/40	10/39		9.6%	1.85[0.99,3.46]
Dolci 1994	49/72	5/76		8.61%	10.34[4.37,24.49]
Cooper 1988	12/36	8/40		8.99%	1.67[0.77,3.61]
Forbes 1990	10/36	0/34		2.8%	19.86[1.21,326.39]
Forbes 1989	6/22	0/23		2.77%	13.57[0.81,227.36]
Sunshine 1986	18/30	6/30		8.99%	3[1.38,6.5]
Cooper 1981	15/37	0/37		2.83%	31[1.92,499.71]
Forbes 1984b	13/39	0/36		2.82%	24.98[1.54,405.42]
Vattaraphudej 1986	6/16	1/19		4.39%	7.13[0.95,53.17]
Subtotal (95% CI)	**365**	**372**		**59.21%**	**4.33[2.19,8.58]**

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours paracetamol



Analysis 2.2. Comparison 2 50% pain relief using pain intensity measures, Outcome 2 Paracetamol versus placebo: number of people with at least 50% pain relief at 6 hours.

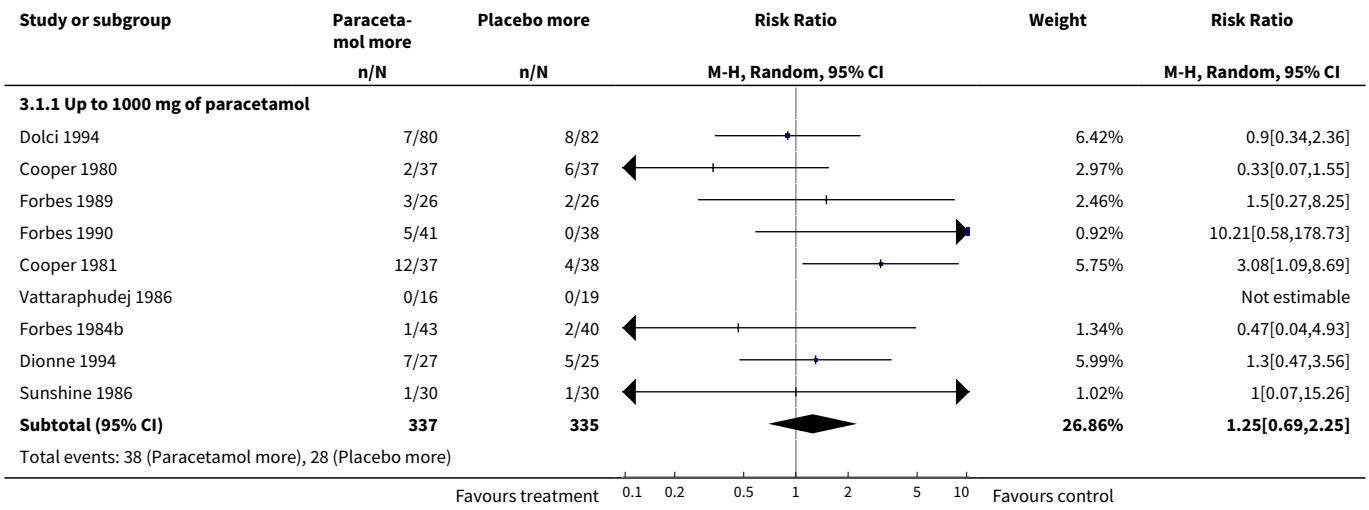


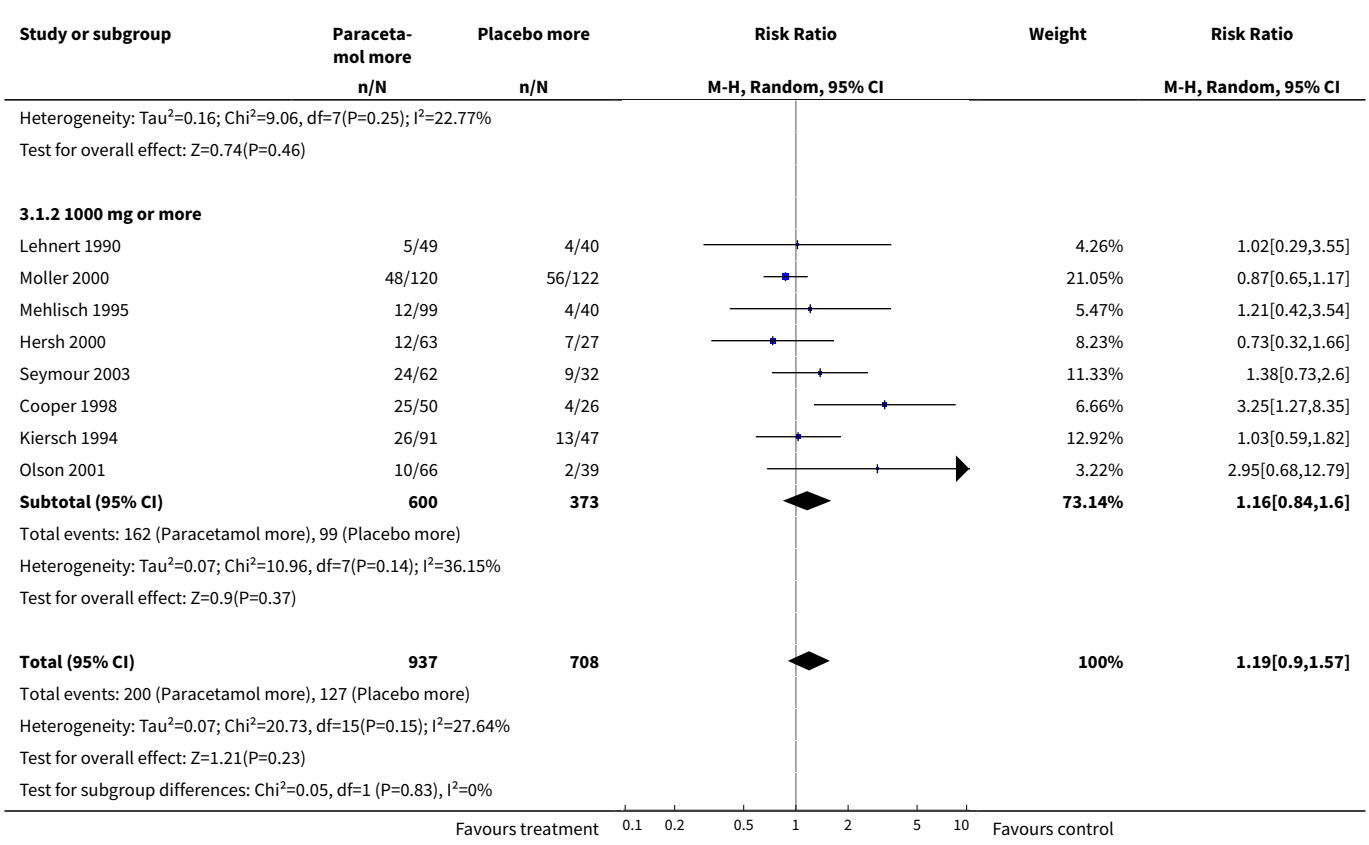


Comparison 3. Number of people with adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with adverse events: paracetamol versus placebo	17	1645	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.90, 1.57]
1.1 Up to 1000 mg of paracetamol	9	672	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.69, 2.25]
1.2 1000 mg or more	8	973	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.60]

Analysis 3.1. Comparison 3 Number of people with adverse events, Outcome 1 Number of patients with adverse events: paracetamol versus placebo.





ADDITIONAL TABLES

Table 1. Random-effects metaregression: < 1000 mg vs 1000 mg, Paracetamol vs Placebo

Outcome	Number of studies	Slope estimate	95% CI	Slope interpretation	P value
50% pain relief at 4 hours (using pain relief)	16	0.94	(0.36 to 1.52)	more pain relief for higher doses	0.001
50% pain relife at 6 hours (using pain relief)	13	1.14	(0.71 to 1.56)	more pain relief for higher doses	<0.001
50% pain relief at 4 hours (using pain intensity)	16	0.23	(-0.84 to 1.30)	more pain relief for higher doses	0.67
50% pain relief at 6 hours (using pain intensity)	14	0.43	(-0.15 to 1.01)	more pain relief for higher doses	0.15

Table 2. Number of patients with adverse events (< 1000 mg Paracetamol/Placebo)

Author	Total: Paracetamol	AEs: Paracetamol	Total: Placebo	AEs: Placebo

Table 2. Number of patients with adverse events (< 1000 mg Paracetamol/Placebo) *(Continued)*

Cooper 1980	37	2	37	6
Cooper 1981	37	12	38	4
Dionne 1994	27	7	25	5
Dolci 1994	80	7	82	8
Forbes 1984b	43	1	40	2
Forbes 1989	26	3	26	2
Forbes 1990	41	5	38	0
Gallardo 1990	15	5	11	3
Seymour 1996	40	0	39	0
Sunshine 1986	30	1	30	1
Vattaraphudej 1986	16	0	19	0
Totals	392	43	385	31

Table 3. Number of patients with adverse effects (< 1000 mg Paracetamol/No placebo)

Author	Total: Paracetamol	Total: Adverse events
Nystrom 1990	45	5
Quiding 1981	27	3
Ragot 1991	40	1
Reijntes 1987	29	2
Selcuk 1996	52	0
Strom 1990	33	6
Totals	226	17

Table 4. Number of patients with adverse events (1000 mg Paracetamol/Placebo)

Author	Total: Paracetamol	AEs: Paracetamol	Total: Placebo	AEs: Placebo
Cooper 1998	50	25	26	4
Hersch 2000	63	12	27	7
Kiersch 1994	91	26	47	13

Table 4. Number of patients with adverse events (1000 mg Paracetamol/Placebo) *(Continued)*

Kubitzek 2003	78	4	84	2
Lehnert 1990	49	5	40	4
Mehlisch 1990	307	32	85	12
Mehlisch 1995	99	12	40	4
Moller 2000	120	48	122	56
Olson 2001	66	10	39	2
Seymour 1996	40	0	39	0
Seymour 2003	62	24	32	9
Totals	1025	198	581	113

Table 5. Number of patients with adverse events (1000 mg Paracetamol/No placebo)

Author	Total: Paracetamol	AEs: Paracetamol
Dionne 1983 (1)	20	12
Nystrom 1990	46	7
Ragot 1991	40	0
Strom 1990	176	19
Totals	282	38

Table 6. Number of patients with adverse events (All doses of Paracetamol/Placebo)

Author	Total: Paracetamol	AEs: Paracetamol	Total: Placebo	AEs: Placebo
Cooper 1980	37	2	37	6
Cooper 1981	37	12	38	4
Cooper 1998	50	25	26	4
Dionne 1994	27	7	25	5
Dolci 1994	80	7	82	8
Forbes 1984b	43	1	40	2
Forbes 1989	26	3	26	2
Forbes 1990	41	5	38	0

Table 6. Number of patients with adverse events (All doses of Paracetamol/Placebo) *(Continued)*

Gallardo 1990	15	5	11	3
Hersch 2000	63	12	27	7
Kiersch 1994	91	26	47	13
Kubitzek 2003	78	4	84	2
Lehnert 1990	49	5	40	4
Mehlisch 1990	307	32	85	12
Mehlisch 1995	99	12	40	4
Moller 2000	120	48	122	56
Olson 2001	66	10	39	2
Seymour 1996	80	0	39	0
Seymour 2003	62	24	32	9
Sunshine 1986	30	1	30	1
Vattaraphudej 1986	16	0	19	0
Totals	1417	241	927	144

Table 7. Number of patients with adverse events (All doses of Paracetamol/No placebo)

Author	Totals: Paracetamol	AEs: Paracetamol
Dionne 1983 (1)	20	12
Nystrom 1990	91	12
Quiding 1981	27	3
Ragot 1991	80	1
Reintjes 1987	29	2
Selcuk 1996	52	0
Strom 1990	209	25
Totals	508	55

Table 8. Total number of adverse events (< 1000 mg Paracetamol/Placebo)

Author	Total: Paracetamol	AEs: Paracetamol	Total: Placebo	AEs: Placebo

Table 8. Total number of adverse events (< 1000 mg Paracetamol/Placebo) *(Continued)*

Cooper 1980	37	6	38	7
Cooper 1981	37	15	37	5
Dionne 1994	27	9	25	5
Dolci 1994	80	7	82	12
Forbes 1984b	43	2	40	2
Forbes 1990	41	5	38	0
Gallardo 1990	15	5	11	3
Sunshine 1986	30	1	30	2
Totals	310	50	301	36

Table 9. Total number of adverse events (< 1000 mg Paracetamol/No placebo)

Author	Total: Paracetamol	AEs: Paracetamol
Haanaes 1986	36	11
Nystrom 1988	45	6
Quiding 1981	27	4
Ragot 1991	40	1
Reintjes 1987	29	2
Selcuk 1996	52	0
Totals	229	24

Table 10. Total number of adverse events (1000 mg Paracetamol/Placebo)

Author	Totals: Paracetamol	AEs: Paracetamol	Totals: Placebo	AEs: Placebo
Breivik 1998	119	17	54	10
Cooper 1998	50	26	26	5
Hersh 2000	63	14	27	8
Kiersch 1994	91	35	47	18
Moller 2000	120	65	122	83
Olson 2001	66	10	39	2

Table 10. Total number of adverse events (1000 mg Paracetamol/Placebo) *(Continued)*

Seymour 2003	62	36	28	13
Skoglund 1991	67	12	33	10
Totals	638	215	376	149

Table 11. Total number of adverse events (1000 mg Paracetamol/No placebo)

Author	Totals: Paracetamol	AEs: Paracetamol
Dionne 1983	20	18
Nystrom 1990	46	10
Ragot 1991	40	0
Totals	106	28

Table 12. Total number of adverse events (All doses of Paracetamol/Placebo)

Author	Totals: Paracetamol	AEs: Paracetamol	Totals: Placebo	AEs: Placebo
Breivik 1998	119	17	54	10
Cooper 1980	37	6	38	7
Cooper 1981	37	15	37	5
Cooper 1998	50	26	26	5
Dionne 1994	27	9	25	5
Dolci 1994	80	7	82	12
Forbes 1984b	43	2	40	2
Forbes 1990	41	5	38	0
Gallardo 1990	15	5	11	3
Hersh	63	14	27	8
Kiersch 1994	91	35	47	18
Moller 2000	120	65	122	83
Olson 2001	66	10	39	2
Seymour 2003	62	36	28	13
Skoglund 1991	67	12	33	10

Table 12. Total number of adverse events (All doses of Paracetamol/Placebo) *(Continued)*

Sunshine 1986	30	1	30	2
Totals	948	265	647	185

Table 13. Total number of adverse events (All doses of Paracetamol/No placebo)

Author	Totals: Paracetamol	AEs: Paracetamol
Dionne 1983	20	18
Haanaes 1986	36	11
Nystrom 1988	91	16
Quiding 1981	27	4
Ragot 1991	80	1
Reijntes 1987	29	2
Selcuk 1996	52	0
Totals	335	52

Table 14. Global assessment - 5-point scale(< 1000 mg Paracetamol)

Author	Total: Paracetamol	Global assessment	Total: Placebo	Global assessment
Cooper 1980	37	0.89	38	0.89
Cooper 1981	37	1.92	37	0.62
Cooper 1988	36	2.38	40	2.05
Dionne 1994	27	2.40	25	2.00
Dolci 1994	72	2.10	76	2.17
Forbes 1984	39	1.26	36	0.28
Mean	248	1.83	252	1.44

Table 15. Global assessment - 4-point scale (< 1000 mg Paracetamol)

Author	Total: Paracetamol	Global assessment	Total: Placebo	Global assessment
Forbes 1989	26	1.00	26	0.30

Table 15. Global assessment - 4-point scale (< 1000 mg Paracetamol) *(Continued)*

Forbes 1990	41	1.47	38	0.56
Sunshine 1986	30	1.20	30	0.93
Vattaraphudej 1986	16	1.6	19	1.16
Mean	113	1.31	113	0.70

Table 16. Global assessment - 5-point scale (1000 mg Paracetamol)

Author	Total: Paracetamol	Global assessment	Total: Placebo	Global assessment
Kiersch 1994	91	1.30	47	0.60
Kubitzek 2003	78	1.98	84	1.45
Mehlisch 1995	101	1.57	40	0.45
Olson 2001	66	2.81	39	1.93
Seymour 2003	62	2.50	32	2.14
Mean	398	1.94	242	1.29

Table 17. Global assessment - 4-point scale (1000 mg Paracetamol)

Author	Total: Paracetamol	Global assessment	Total: Placebo	Global assessment
Hersh 2000	63	2.29	27	0.85
Moller 2000	120	1.88	122	1.54
Mean	183	2.02	149	1.41

Table 18. Quality assessment

Author	Allocation concealment	Follow up	Total (Max-3)
Cooper 1980	1	0	1
Cooper 1981	1	0	1
Cooper 1988	1	0	1
Cooper 1998	1	1	2
Dionne 1994	1	0	1

Table 18. Quality assessment *(Continued)*

Dolci 1994	1	0	1
Forbes 1984b	2	0	2
Forbes 1989	1	0	1
Forbes 1990	2	0	2
Hersh 2000	1	1	2
Kiersch 1994	1	1	2
Kubitzek 2003	1	1	2
Lehnert 1990	1	1	2
Mehlisch 1995	2	1	3
Moller 2000	1	1	2
Olson 2001	2	1	3
Seymour 1996	1	1	2
Seymour 2003	2	0	2
Skoglund 1991	2	0	2
Sunshine 1986	2	1	3
Vattaraphudej 1986	1	1	2

Table 19. Sample size calculation

Author	Yes/No
Cooper 1980	No
Cooper 1981	No
Cooper 1988	No
Cooper 1998	No
Dionne 1994	No
Dolci 1994	No
Forbes 1984	No
Forbes 1989	No
Forbes 1990	No

Table 19. Sample size calculation *(Continued)*

Hersh 2000	No
Kiersch 1994	No
Kubitzek 2003	Yes
Lehnert 1990	No
Mehlisch 1995	No
Moller 2000	Yes
Olson 2001	No
Seymour 1996	No
Seymour 2003	Yes
Skoglund 1991	No
Sunshine 1986	No
Vattaraphudej 1986	No

Table 20. Agreement between quality assessors

Author	Yes/No
Cooper 1980	Yes
Cooper 1981	Yes
Cooper 1988	Yes
Cooper 1998	Yes
Dionne 1994	Yes
Dolci 1994	Yes
Forbes 1984	Yes
Forbes 1989	Yes
Forbes 1990	Yes
Hersh 2000	Yes
Kiersch 1994	Yes
Kubitzek 2003	Yes
Lehnert 1990	Yes

Table 20. Agreement between quality assessors *(Continued)*

Mehlisch 1995	Yes
Moller 2000	Yes
Olson 2001	Yes
Seymour 1996	Yes
Seymour 2003	Yes
Skoglund 1991	No
Sunshine 1986	Yes
Vattaraphudej 1986	No

Table 21. List of adverse events

Adverse events	Paracetamol	Placebo
Nausea	21	11
Vomiting	11	3
Nausea and/or vomiting, stomach cramps, abdominal pain	3	3
Headache	47	31
Drowsiness, sleepiness, somnolence	36	13
Dizziness, fainting, syncope	9	4
Bleeding	11	7
Chills, flushes, fever, flu-like symptoms	5	0
Paraesthesia	4	2
Jawache	1	0
Swelling	1	6
Cellulitis	1	0
Dry socket	11	12
Surgical complications	6	13
CNS	5	6
GI	12	2
Body as a whole	8	3

Table 21. List of adverse events *(Continued)*

Respiratory	2	0
Psychiatric	0	1
Other, hiccups, hearing/vestibular, miosis,	5	1

APPENDICES

Appendix 1. CENTRAL search strategy

#1. MOLAR THIRD single term (MeSH)
#2. (wisdom next tooth)
#3. (wisdom next teeth)
#4. (third near molar*)
#5. (#1 or #2 or #3 or #4)
#6. TOOTH EXTRACTION single term (MeSH)
#7. (extract* near tooth)
#8. (extract* near teeth)
#9. (extract* near (third next molar*))
#10. (extract* near (third near molar*))
#11. (remov* near tooth)
#12. (remov* near teeth)
#13. (surgical* near remov*)
#14. (surgery near remov*)
#15. (surgical* near extract*)
#16. (surgery near extract*)
#17. (#6 or #7 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
#18. (#5 and #17)

WHAT'S NEW

Date	Event	Description
4 February 2014	Review declared as stable	This review is no longer being updated as it has been superseded by reviews conducted by the Cochrane Pain, Palliative and Supportive Care Group (PaPaS).

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 3, 2007

Date	Event	Description
6 March 2012	Amended	Additional tables linked to text.
31 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving, designing and co-ordinating the review (Kiaran Weil (KW), Paul Coulthard (PC)).
Developing search strategy and undertaking searches (Zahid Afzal (ZA), Arjen van Wijk (AJW), KW).
Screening search results and retrieved papers against inclusion criteria (ZA, KW), Marco Esposito (ME), Lee Hooper (LH), PC).
Appraising quality (KW, ZA).
Extracting data from papers (KW, LH, Helen Worthington (HW)).
Writing to authors for additional information (KW).
Data management for the review and entering data into RevMan (KW).
Analysis and interpretation of data (KW, LH, HW).
Writing the review (KW).
Providing general advice on the review (ME, LH, PC, HW).
Performing previous work that was the foundation of current study (PC).

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The University of Manchester, UK.
- The University of Amsterdam, Netherlands.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [adverse effects] [*therapeutic use]; Analgesics, Non-Narcotic [adverse effects] [*therapeutic use]; Molar, Third [*surgery]; Outcome Assessment, Health Care; Pain Measurement; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Tooth Extraction [*adverse effects]

MeSH check words

Humans