Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth (Review)

Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z

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[Intervention Review]

Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

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ABSTRACT

Background

Both paracetamol and ibuprofen are commonly used analgesics for the relief of pain following the surgical removal of lower wisdom teeth (third molars). In 2010, a novel analgesic (marketed as Nuromol) containing both paracetamol and ibuprofen in the same tablet was launched in the United Kingdom, this drug has shown promising results to date and we have chosen to also compare the combined drug with the single drugs using this model. In this review we investigated the optimal doses of both paracetamol and ibuprofen via comparison of both and via comparison with the novel combined drug. We have taken into account the side effect profile of the study drugs. This review will help oral surgeons to decide on which analgesic to prescribe following wisdom tooth removal.

Objectives

To compare the beneficial and harmful effects of paracetamol, ibuprofen and the novel combination of both in a single tablet for pain relief following the surgical removal of lower wisdom teeth, at different doses and administered postoperatively.

Search methods

We searched the Cochrane Oral Health Group'sTrials Register (to 20 May 2013); the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 4); MEDLINE via OVID (1946 to 20 May 2013); EMBASE via OVID (1980 to 20 May 2013) and the *meta*Register of Controlled Trials (to 20 May 2013). We checked the bibliographies of relevant clinical trials and review articles for further studies. We wrote to authors of the identified randomised controlled trials (RCTs), and searched personal references in an attempt to identify unpublished or ongoing RCTs. No language restriction was applied to the searches of the electronic databases.

Selection criteria

Only randomised controlled double-blinded clinical trials were included. Cross-over studies were included provided there was a wash out period of at least 14 days. There had to be a direct comparison in the trial of two or more of the trial drugs at any dosage. All trials used the third molar pain model.

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 (based on total pain relief (TOTPAR) and summed pain intensity difference (SPID) data) was calculated for all three drugs at both two and six hours postdosing and meta-analysed for comparison. The proportion of participants using rescue medication over both six and eight hours was also collated and compared. The number of patients experiencing adverse events or the total number of adverse events reported or both were analysed for comparison.

Main results

Seven studies were included, they were all parallel-group studies, two studies were assessed as at low risk of bias and three at high risk of bias; two were considered to have unclear bias in their methodology. A total of 2241 participants were enrolled in these trials.

Ibuprofen was found to be a superior analgesic to paracetamol at several doses with high quality evidence suggesting that ibuprofen 400 mg is superior to 1000 mg paracetamol based on pain relief (estimated from TOTPAR data) and the use of rescue medication meta-analyses. The risk ratio for at least 50% pain relief (based on TOTPAR) at six hours was 1.47 (95% confidence interval (CI) 1.28 to 1.69; five trials) favouring 400 mg ibuprofen over 1000 mg paracetamol, and the risk ratio for not using rescue medication (also favouring ibuprofen) was 1.50 (95% CI 1.25 to 1.79; four trials).

The combined drug showed promising results, with a risk ratio for at least 50% of the maximum pain relief over six hours of 1.77 (95% CI 1.32 to 2.39) (paracetamol 1000 mg and ibuprofen 400 mg) (one trial; moderate quality evidence), and risk ratio not using rescue medication 1.60 (95% CI 1.36 to 1.88) (two trials; moderate quality evidence).

The information available regarding adverse events from the studies (including nausea, vomiting, headaches and dizziness) indicated that they were comparable between the treatment groups. However, we could not formally analyse the data as it was not possible to work out how many adverse events there were in total.

Authors' conclusions

There is high quality evidence that ibuprofen is superior to paracetamol at doses of 200 mg to 512 mg and 600 mg to 1000 mg respectively based on pain relief and use of rescue medication data collected at six hours postoperatively. The majority of this evidence (five out of six trials) compared ibuprofen 400 mg with paracetamol 1000 mg, these are the most frequently prescribed doses in clinical practice. The novel combination drug is showing encouraging results based on the outcomes from two trials when compared to the single drugs.

PLAIN LANGUAGE SUMMARY

Ibuprofen versus paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Review question

This review, carried out by the Cochrane Oral Health Group, seeks to compare the effectiveness of two commonly used painkillers, paracetamol and ibuprofen and the combination of both in a single tablet in the relief of pain following surgical removal of lower wisdom teeth.

Background

Worldwide the number of surgical operations to remove wisdom teeth is immense, in England alone approximately 63,000 are removed in National Health Service (NHS) hospitals each year. Many patients need time off work and their quality of life is significantly affected. However, despite these consequences, people are often most concerned about pain following the operation which can be severe. It is suggested that the most intense pain is felt three to five hours after surgery. The pain experienced after oral surgery is widely used as a model to measure the effectiveness of painkillers in general.

Both paracetamol and ibuprofen are commonly used for the relief of pain following the surgical removal of lower wisdom teeth. In 2010, a new painkiller (marketed as Nuromol) containing paracetamol and ibuprofen in the same tablet was licensed for use in the United Kingdom.

All the drugs studied in this review had minimal side effects noted when used correctly for short-term pain relief.

Study characteristics

The evidence on which this review is based was current as of 20 May 2013. Seven studies with a total of 2241 participants all involving a direct comparison of ibuprofen to paracetamol or the combination of both were included in this review. All participants had surgery to remove a lower wisdom tooth or teeth that required bone removal or at least caused moderate to severe pain. Painkillers were taken after surgery and different doses of the drugs were compared.

The majority of the studies took place in the USA with one in Puerto Rico. Four of the trials took place in clinical research facilities, two in university dental hospitals and one in a private oral surgery clinic. The age of participants differed slightly between studies but was broadly similar, ranging from 15 to 65 years old. All studies included male and female participants.

All the studies included in this review looked only at pain relief and intensity information after a single dose of the painkiller after surgery. It is known that pain does continue after this and the drugs evaluated in this review are normally taken every six to eight hours (maximum of four times per day).

Key results

Ibuprofen is more effective than paracetamol at all doses studied in this review. On limited evidence, the combination of ibuprofen and paracetamol appeared to be no more effective than the single drugs when measured two hours after surgery. However, again on limited evidence, it was found to be more effective than the drugs taken singly when measured at six hours after surgery. Participants taking the combined drug also had a smaller chance of requiring rescue medication.

The information available regarding adverse events from the studies (including nausea, vomiting, headaches and dizziness) indicated that they were comparable between the treatment groups. However, review authors could not formally analyse the data as it was not possible to work out how many adverse events there were in total.

Quality of the evidence

All of the results (outcomes) comparing ibuprofen to paracetamol are of high quality. This means that further research is very unlikely to change our confidence in the estimates of the effect.

When comparing combined versus single drugs, the body of evidence for the proportion of patients with > 50% maximum pain relief (TOTPAR) over two and six hours, was assessed as of moderate quality due to imprecise estimates based on single studies. This means that further research is likely to have an important impact on our confidence in the estimate of the effect. The body of evidence for the use of rescue medication was assessed as being of high quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Ibuprofen versus paracetamol for pain relief following the surgical removal of lower wisdom teeth

Patient or population: Patients with pain after surgical removal of lower wisdom teeth
Intervention: Ibuprofen
Control: Paracetamol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed[1] risk	Corresponding risk				
	Control	Ibuprofen				
Proportion of patients with > 50% maximum pain relief (TOTPAR) over 6 hours - Ibuprofen 400 mg versus paracetamol 1000 mg Categorical scale Follow-up: 6 hours	**Study population**		**RR 1.47** (1.28 to 1.69)	646 (5 studies)	⊕⊕⊕⊕ **high**	When all doses considered RR = 1.45 (95% CI 1.31 to 1.61) (6 studies, 926 participants; high quality evidence)
	56 per 100	**83 per 100** (72 to 95)				
Proportion of patients with > 50% maximum pain relief (TOTPAR) over 2 hours - Ibuprofen 400 mg versus paracetamol 1000 mg Categorical scale Follow-up: 2 hours	**Study population**		**RR 1.30** (1.09 to 1.55)	645 (5 studies)	⊕⊕⊕⊕ **high**	When all doses considered RR = 1.29 (95% CI 1.13 to 1.46) (6 studies, 926 participants; high quality evidence)
	62 per 100	**81 per 100** (68 to 97)				
Number of patients not using rescue medication at 6 hours (*non-event*) - Ibuprofen 400 mg versus paracetamol 1000	**Study population**		**RR 1.50** (1.25 to 1.79)	542 (4 studies)	⊕⊕⊕⊕ **high**	When all doses considered RR = 1.44 (95% CI 1.13 to 1.64) (5 studies, 823 participants; high quality evidence)

mg Follow-up: 6 hours			
	50 per 100	**75 per 100** (63 to 90)	
Adverse events	The majority of adverse events were minor in nature and usually included nausea, vomiting, headaches and dizziness Side effect profiles have not been included in a meta-analysis as multiple adverse events were recorded in single patients. However, the differences in the observed adverse events for ibuprofen and paracetamol were small		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] This is the median control group risk based on paracetamol being the control group.

BACKGROUND

Description of the condition

In England alone, approximately 63,000 third molars are removed in National Health Service (NHS) hospitals each year (calculated from data available from Hospital Episode Statistics (HES)). Worldwide the number of surgical operations to remove wisdom teeth is immense. Research suggests that wisdom tooth removal has an immediate negative impact on patients' working and social lives: in one study patients took an average of 1.6 days off work, with over one third of patients stating that the surgery had affected their performance at work (Colorado-Bonnin 2006), and participation in social activities, sports and other hobbies is also negatively affected (Conrad 1999). For many patients quality of life (QoL) is reduced for one to two weeks after surgery (Savin 1997). Postoperative complications may include swelling, bruising and limited mouth opening along with difficulty with eating which can be a major concern to patients and has not been appreciated by healthcare professionals in the past (Ogden 1998). However, patients are often most concerned about postoperative pain, which may be severe. Approximately one in two patients will experience pain despite analgesic therapy, even one week after surgery (Savin 1997). 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).

Description of the intervention

Many textbooks of oral surgery practice and drug formularies advocate the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of postoperative pain, and these drugs have been widely used for pain relief in dentistry for some time (Gobetti 1992). There are now over 50 different NSAIDs on the global market. One of the most commonly prescribed NSAIDs is ibuprofen, with 4.5 million prescriptions for ibuprofen being issued in the United Kingdom (UK) during 2007 (Derry 2009). Ibuprofen has been the subject of much research into its efficacy in postoperative dental pain (Derry 2009). The newer drugs decrease the incidence of gastric perforation, obstruction and bleeding by at least 50% (Boers 2001). However, these drugs provide no cardio-protection and may be associated with an increased risk of myocardial infarction (Rang 2012).

Ibuprofen has been shown to be an effective analgesic in the control of postoperative dental pain in a number of clinical trials (Hersh 2000; Seymour 1998; Winter 1978). Paracetamol (acetaminophen) has been commercially available since 1953 making it one of the oldest analgesics on the market. Both ibuprofen and paracetamol are amongst the most commonly used analgesics and are widely available without prescription around the world. Paracetamol is of particular value when NSAIDS are contraindicated, perhaps by known hypersensitivity or a history of gastrointestinal ulceration or bleeding (Nguyen 1999). It is also the analgesic of choice to supplement NSAIDS when these alone are expected to be ineffective to control pain (McQuay 1998). Pain intensity following third molar surgery has been suggested to reach its maximum between three to five hours following surgery (Fisher 1988; Seymour 1985) and therefore this pain model is used to test the efficacy of a single analgesic dose.

The combining of analgesic drugs with different modes of action in order to increase the analgesic effect has been well documented (Bromley 2010; Mehlisch 2002). In 2010, a single combination drug containing both paracetamol and ibuprofen was first licensed for use in the UK. In one study using the third molar pain model, the combination analgesic was shown to be a highly effective drug that was comparable with, or superior to, other combination analgesics marketed for severe pain (Daniels 2011). This drug continues to provide encouraging results in analgesic trials. Indeed, a recent Cochrane review (Derry 2013) compared the combined drug (paracetamol plus ibuprofen) with placebo or the same dose of oral ibuprofen alone using the postoperative dental pain model. The authors concluded that ibuprofen plus paracetamol combinations provided better analgesia than either drug alone (at the same dose), with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event.

Recent systematic reviews (Collins 1999; Toms 2008) have looked at the efficacy and safety of ibuprofen and paracetamol individually, without direct comparison, for postoperative pain management. These reviews have included the findings of studies involving a wide variety of types of surgery such as inguinal hernia surgery, caesarean section, orthopaedic surgery and including the removal of wisdom teeth. Only one review to date looks at paracetamol specifically in relation to postoperative third molar removal pain (Weil 2007), although two other reviews of single dose postoperative analgesics include subgroup analyses for dental pain only (Moore 2011; Toms 2008). 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 was worse for dental pain than for other types of postsurgical pain (Moore 1997).

How the intervention might work

NSAIDs are assumed largely to produce their analgesia as a result of the inhibition of prostaglandin production by the enzyme cyclol-oxygenase (Malmberg 1992). This prostaglandin inhibition is also responsible for the loss of gastric protection and consequent ulceration and bleeding that can occur. NSAIDs have the ability to inhibit the fatty acid cyclo-oxygenase enzyme, thereby inhibit-

ing the production of prostaglandins and thromboxanes (Rang 2012). Cyclo-oxygenases (COX) oxidise arachidonate producing unstable intermediate prostaglandins PGG_2 and PGH_2. There are two main isoforms of COX: COX-1 is a constitutive enzyme and COX-2 is often induced by inflammatory stimuli. Prostaglandins and thromboxanes are nociceptive initiators which lead to painful sensations in the body. It is thought that the anti-inflammatory, analgesic and antipyretic actions of the NSAIDs are related to inhibition of COX-2 and that the unwanted effects, particularly the gastrointestinal consequences are related to inhibition of COX-1. A recent development has been the synthesis of selective COX-2 inhibitors; examples include celecoxib, etoricoxib and lumiracoxib (Neal 2012).

Paracetamol (acetaminophen) is a non-opioid analgesic possessing antipyretic activity and is effective in relieving pain with a low incidence of adverse effects, it has proven to be a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth (Weil 2007). Paracetamol is often grouped with the NSAID family, however, it is considered only to have relatively weak anti-inflammatory activity (Rang 2012). Although the mechanism of action was not fully understood until recently, it is now thought that paracetamol is a selective inhibitor of the newly described COX-3 enzyme, a cyclo-oxygenase-1 variant, in the central nervous system where it acts as a prodrug. It is deacylated to p-aminophenol and in turn conjugated with arachidonic acid to form N-arachidonoyl-phenolamine. This compound is an endogenous cannabinoid, acting on CB1 receptors, and is also an agonist at TRPV1 receptors (Bromley 2010). This inhibition could represent a primary central mechanism by which paracetamol decreases pain and possibly fever (Chandrasekharan 2002). It also 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).

Why it is important to do this review

In this review we investigated the optimal dose of ibuprofen versus paracetamol by direct comparison, taking into account the side effects of different doses of the drugs. This would inform dentists, oral surgeons and their patients of the best strategy for best pain relief when considering ibuprofen or paracetamol (or a combination of both) following the surgical removal of wisdom teeth.

OBJECTIVES

- To discover which analgesic has the best efficacy for managing postoperative pain using the third molar model.
- To assess the efficacy of novel combination drugs including both agents in the same tablet and to compare this to the individual drugs being administered at the same time.
- To assess the harmful effects of ibuprofen and paracetamol, and the combination drugs at different doses administered postoperatively.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled double-blinded clinical trials. Crossover studies were included provided there was a wash out period of at least 14 days.

Types of participants

Patients of all health states without intolerances/allergies to the study drugs who required the surgical removal of a lower wisdom tooth or teeth that required bone removal or at least having a baseline pain intensity of moderate to severe pain. Patients who required removal of an additional tooth or teeth were also included. Surgery was undertaken under local anaesthesia, intravenous sedation or general anaesthesia. Patients taking concurrent analgesia were excluded.

Types of interventions

Ibuprofen, paracetamol or a combination of both given as a single dose postoperatively by mouth in any dose and in any formulation (for example, immediate or slow release).

Types of outcome measures

- Pain relief (visual analogue scale (VAS), categorical verbal rating, verbal numerical scale, global subjective efficacy ratings and other categorical rating scales) and derived pain relief outcomes extracted were TOTPAR (total pain relief), and SPID (summed pain intensity difference) over two to six hours (dichotomous).
- Side effects (for example, gastrointestinal, hepatic and renal) (binary).
- Use of rescue medication within six to eight hours of single dose analgesic administration.

Search methods for identification of studies

For the identification of studies included or considered for this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database

(Appendix 3). The search strategy used a combination of controlled vocabulary and free text terms and was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins 2011). The search of EMBASE was linked to the Cochrane Oral Health Group filter for identifying RCTs.

Electronic searches

We searched the following electronic databases:

- the Cochrane Oral Health Group's Trials Register (to 20 May 2013) (Appendix 1);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochane Library* 2013, Issue 4) (Appendix 2);
- MEDLINE (1946 to 20 May 2013) (Appendix 3);
- EMBASE (1980 to 20 May 2013) (Appendix 4);
- *meta*Register of Controlled Trials (www.controlled-trials.com) (to 20 May 2013) (Appendix 5).

There were no language restrictions applied in the searches of the electronic databases. Where necessary, translations into English were obtained.

Searching other resources

Unpublished studies

Authors of RCTs identified were contacted 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

Only handsearching done as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL was included (see the Cochrane Masterlist for details of journal issues searched to date).
The bibliographies of papers and review articles were checked for further studies. Personal references were also searched.

Data collection and analysis

Selection of studies

Two review authors independently and in duplicate scanned the titles and abstracts (when available) of all reports identified. 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 underwent a risk of bias assessment and data extraction. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

Data extraction and management

Two review authors independently and in duplicate extracted data 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 was not 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.
- Details of withdrawals and drop-outs by study group.
- Details of side effects and adverse events.

Assessment of risk of bias in included studies

The domains considered were: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) along with any other bias thought to be relevant by the authors.
In summary, risk of bias in the included analgesic studies was assessed by the following criteria.

Bias	Criteria for low risk of bias in included studies
Random sequence generation (selection bias)	Method of randomisation must be clearly stated
Allocation concealment (selection bias)	Method of concealment of allocation to interventions must be clearly stated
Blinding (performance and detection bias)	Method of blinding of all parties involved in the study must be detailed
Incomplete outcome data (attrition bias)	All primary outcome measures must be reported on as detailed in the method
Selective reporting (reporting bias)	All drop-outs and missing data must be accounted for, adverse events must be included in the analysis
Other bias	Method of anaesthetic given is clearly defined and unlikely to be a cause of bias in the trial

Measures of treatment effect

Authors commonly report on the results of analgesic trials using mean data with associated standard deviations, this is a problem as the data may be asymmetrically distributed and if used in meta-analyses will lead to potentially erroneous conclusions (Moore 1997a). It is therefore important to derive dichotomous data from the continuous data presented in trials prior to using the data in meta-analyses. The team at the Oxford Pain Relief Unit and Nuffield Department of Anaesthetics have derived a method for dichotomising these data; the detailed background and verification were published over three papers (Moore 1996; Moore 1997a; Moore 1997b).

From the data presented in the trials, the proportion of patients achieving 50% pain relief (50% maximum TOTPAR) was calculated and used in the meta-analysis. Other Cochrane reviews have made use of these measures in their analyses (Derry 2009; Toms 2008; Weil 2007). SPID essentially measures the same thing as TOTPAR. If data were unavailable to calculate TOTPAR, SPID would have been calculated. If data on both TOTPAR and SPID were available, TOTPAR was chosen in preference. Outcomes were assessed for two hours and six hours postdosing (where possible). For these dichotomous outcomes, the estimate of an intervention was expressed as risk ratios together with 95% confidence intervals.

Unit of analysis issues

The unit of analysis is individual patients, although appropriate cross-over studies were included. If data from patients in the same treatment group were used in more than one dose comparison for meta-analysis, the number of patients was split between the groups. For example, if 50 out of 100 patients achieved the desired outcome by taking 1000 mg of paracetamol and these data were to be compared with two different doses of ibuprofen, the figures for the analysis were halved (25 out of 50 for each comparison).

Dealing with missing data

As described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), there are several types of missing data in a systematic review or meta-analysis. The problem of missing studies and outcomes is addressed in the Assessment of reporting biases part of this review. A common problem is missing summary data, such as standard deviations for continuous outcomes, or separate sample sizes for each intervention group. Missing summary data were not a reason to exclude a study from the review and methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) were used for imputing missing standard deviations. In the analysis we made the assumption that the data were missing at random, so we included only available data. The authors were contacted where possible for missing data. Cross-over studies data would be meta-analysed according to the methods outlined in Elbourne 2002.

Assessment of heterogeneity

Prior to meta-analysis, studies were assessed for clinical homogeneity with respect to type of therapy, control group and the outcomes. Clinically heterogeneous studies were not combined in a meta-analysis, but described in a narrative way. For studies judged as clinically homogeneous, statistical heterogeneity was tested by

Q test (Chi^2) and the I^2 statistic. We interpreted a Chi^2 test resulting in a P value < 0.10 as indicating statistically significant heterogeneity. In order to assess and quantify the possible magnitude of inconsistency (i.e. heterogeneity) across studies, we used the I^2 statistic with a rough guide for interpretation as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity.

Assessment of reporting biases

Possible reporting biases were assessed on two levels: within-study and between-study.

Within-study selective outcome reporting was examined as part of the overall risk of bias assessment (Assessment of risk of bias in included studies). Outcomes listed in the methods sections on a publication were compared against those whose results were reported. Where some indications of reporting bias were found, study authors were contacted for clarification.

If there were least 10 studies included in a meta-analysis in the review, a funnel plot of effect estimates against their standard errors was planned to assess a possible between-study reporting bias. If an asymmetry of the funnel plot was found by inspection and confirmed by statistical tests, possible explanations would be considered and taken into account in the interpretation of the overall estimate of treatment effects.

Data synthesis

Meta-analysis was conducted only for studies with similar comparisons reporting the same outcome measures. Risk ratios were used to combine dichotomous data, and weighted mean differences for continuous data (if data had been available), using random-effects models provided there were more than three studies eligible for meta-analysis. Different dose comparisons were presented as subgroups and we divided up the numbers of patients between subgroups to avoid 'double counting'.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was conducted for.

- Subgroups were used for different dose comparisons.
- Where different types of formulation of ibuprofen or paracetamol were used: for instance, immediate release versus slow release.

Had data allowed, the following subgroup analyses would have been undertaken:

Where patients had undergone surgery with local anaesthesia alone, local anaesthesia and intravenous sedation, general anaesthesia alone and general anaesthesia with local anaesthetic.

Sensitivity analysis

Primary meta-analyses included all studies irrespective of their risk of bias. Sensitivity analysis was planned to assess how the results of meta-analysis were affected if studies at high risk of bias were excluded from the analysis. A sensitivity analysis was also planned to take into account the sources of funding of the included studies.

RESULTS

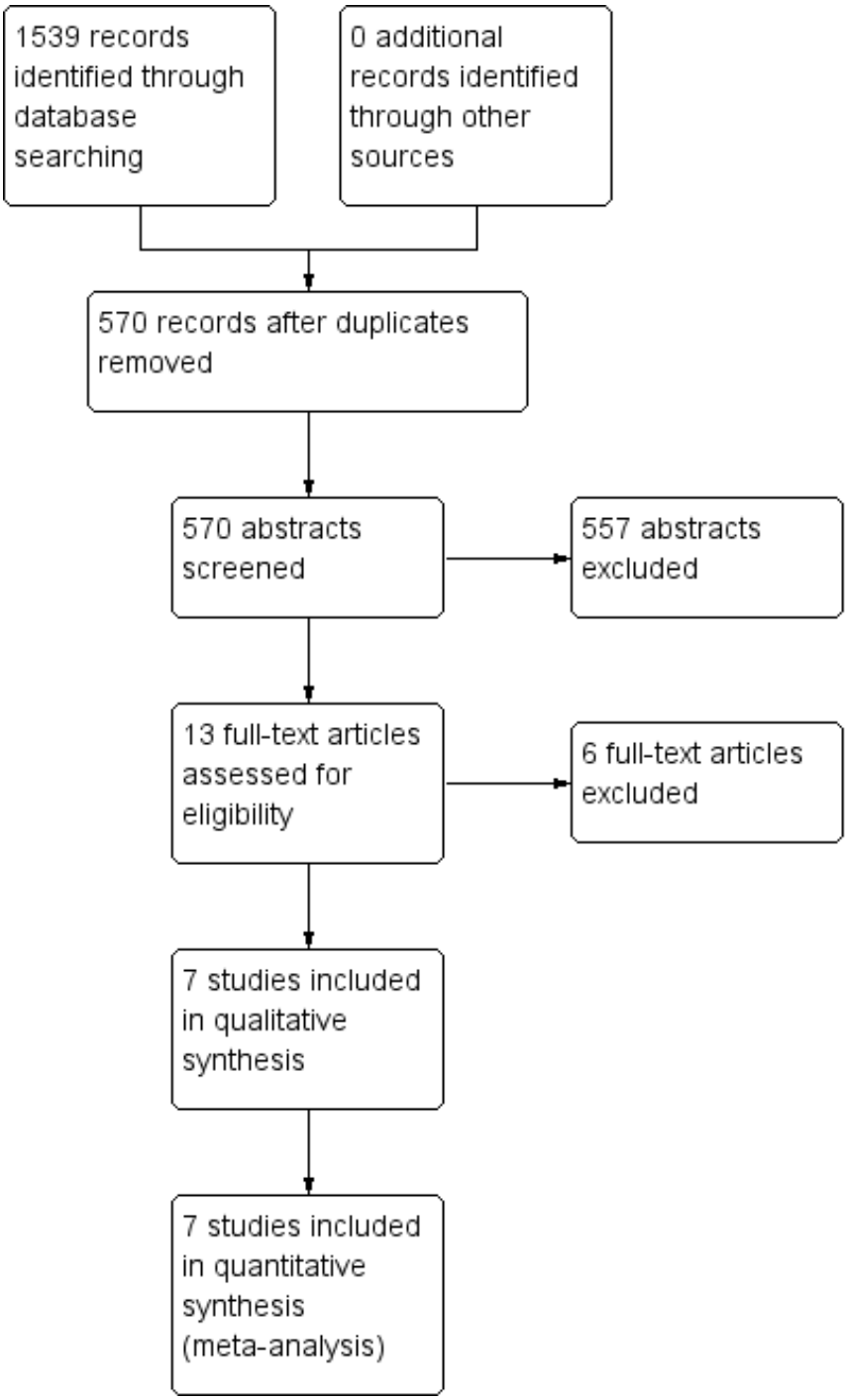
Description of studies

Seven studies were included, they were all parallel-group studies (Characteristics of included studies).

Results of the search

1539 studies were identified through the searching. Initial screening identified 13 potential articles for which full-text was retrieved (Figure 1). After closer examination, six were excluded (Characteristics of excluded studies), leaving seven included studies (Characteristics of included studies).

Figure 1. Study flow diagram.



Included studies

Seven studies were included in this review. The seven studies contained data on 2241 participants. All of these studies included a direct comparison of ibuprofen to paracetamol or the combination of both agents in the same drug (along with other analgesics in some trials: data not used in this review) in the postoperative third molar surgery pain model.

Characteristics of the trial setting and investigators

The majority of the trials (six) were conducted in the USA, with one trial conducted in Puerto Rico (Olson 2001). Three of the trials were conducted by the same lead author, albeit with different collaborators (Mehlisch 1995; Mehlisch 2010; Mehlisch 2010a). Four of the trials were completed in clinical research facilities (Daniels 2009; Mehlisch 1995; Mehlisch 2010; Mehlisch 2010a), two in university dental hospitals (Hersh 2000; Olson 2001) and one in a private oral surgery clinic (Forbes 1990).

Characteristics of the participants

The participants were broadly similar in the included trials, all contained the following exclusion criteria:

- history of significant disease
- ongoing painful conditions (other than the third molar(s) scheduled for removal)
- allergy/intolerance to the study drugs
- patients currently taking long-term analgesics
- malabsorption states (not mentioned in Mehlisch 1995)
- gastrointestinal complaints (not mentioned in Mehlisch 1995)
- psychotic illness or drug abuse (not mentioned in Mehlisch 1995)
- concomitant medication that would interfere with the study drugs (not mentioned in Forbes 1990)
- pregnancy and/or breastfeeding (not mentioned in Mehlisch 1995)
- migraine (not mentioned in Forbes 1990; Hersh 2000 or Olson 2001).

The age range of the participants was slightly different across the studies but broadly similar. All studies included both male and female participants. In Forbes 1990 and Mehlisch 1995, the age range was $\geq$ 15 years, in Hersh 2000 and Mehlisch 2010a, it was $\geq$ 16 years. Age ranges applied in Daniels 2009 and Mehlisch 2010 (16 to 40 years), with a range of 16 to 65 years used by Olson 2001.

Characteristics of the interventions

All seven studies compared paracetamol with ibuprofen and two compared the combination drugs with their individual constituents (Mehlisch 2010; Mehlisch 2010a) (Characteristics of included studies; Additional Table 1). The studies included data on the following doses of analgesics.

- Paracetamol 500 mg (Mehlisch 2010a).
- Paracetamol 600 mg (Forbes 1990).
- Paracetamol 1000 mg (Daniels 2009; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Mehlisch 2010a; Olson 2001).
- Ibuprofen 200 mg Hersh 2000; Mehlisch 2010a).
- Ibuprofen 400 mg: all of the included studies had data on this drug (Daniels 2009; Forbes 1990; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Mehlisch 2010a; Olson 2001).
- Ibuprofen 512 mg liquigel formula (Daniels 2009).
- Paracetamol 250 mg/ibuprofen 100 mg combined drug (Mehlisch 2010a).
- Paracetamol 1000 mg/ibuprofen 400 mg combined drug (Mehlisch 2010; Mehlisch 2010a).
- Paracetamol 500 mg/ibuprofen 200 mg combined drug (Mehlisch 2010; Mehlisch 2010a).

All of the studies were double-blinded, parallel-group randomised controlled trials with dummy medications being issued in Daniels 2009; Mehlisch 1995 and Olson 2001. All of the studies provided rescue medication (Additional Table 2), the drug(s) provided were not detailed in Mehlisch 1995 and Olson 2001 and included a variety of different drugs, with some being administered intramuscularly (Characteristics of included studies).

Use of rescue medication

Rescue medication was provided in all studies, all studies contained data on the percentage of patients taking rescue medication over the study period which was six hours in all of the studies with the exception of Mehlisch 2010 and Mehlisch 2010a which had eight-hour periods of assessment.

Number of third molars removed

In Daniels 2009; Hersh 2000 and Olson 2001, at least one third molar impacted in bone was removed, in Forbes 1990 it states that at least one third molar was removed but it does not state whether bone removal was carried out. In Mehlisch 1995, at least two third molars were removed, one of which was impacted in bone. In the later Mehlisch studies (Mehlisch 2010; Mehlisch 2010a), the participants had three or four third molars removed, two of which had to be impacted in bone in the mandible. It is thought that the removal of bone causes severe pain following the removal of third molars (Coulthard 2009).

Type of anaesthetic used

The anaesthetic used for the surgical procedure varied in the studies. In two studies, general anaesthetic with supplemental local anaesthetic was used (Forbes 1990; Mehlisch 1995). Local anaesthetic alone was used in one study (Olson 2001). Local anaesthetic with supplemental sedation was used in four studies, one using inhalation sedation with nitrous oxides (Daniels 2009), two with nitrous oxide, diazepam and a barbituate (Mehlisch 2010; Mehlisch 2010a) and in one study (Hersh 2000) "most patients" received intravenous conscious sedation. It is important to be aware of whether trial participants were sedated as certain sedative agents commonly used in oral surgery, namely midazolam, have been shown to have an analgesic effect (Coulthard 1992; Coulthard 1993). This effect could have influenced the results of the trials.

Number of doses of analgesic given

For the purposes of data extraction in this review, only the data from the first postoperative dose were used. In Daniels 2009; Hersh 2000; Mehlisch 1995; Mehlisch 2010 and Olson 2001 the study period included only the data for the first six to eight hours following the first dose of analgesic. In Mehlisch 2010a, three doses were provided and in Forbes 1990 there were 15. None of the included studies provided preoperative analgesics.

Baseline pain intensity

It is important that baseline pain intensity measures are included in trials; baseline pain provides the reference point from which the degree of pain relief or an increase or decrease in pain intensity can be measured. In analgesic trials, it is necessary for participants to be experiencing a certain amount of pain before the analgesic is administered in order for the efficacy of the drug to be tested. If participants have no pain at the outset then there is no point in providing analgesics as there will be no improvement in pain scores. The included studies varied in their criteria for baseline pain intensity (as in how much pain a participant has to be experiencing prior to receiving a dose of the test analgesic). Five of the studies used a visual analogue scale (VAS) with a dosing threshold of $\geq$ 50 mm (Daniels 2009; Hersh 2000; Mehlisch 2010; Mehlisch 2010a; Olson 2001); in the Daniels 2009 study, the VAS had to be between 50 mm and 85 mm prior to dosing, the reason for defining an upper limit for VAS was not specified. In the other two trials (Forbes 1990 and Mehlisch 1995), the dosing threshold was described using a categorical scale whereby the participant had to state that they were suffering from moderate or severe pain prior to dosing (this roughly translates to the VAS threshold used by the more recent studies).

Excluded studies

Refer to Characteristics of excluded studies for details of the excluded studies. In total, six studies were excluded following a thorough read through by two of the review authors. Bjornsson 2003 and Chopra 2009 were excluded due to being multiple dose studies, we were also unable to extract reliable single dose data from these trials. Dionne 1983; Merry 2010 and Ozkan 2010 were also excluded for these reasons and the use of pre-emptive analgesia in the trials, it was felt that this would introduce an unacceptable level of bias to the review if included. Ikeda 2002 was excluded due to there being no published paper with the results from the trial available, only an abstract from a conference.

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of risk of bias in the included trials. Two studies were shown to be at low risk of bias across all of the domains (Mehlisch 2010; Mehlisch 2010a). Three studies were assessed as at high risk of bias overall (Forbes 1990; Hersh 2000;Mehlisch 1995) and two were considered to have unclear bias in their methodology (Daniels 2009; Olson 2001).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

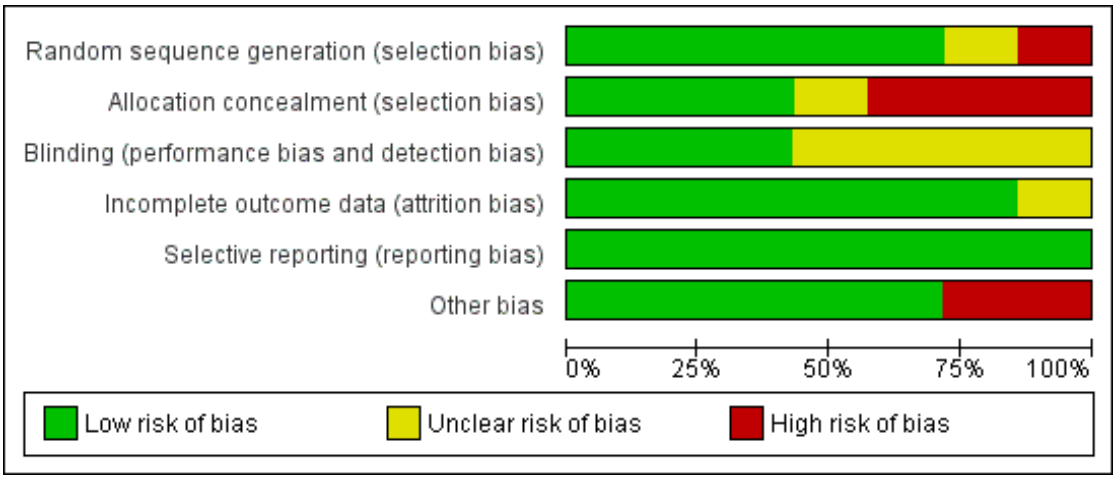
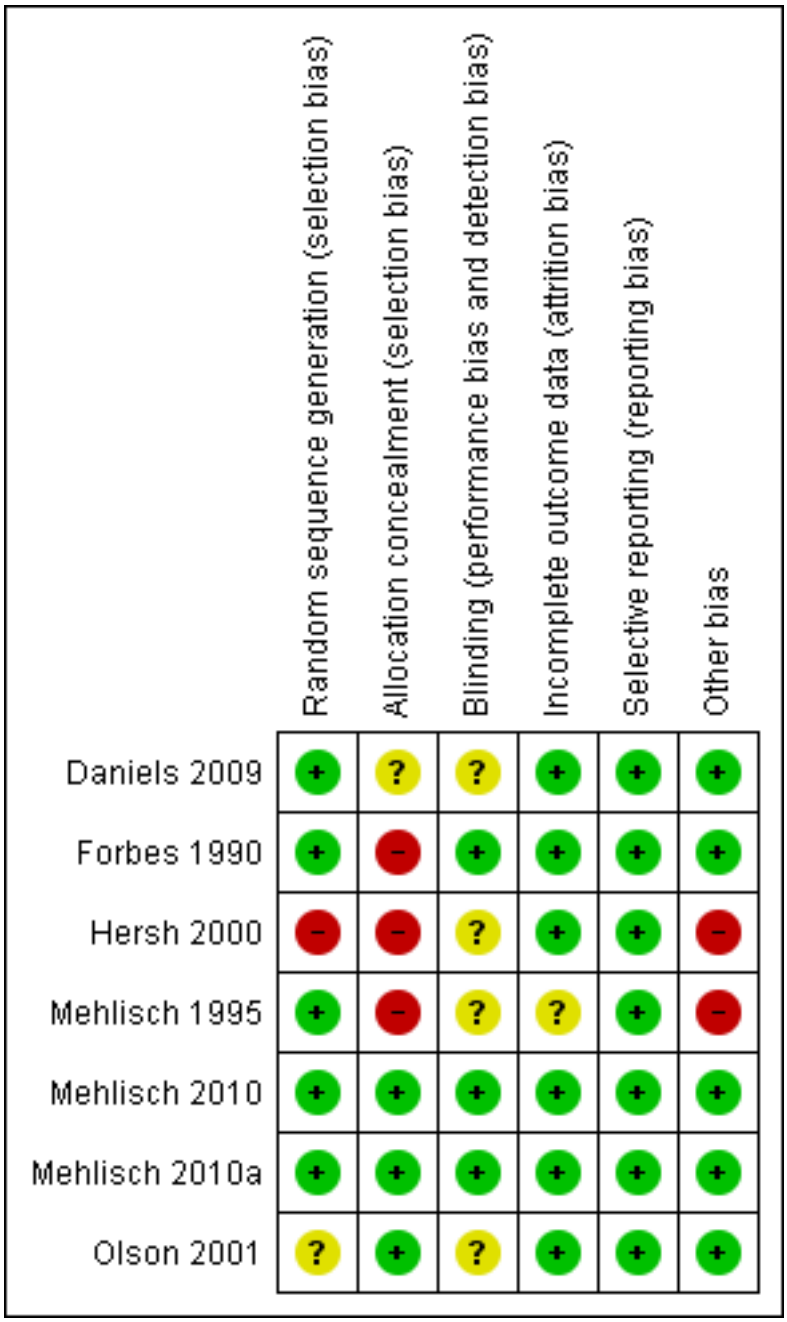


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Five out of the seven studies reported the random sequence and were assessed at low risk, Olson 2001 was shown to have unclear risk of bias in this area due to the sponsor being responsible for the allocation of interventions, and Hersh 2000 was found to be at high risk where no detail was given as to how the patients were randomised.

Mehlisch 2010; Mehlisch 2010a and Olson 2001 reported on allocation concealment and were judged to be at low risk of bias. Forbes 1990; Hersh 2000 and Mehlisch 1995 did not give any information on allocation concealment and were found to be at high risk of bias. In Daniels 2009 study medication appeared to have been matched with placebo, however, the study was judged to be at unclear risk of bias because it was not clear whether the allocation concealment was adequate.

In analgesic trials it is important that the dosing sequence is blinded to the clinicians, pharmacists, nurses and participants. The randomisation sequence is usually kept by a third party and only broken if patient safety is at risk.

Blinding

Forbes 1990; Mehlisch 2010 and Mehlisch 2010a were judged to be at low risk of bias. Daniels 2009; Hersh 2000; Mehlisch 1995 and Olson 2001 were found to be at unclear risk of bias as they claimed to be 'double blind' but did not state explicitly how the blinding process was performed.

Incomplete outcome data

All of the studies were found to be at low risk with the exception of Mehlisch 1995, which was found to be at unclear risk of bias due to one patient not completing any analysis and therefore being excluded from data collection. The reasons for this were not fully explored in the paper.

It is important to note that in analgesic trials, the majority of data is gained from participant-reported outcomes, this therefore limits the influence the investigators can have over the results.

Selective reporting

All seven of the trials were found to be at low risk of bias in this domain. All adverse effects and intended outcomes were reported on.

Other potential sources of bias

Five trials were found to be at low risk of bias with two (Hersh 2000; Mehlisch 1995) being judged as at high risk of other potential sources of bias. In Hersh 2000, this was due to the use of sedation for some patients and not others, with no indication as to how the decision was reached or the randomisation involved in the choice of anaesthetic. This was thought to introduce a potential bias in the results. In Mehlisch 1995, no detail was given on how the study medications were distributed and it was not clear as to whether the medications would be identifiable to the study participants or the assessors.

In analgesic trials, it is important that the participants do not know which medication they are taking, this is usually achieved by producing identical packaging/tablet size for all of the potential dosing regimens. Three of the included studies also used dummy medication (Daniels 2009; Mehlisch 1995; Olson 2001), so that the participants would all have an identical number of pills to take regardless of their dosing regimen.

Effects of interventions

See: **Summary of findings for the main comparison** Ibuprofen versus paracetamol for pain relief following the surgical removal of lower wisdom teeth; **Summary of findings 2** Combined (ibuprofen and paracetamol) versus single drugs for pain relief after surgical removal of lower wisdom teeth

Comparison 1: Ibuprofen versus paracetamol

Outcome TOTPAR (total pain relief) - greater than 50% pain relief over six hours

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (n = 926) (Daniels 2009; Forbes 1990; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Olson 2001) (Analysis 1.1). There was no difference between the subgroups (P value = 0.53), and the overall risk ratio was 1.45 (95% confidence interval (CI) 1.31 to 1.61; P value < 0.00001), indicating that 45% more patients achieved at least 50% of the maximum pain relief over six hours in the ibuprofen group (with doses between 200 mg and 512 mg) compared to the paracetamol group (doses 600 mg and 1000 mg). There was no evidence of any heterogeneity (P value = 0.41; I^2 = 3%).

The most frequently assessed dose was ibuprofen 400 mg compared with paracetamol 1000 mg (five trials; n = 646) (Daniels 2009; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Olson 2001). The pooled risk ratio was 1.47 (95% CI 1.28 to 1.69; P value < 0.00001), indicating 47% more patients achieved at least 50% of the maximum pain relief over six hours in the ibuprofen group. There was no evidence of statistical heterogeneity (P value = 0.30; I^2 = 19%).

Outcome TOTPAR - greater than 50% pain relief over two hours

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including six trials (Daniels 2009; Forbes 1990; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Olson 2001) (Analysis 1.2). There was no difference between the subgroups (P value = 0.48), and the overall risk ratio was 1.29 (95% CI 1.13 to 1.46; P value < 0.00001), indicating that 29% more patients achieved at least 50% of the maximum pain relief over two hours in the ibuprofen group (doses 200 mg to 512 mg) compared to the paracetamol group (doses 600 mg and 1000 mg). There was little evidence of any heterogeneity (P value = 0.13; I^2 = 38%).

Again, the most frequently assessed comparison was ibuprofen 400 mg compared with paracetamol 1000 mg (five trials; n = 645) (Daniels 2009; Hersh 2000; Mehlisch 1995; Mehlisch 2010; Olson 2001). The pooled risk ratio was 1.30 (95% CI 1.09 to 1.55; P value = 0.003), indicating 30% more patients achieved at least 50% of the maximum pain relief over two hours in the ibuprofen group. There was evidence of statistical heterogeneity (P value = 0.08; I^2 = 52%).

Number of patients using rescue medication at six hours

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including five trials (Daniels 2009; Forbes 1990; Hersh 2000; Mehlisch 1995; Olson 2001) (Analysis 1.3). There was no difference between the subgroups (P value = 0.49), and the overall risk ratio was 1.44 (95% 1.26 to 1.64; P value < 0.00001), indicating that 44% fewer patients used rescue medication over six hours in the ibuprofen group (doses 200 mg to 512 mg) compared to the paracetamol group (doses 600 mg and 1000 mg). There was no evidence of any heterogeneity (P value = 0.30; I^2 = 16%).

Number of patients using rescue medication at eight hours

This comparison comprised four subgroups with different doses of ibuprofen and paracetamol, including two trials (Mehlisch 2010; Mehlisch 2010a) (Analysis 1.4). There was no difference between the subgroups (P value = 0.48), and the overall risk ratio was 2.02 (95% CI 1.57 to 2.60; P value < 0.00001), indicating that twice as many patients used rescue medication in the paracetamol groups (doses 600 mg and 1000 mg) than did in the ibuprofen groups (doses 200 mg to 512 mg) over an eight-hour period. There was possible evidence of some heterogeneity (P value = 0.22; I^2 = 30%).

Comparison 2: Combined (ibuprofen and paracetamol) versus single drugs

The four outcomes for TOTPAR were based on data from one trial Mehlisch 2010, therefore they cannot be considered as meta-analyses. All of the comparisons were between paracetamol 1000 mg and ibuprofen 400 mg in the same tablet, and the same constituent drugs given as single tablets. It was not possible to derive TOTPAR and/or SPID (summed pain intensity difference) data from Mehlisch 2010a as the trial used a two-stage design, despite contact with the authors, we did not obtain the specific data required to dichotomise the trial results for meta-analysis.

Outcome TOTPAR - greater than 50% pain relief over six hours

This comparison demonstrates a risk ratio of 1.77 (95% CI 1.32 to 2.39; P value = 0.0002), indicating that 77% more patients achieved at least 50% of the maximum pain relief over six hours in the combined drug group as did in the single drug group (paracetamol 1000 mg and ibuprofen 400 mg) (Analysis 2.1).

Outcome TOTPAR - greater than 50% pain relief over two hours

The results for TOTPAR at two hours showed a similar preference for the combined drug formulation over the single drugs with TOTPAR demonstrating a risk ratio of 1.29 (95% CI 0.91 to 1.85; P value = 0.15), indicating that 29% more patients achieved maximum pain relief over two hours in the combined drug group as did in the single drug group (paracetamol 1000 mg and ibuprofen 400 mg). The confidence interval is wide so therefore there is no evidence to suggest that the combined drug is any better or worse than the single drugs (Analysis 2.2).

Number of patients using rescue medication at eight hours - Combined drug versus single drugs

The results of two studies were analysed (Mehlisch 2010; Mehlisch 2010a) (Analysis 2.3) comparing the efficacy of a combination of paracetamol 1000 mg/500 mg with ibuprofen 400 mg/200 mg in the same pill with the individual constituent drugs taken together. The overall risk ratio was 1.60 (95% CI 1.36 to 1.88; P value < 0.00001) indicating that 60% more patients used rescue medication over six hours in the individual constituent drug group compared to the combined drug group. There was evidence of substantial heterogeneity (P value = 0.02; I^2 = 82%), however this meta-analysis included only data from two trials and has to be interpreted with caution.

In all of the above comparisons, the combined formula of the drug was favoured (see forest plots).

Side effects profile

All studies had information on the adverse events observed during the entire study period. This information is used to create the safety profile of the study drugs. Data on serious or severe adverse events were also collected and collated as a percentage of

total adverse events (Additional Table 3). The vast majority of adverse events were minor in nature and usually included nausea, vomiting, headaches and dizziness. No severe adverse events were thought to be definitely linked to the analgesic drugs or placebos used. It is worth noting that these data were collected in the immediate postoperative period following surgery under local anaesthetic with additional sedation or general anaesthetic in most cases (all studies except Olson 2001 which used local anaesthetic alone), the anaesthetic drugs could be related to the adverse events observed. In Additional Table 3, there is evidence that the frequency of observed adverse events is slightly lower in the Olson 2001 study, adding further weight to this argument. In Mehlisch 2010, the observed frequency of adverse events was high, the authors explained that the events were likely to have been caused by the heavy sedation used for surgery.

Side effect profiles have not been included in a meta-analysis as multiple adverse events were recorded in single patients, it was not possible from the data to work out how many adverse events there were in total. However, Additional Table 3 shows that the differences in the observed adverse events for ibuprofen and paracetamol were small and there were no apparent differences between the groups.

Summary of findings

Using the software GRADEprofiler 3.6, the quality of the body of evidence was assessed for both comparisons: ibuprofen versus paracetamol, and combined (ibuprofen and paracetamol) versus single drugs. TOTPAR, and use of rescue medication were assessed as SPID is measuring the same thing as TOTPAR. A summary of these findings for the two comparisons is shown in Summary of findings for the main comparison and Summary of findings 2. These tables show that all of the outcomes for comparing ibuprofen versus paracetamol are assessed as at high quality. The comparisons for combined (ibuprofen and paracetamol) versus single drugs for TOTPAR are both moderate as they were downgraded due to being based on single studies and the imprecision of estimate. The evidence for use of rescue medication was assessed as high quality.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Combined (ibuprofen and paracetamol) versus single drugs for pain relief after surgical removal of lower wisdom teeth

Patient or population: Patients with pain after surgical removal of lower wisdom teeth
Intervention: Combined (ibuprofen and paracetamol) versus single drugs
Control: Single drugs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed[1] risk	Corresponding risk				
	Control	Combined (ibuprofen and paracetamol)				
Proportion of patients with > 50% maximum pain relief (TOTPAR) over 6 hours - Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg Categorical scale Follow-up: 6 hours	**Study population**		**RR 1.77** (1.32 to 2.39)	170 (1 study)	⊕⊕⊕◯ **moderate**[2]	
	38 per 100	**67 per 100** (50 to 91)				
Proportion of patients with > 50% maximum pain relief (TOTPAR) over 2 hours - Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg Categorical scale Follow-up: 2 hours	**Study population**		**RR 1.29** (0.91 to 1.85)	170 (1 study)	⊕⊕⊕◯ **moderate**[2]	

	37 per 100	**48 per 100** (34 to 68)			
Number of patients not using rescue medication at 8 hours - Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg Follow-up: 8 hours	**Study population**		**RR 1.60** (1.36 to 1.88)	467 (2 studies)	⊕⊕⊕⊕ **high**
	50 per 100	**80 per 100** (68 to 94)			
Adverse events	The majority of adverse events were minor in nature and usually included nausea, vomiting, headaches and dizziness. Side effect profiles have not been included in a meta-analysis as multiple adverse events were recorded in single patients. However, the differences in the observed adverse events for ibuprofen and paracetamol were small				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] This is the median control group risk based on paracetamol/ibuprofen as single drugs being the control group.
[2] Quality of evidence downgraded due to single study and serious imprecision.

DISCUSSION

The surgical removal of lower third molar teeth continues to be a frequently performed surgical procedure carried out by oral surgeons worldwide. Adequate management of pain is of paramount importance to both the patient and surgeon, and also those involved in the commissioning of services as pain experience can be used as a method for measuring the quality of an oral surgey service. All healthcare decisions should be supported by a sound evidence base, this review will form part of the evidence base that oral surgeons should look to when making decisions on how best to manage their patient's postoperative pain.

Summary of main results

Ibuprofen has superior efficacy to paracetamol at all doses studied in this review. Novel drugs which combine paracetamol and ibuprofen formulations within the same tablet are showing encouraging results and based on limited evidence largely based on time to re-medication, appear to be superior analgesics to the constituent drugs taken individually. The reasons for this could be related to the formulation of the combination drug, although this is by no means confirmed in the literature at present. The rationale for combined analgesia is that enhanced pain relief can potentially be achieved from two drugs with different modes of action using a lower dose and with reduced side effects, this is the basis for developing combination analgesics (Daniels 2011; Derry 2013).

Overall completeness and applicability of evidence

All of the included trials only looked at pain relief and intensity data following a single dose of the trial analgesic in a postoperative pain setting. From a clinical point of view, this model has limitations although it is the most frequently used method to assess the efficacy of analgesics. As we know, pain does continue following the initial analgesic dose and the drugs evaluated in this review are normally prescribed to be taken at a frequency of every six to eight hours (maximum of four times per day allowing for time spent sleeping). It would be of interest to know what the pain experience is following the second and subsequent doses of these medications.

All included studies used the 'third molar' pain model or 'dental pain' model to assess their outcomes. This method of pain modelling has been criticised due to not being representative of the entire population. The patients who are enrolled on to these studies would typically be:

- aged under 30 years;
- in good general health;
- lacking in previous surgical interventions; and
- physically fit and active.

These categories will not apply to the entire population (Daniels 2011).

Within the review we presented TOTPAR (total pain relief) data at two and six hours postdosing. We are aware that TOTPAR equations have only been validated for four- and six-hour data (Moore 1996; Moore 1997a; Moore 1997b). Results for two hours, presented within this review, should be interpreted with caution, although from a clinical perspective it was felt that two-hour data were more clinically relevant than four-hour.

Quality of the evidence

As only double-blinded (for participant and outcome assessor) randomised controlled trials were included, the risk of bias was low for two trials, unclear for two trials and high for three trials where there was concern that the type of anaesthetic given may have introduced bias and some lack of detail as to how the participants were randomised. The summary of findings tables present the overall quality of the evidence for each comparison and this was assessed as high quality for comparing paracetamol and ibuprofen; this means that further research is very unlikely to change our confidence in the estimates of the effect. The body of evidence for the proportion of patients with > 50% maximum pain relief (TOTPAR) over two and six hours, when comparing combined (ibuprofen and paracetamol) versus single drugs, was assessed as moderate quality due to these being single studies or based on high risk of bias trials; this means that further research is likely to have an important impact on our confidence in the estimate of the effect. The body of evidence for the use of rescue medication was assessed as being of high quality.

Potential biases in the review process

A thorough search was conducted to locate the included studies, it is highly unlikely that any relevant studies were missed in our search process. None of the authors are featured on any of the included studies and there are no known conflicts of interest.

Agreements and disagreements with other studies or reviews

Based on previously published Cochrane reviews using only the third molar model for assessing analgesics, 400 mg ibuprofen has a number needed to treat (NNT) of 2.3 (95% confidence interval 2.2 to 2.4) (Derry 2009; Moore 2011), and 975 mg to 1000 mg paracetamol has an NNT of 3.6 (95% confidence interval 3.2 to 4.0) (Moore 2011; Toms 2008). Therefore the conclusions from this review are in agreement with those from existing Cochrane reviews demonstrating that ibuprofen is a more effective analgesic than paracetamol at the most frequently prescribed doses. The superiority of the combined drugs over the individual drugs is

also echoed by another recent Cochrane review which found that participants had a smaller chance of requiring rescue medication over eight hours if they took the combined drug compared to the individual agents (Derry 2013).

AUTHORS' CONCLUSIONS

Implications for practice

There is high quality evidence that ibuprofen is superior to paracetamol at doses of 200 mg to 512 mg and 600 mg to 1000 mg respectively based on pain relief, pain intensity difference and use of rescue medication data collected at six hours postoperatively. The majority of this evidence (five out of six trials) compared ibuprofen 400 mg with paracetamol 1000 mg, these are the most frequently used doses in clinical practice.

This review proves ibuprofen to be superior to paracetamol in terms of analgesic efficacy when used postoperatively for pain management following the surgical removal of lower wisdom teeth (third molars). It is important to be aware that the data in this review only relate to single dose postoperative usage of the trial drugs. The combined drugs containing both agents show promising outcomes, with meta-analysis of use of rescue medication at eight hours providing high quality evidence that the combined drugs are superior to the single drugs. It has been suggested that these findings could be due to the formulation of the combined drug having a faster onset of analgesia (Daniels 2011). However, we found that at two hours postoperatively, there was no significant difference between the paracetamol, ibuprofen and combined drug, implying that the drug had a 'delayed' effect relative to the single drug. That is, at six hours the combined drug was more effective.

All drugs studied in this review are generally considered safe with minimal side effects noted when used for short-term pain relief.

It is important to remember that many patients are able to tolerate paracetamol and ibuprofen, and on the basis of evidence in this review prescribing both analgesics either as individual tablets or in combination would take advantage of their differing pharmacological properties and achieve adequate pain relief following the surgical removal of lower third molar teeth.

Implications for research

There is a vast amount of evidence demonstrating that both paracetamol and ibuprofen are effective and safe for managing postoperative pain for minor surgical procedures such as the removal of wisdom teeth (Moore 2011; Toms 2008; Weil 2007). An area where further research is necessary is determining the efficacy and safety profile for the novel combination drugs that include both paracetamol and ibuprofen as active drugs in the same tablet.

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REFERENCES

References to studies included in this review

Daniels 2009 *{published data only}*
Daniels S, Reader S, Berry P, Goulder M. Onset of analgesia with sodium ibuprofen, ibuprofen acid incorporating poloxamer and acetaminophen--a single-dose, double-blind, placebo-controlled study in patients with post-operative dental pain. *European Journal of Clinical Pharmacology* 2009;**65**(4):343–53.

Forbes 1990 *{published data only}*
Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990;**10**(6 (Pt 2)): 94S–105S.

Hersh 2000 *{published data only}*
Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D, et al.Ibuprofen liquigel for oral surgery pain. *Clinical Therapeutics* 2000;**22**(11):1306–18.

Mehlisch 1995 *{published data only}*
Mehlisch DR, Jasper RD, Brown P, Korn SH, McCarroll K, Murakami AA. Comparative study of ibuprofen lysine and acetaminophen in patients with postoperative dental pain. *Clinical Therapeutics* 1995;**17**(5):852–60.

Mehlisch 2010 *{published data only}*
Mehlisch DR, Aspley S, Daniels SE, Bandy DP. Comparison of the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults: a randomized, double-blind, placebo-controlled, parallel-group, single-dose, two-center, modified factorial study. *Clinical Therapeutics* 2010; **32**(5):882–95.

Mehlisch 2010a *{published data only}*
Mehlisch DR, Aspley S, Daniels SE, Southerden KA, Christensen KS. A single-tablet fixed-dose combination of racemic ibuprofen/paracetamol in the management of

moderate to severe postoperative dental pain in adult and adolescent patients: a multicenter, two-stage, randomized, double-blind, parallel-group, placebo-controlled, factorial study. *Clinical Therapeutics* 2010;**32**(6):1033–49.

Olson 2001 ***{published data only}***
Olson NZ, Otero AM, Marrero I, Tirado S, Cooper S, Doyle G, et al.Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. *Journal of Clinical Pharmacology* 2001;**41**(11):1238–47.

References to studies excluded from this review

Bjornsson 2003 ***{published data only}***
Bjornsson GA, Haanaes HR, Skoglund LA. A randomized, double-blind crossover trial of paracetamol 1000 mg four times daily vs ibuprofen 600 mg: effect on swelling and other postoperative events after third molar surgery. *British Journal of Clinical Pharmacology* 2003;**55**(4):405–12.

Chopra 2009 ***{published data only}***
Chopra D, Rehan HS, Mehra P, Kakkar AK. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen and betamethasone using the dental impaction pain model. *International Journal of Oral and Maxillofacial Surgery* 2009;**38**(4):350–5.

Dionne 1983 ***{published data only}***
Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. *Journal of Clinical Pharmacology* 1983;**23**(1):37–43.

Ikeda 2002 ***{published data only}***
Ikeda MC, Arrascue M, Carbajal L, Saravia MA. Ibuprofen, paracetamol and diclofenac plus paracetamol in third molar extractions - a double-blind post-operative study. *Journal of Dental Research* 2002;**81**(Spec Iss A):A-316 (Abstract no: 2510).

Merry 2010 ***{published data only}***
Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E, et al.Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. *British Journal of Anaesthesia* 2010;**104**(1): 80–8.

Ozkan 2010 ***{published data only}***
Ozkan BT, Durmus E, Kalayci A, Kurban S, Akca CN. The evaluation of safety and analgesic efficacy of paracetamol and ibuprofen followed by impacted third molar surgery. *European Journal of General Medicine* 2010;**7**(3):310–6.

Additional references

Bentley 1987
Bentley KC, Head TW. The additive analgesic efficacy of acetaminophen 1000mg and codeine 60mg in dental pain. *Clinical Pharmacology and Therapeutics* 1987;**42**:634–40.

Boers 2001
Boers M. NSAIDs and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection. *Lancet* 2001;**357**(9264):1222–3.

Bromley 2010
Bromley L, Brandner B. *Oxford Pain Management Library: Acute Pain*. Oxford: Oxford University Press, 2010.

Chandrasekharan 2002
Chandrasekharan NV, Dai H, Roos KLC, Evanson NK, Tomsik J, Elton TS, et al.COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. *Proceedings of the National Academy of Sciences* 2002;**99**(21):13926–31.

Collins 1999
Collins S, Moore RA, McQuay HJ, Wiffen PJ, Rees J, Derry S. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: 10.1002/14651858.CD001548]

Colorado-Bonnin 2006
Colorado-Bonnin M, Valmaseda-Castellón E, Berini-Aytés L, Gay-Escoda C. Quality of life following lower third molar removal. *International Journal of Oral and Maxillofacial Surgery* 2006;**35**(4):343–7.

Conrad 1999
Conrad SM, Blakey GH, Shugars DA, Marciani RD, Phillips C, White RP Jr. Patients' perception of recovery after third molar surgery. *Journal of Oral and Maxillofacial Surgery* 1999;**57**(11):1288–94.

Cooper 1976
Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. *Clinical Pharmacology and Therapeutics* 1976;**20**:241–50.

Coulthard 1992
Coulthard P, Rood JP. An investigation of the effect of midazolam on the pain experience. *British Journal of Oral and Maxillofacial Surgery* 1992;**30**:248.

Coulthard 1993
Coulthard P, Rood JP. Midazolam and somatosensory evoked potentials. *British Journal of Oral and Maxillofacial Surgery* 1993;**31**:28–31.

Coulthard 2009
Coulthard P. Post-operative oral surgery pain: a review. *Oral Surgery* 2009;**1**:167–77.

Daniels 2011
Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. *Pain* 2011;**152**:632–42.

Derry 2009
Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001548.pub2]

Derry 2011
Derry S, Wiffen PJ, Moore RA. Relative efficacy of oral analgesics after third molar extraction - a 2011 update. *British Dental Journal* 2011;**211**(9):419–20.

Derry 2013
Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD010210.pub2]

Dray 1997
Dray A. Kinins and their receptors in hyperalgesia. *Canadian Journal of Pharmacology* 1997;**75**:704–12.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials. *International Journal of Epidemiology* 2002;**31** (1):140–9.

Fisher 1988
Fisher SE, Frame JW, Rout PG, McEntegart DJ. Factors affecting the onset and severity of pain following the surgical removal of unilateral impacted third molar teeth. *British Dental Journal* 1988;**164**:351–4.

Gobetti 1992
Gobetti JD. Controlling dental pain. *Journal of the American Dental Association* 1992;**123**:47–52.

Hersh 2000
Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D, et al.Ibuprofen liquigel for oral surgery pain. *Clinical Therapeutics* 2000;**22**(11):1306–18.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kiersch 1994
Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen and placebo in postoperative dental pain. *Clinical Therapeutics* 1994;**16**:394–404.

Loeser 1999
Loeser JD. Pain: an overview. *Lancet* 1999;**353**:1607–9.

Malmberg 1992
Malmberg AB, Yaksh TL. Antinociceptive effects of spinal non-steroidal anti-inflammatory agents on the formalin test in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1992;**263**:136–46.

McQuay 1998
McQuay H, Moore A. *An Evidence Based Resource for Pain*. Oxford: Oxford University Press, 1998:187–92.

Mehlisch 1990
Mehlisch DR, Sollecito WA, Helfrick JF, Leibold DG, Markowitz R, Schow CE Jr, et al.Multicenter clinical trial of ibuprofen and acetaminophen in the treatment of postoperative dental pain. *Journal of the American Dental Association* 1990;**121**(2):257–63.

Mehlisch 2002
Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. *Journal of the American Dental Association* 2002;**133**:861–71.

Moore 1996
Moore RA, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996;**66**: 229–37.

Moore 1997
Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: Oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997; **69**:287–94.

Moore 1997a
Moore RA, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997;**69**:311–5.

Moore 1997b
Moore RA, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997;**69**:127–30.

Moore 1998
Moore A, Collins S, Caroll D, McQuay H, Edwards J. Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD001547]

Moore 2011
Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD008659.pub2]

Neal 2012
Neal MJ. *Medical Pharmacology at a Glance*. 7th Edition. Oxford: Wiley-Blackwell, 2012.

Nguyen 1999
Nguyen AM, Graham DY, Gage T, Griffiths GR. Nonsteroidal anti-inflammatory drug use in dentistry: gastrointestinal implications. *General Dentistry* 1999;**47**(6): 590–6.

Ogden 1998
Ogden GR, Bissias E, Ruta DA, Ogston S. Quality of life following third molar removal: a patient versus professional perspective. *British Dental Journal* 1998;**185**:407–10.

Rang 2012
Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Anti-inflammatory and immunosuppresant drugs. *Pharmacology*. 7th Edition. Churchill Livingstone, 2012.

Savin 1997

Savin J, Ogden GR. Third molar surgery--a preliminary report on aspects affecting quality of life in the early postoperative period. *British Journal of Oral and Maxillofacial Surgery* 1997;**35**(4):246–53.

Seymour 1985

Seymour RA, Meechan JG, Blair GS. An investigation into post-operative pain after third molar surgery under local anaesthesia. *British Journal of Oral and Maxillofacial Surgery* 1985;**23**:410–8.

Seymour 1998

Seymour RA, Frame J, Negus TW, Hawkesford JE, Marsden J, Matthew IR. The comparative efficacy of aceclofenac and ibuprofen in postoperative pain after third molar surgery. *British Journal of Oral and Maxillofacial Surgery* 1998;**36**: 375–9.

Toms 2008

Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004602.pub2]

Weil 2007

Weil K, Hooper L, Afzal Z, Esposito M, Worthington HV, van Wijk A, et al.Paracetamol for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD004487.pub2]

Winter 1978

Winter L, Bass E, Recant B, Cahaly JF. Analgesic activity of ibuprofen (Motrin) in postoperative oral surgery pain. *Oral Surgery, Oral Medicine, Oral Pathology* 1978;**45**(2):159–66.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Daniels 2009

Methods	Double-blinded, randomised, placebo-controlled, active comparator, 2-centre study Parallel group. Dummy medications given. Single dose. Postoperative dosing.
Participants	Males and females 16-40 years of age with at least 1 bony impacted third molar or 2 ipsilateral impacted third molars. An impaction score was assigned to the third molars to demonstrate that they were suitably impacted in bone for inclusion The main exclusion criteria were history of significant disease, ongoing painful conditions (other than the third molar), migraine, malabsorption states, allergy/intolerance to the study medication, gastrointestinal complaints, psychotic illness or drug abuse, concomitant medication that would have interfered with the study drugs, pregnancy/lactation and taking NSAIDs from midnight the night before surgery 614 patients screened, 322 randomised and 318 completed study
Interventions	Patients underwent surgical removal of 1 partially or full bone impacted mandibular third molar, or 2 ipsilateral third molars under local anaesthetic with nitrous oxide sedation. Following surgery, patients who fulfilled the inclusion criteria regarding baseline pain intensity were randomly allocated to 1 of 4 treatment groups in the ratio 1:1:1:1. These were • Sodium ibuprofen: 2×256 mg plus 2 matched placebo for ibuprofen/poloxamer tablets plus 2 matched placebo for 500 mg acetaminophen caplets (n = 80). • Ibuprofen/poloxamer: 2×200 mg ibuprofen acid tablets, each tablet incorporating 60 mg of the surfactant poloxamer 407, plus 2 matched placebo for sodium ibuprofen tablets plus 2 matched placebo for 500 mg acetaminophen caplets (n = 80). • Acetaminophen: 2×500 mg acetaminophen (Tylenol Extra Strength) caplets plus 2 matched placebo for sodium ibuprofen tablets plus 2 matched placebo for ibuprofen/poloxamer tablets (n = 81). • Placebo: 2 matched placebo for sodium ibuprofen tablets plus 2 matched placebo for ibuprofen/poloxamer tablets plus 2 matched placebo for 500 mg acetaminophen caplets (n = 81). Rescue medication was provided, if required within the first 4 hours following surgery, an intramuscular injection of ketorolac tromethamine (60 mg) was given. After 4 hours, acetaminophen 500 mg/hydrocodone 5 mg or ketorolac tromethamine was given. Antibiotics were prescribed postoperatively. Caffeine-containing foods and drinks were to be discontinued from midnight prior to surgery until the end of the 6-hour postdose assessment period Patients were randomised to treatment when they rated their baseline PI as moderate or severe, and the score on the VAS was $\geq$ 50 mm but $\leq$ 85 mm

Outcomes	Pain intensity at baseline (immediately following surgery), 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90, 120, 180, 240, 300 and 360 minutes after dosing measured using VAS and categorical scale of 0 (none) to 3 (severe) Pain relief measured at the same time as PI with the exception of baseline. Scale of 0-4 used (0 = none and 4 = complete). Also asked whether starting pain has at least half gone (no = 0, yes = 1) Stopwatches were started at the time of dosing, 1 was stopped when the patient felt any pain relief whatsoever and the second was stopped when the patient decided that the relief was meaningful to them. If the patient did not stop the watches within the first 4 hours or if rescue medication was used, the stopwatches were discontinued for that patient Distractibility from pain was assessed at baseline and at 60% 360 minutes after dosing. VAS was used in response to the question 'How easy is it for you to distract yourself from your pain?.' The Rainier Scale was completed at baseline and at 60 and 360 minutes after dosing. This assessed perceived functional impairment of activities of daily living, measured on a 1-10 scale (1 = wound not interfere at all, 10 = would completely interfere) Time of rescue medication was recorded, patients taking rescue medication completed all pain intensity and pain relief assessments immediately before medication was taken and continued to record their pain assessments throughout the 6-hour assessment period Global evaluation was scored at the end of the 6-hour period or at the time of rescue medication. Patients were asked, 'How effective do you think the study medication is as a treatment for pain?.' Response choices were 1 = excellent, 2 = very good, 3 = good, 4 = fair or 5 = poor A postoperative review was conducted 5-12 days after surgery
Notes	Sodium ibuprofen 256 mg is equivalent to 200 mg ibuprofen acid

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients "were randomly allocated to one of four treatment groups... in a 1:1:1:1 ratio according to a computer-generated randomisation schedule that stratified patients by sex and baseline pain intensity."
Allocation concealment (selection bias)	Unclear risk	This is unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study claims to be double blinded, but no indication of how blinding of study participants, nurses or assessors was implemented
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported on with intention-to-treat flow diagram presented in paper. All drop-outs accounted for

Daniels 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	All adverse events and outcomes reported as planned.
Other bias	Low risk	Drop-outs, end points and adverse effects were all documented

Forbes 1990

Methods	Double-blinded, randomised, placebo-controlled, single centre study (2 sites) Parallel group. Single dose. Postoperative dosing. Pennsylvania, USA and other collaborators.
Participants	Private outpatients at least 15 years of age who had 1 or more impacted third molars surgically removed Patients were excluded if they were pregnant or lactating; had any history of hypersensitivity or serious adverse reaction to any agent similar to the study medications; had any clinically significant condition that would affect the absorption, metabolism, or excretion of the study medications; or required concomitant medication that would make it difficult to quantify analgesia Long-term users of analgesics and tranquillisers were also excluded 269 patients were randomised, 206 patients completed the study
Interventions	Treatments (1 or more third molar surgical extractions) were carried out under general anaesthetic with additional local anaesthetic (lignocaine). Patients were instructed to take the study medication when they had moderate or severe pain (not specified as VAS equivalent) Interventions. • Ketorolac 10 mg (n = 31). • Ketorolac 20 mg (n = 35). • Ibuprofen 400 mg (n = 32). • Acetaminophen 600 mg (n = 36). • Acetaminophen 600 mg + codeine 60 mg (n = 38). • Placebo (n = 34). The medications were issued as 2 tablets identical in appearance Rescue medication was provided: combinations of acetaminophen with codeine and/or oxycodone The patients returned to the surgeon's office 5 days postoperatively for a follow-up visit
Outcomes	Following the first dose of study medication, subjects responded to the following statements at hourly intervals up to 6 hours • My pain at this time is none (0), slight (1), moderate (2), severe (3). • My relief from starting pain is: none (0), a little (1), some (2), a lot (3), complete (4). • My starting pain is at least half gone: no (0), yes (1). • At the end of the 6-hour observation period, or when the participant took the second dose of medication, participants made a global evaluation of the study

Forbes 1990 (*Continued*)

	medication ranging from poor (0) to excellent (4). Participants continued with the study drugs for 15 doses. Adverse effect data were also collected and summarised in the paper
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a random numbers generator, a computer assigned patient numbers, in blocks of 12, to the six treatment groups."
Allocation concealment (selection bias)	High risk	No details given.
Blinding (performance bias and detection bias) All outcomes	Low risk	The study personnel were not aware of the identity of the study medication at the time it was administered and evaluated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All missing data accounted for, reasons for not completing study included in paper
Selective reporting (reporting bias)	Low risk	All adverse events and outcomes reported as planned.
Other bias	Low risk	All outcomes well documented.

Hersh 2000

Methods	RCT, double-blinded. Single dose. Postoperative dosing. Single centre: University Dental Hospital, Pennsylvania.
Participants	210 participants. Participants had to be at least 16 years of age, be in good general health, requiring removal of > 1 bony impacted wisdom teeth, and have no specific contraindications to the use of ibuprofen, aspirin, related NSAIDs, or acetaminophen. Women who were sexually active had to be using a medically approved method of contraception and had to have a negative urine pregnancy test on the day of surgery. Pregnant or lactating women and any patient who had received other analgesics, anti-inflammatory drugs, sedatives (except for conscious sedation during the surgical procedure), or psychotropic agents within 12 hours of the study were excluded
Interventions	All surgery carried out under local anaesthetic with "most patients" also receiving intravenous conscious sedation Treatment groups.

	• Ibuprofen liquigel 200 mg (n = 61). • Ibuprofen liquigel 400 mg (n = 59). • Acetaminophen caplets 1000 mg (n = 63). • Placebo (n = 27). Administered by mouth with water when postsurgical pain became moderate or severe (> 50 mm on a 100 mm VAS severity scale). Patients who did not experience pain within 5 hours were not given medication Rescue medication (500 mg acetaminophen plus hydrocodone bitartrate 5 mg) was given at any time after the 1 hour assessment period
Outcomes	Pain relief and pain intensity at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5 and 6 hours after initial dosing. Pain relief was assessed on a 5-point scale on 0 (no relief) to 4 (complete relief). Pain intensity was assessed on a 3-point scale 0 (none) to 3 (severe). Exact timings of onset of first perceptible relief and meaningful relief were both recorded using stopwatches Derived data: Hourly categorical scores for PID. SPID was scored at 2 and 6 hours (SPID2 and SPID6). Time weighted pain relief scores summed to derive 2- and 6-hour total pain relief (TOTPAR2 and TOTPAR6). At conclusion patients were asked to provide a global assessment of study medication and adverse reactions if and when occurred were recorded
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "..double blind, double dummy, placebo controlled, randomised, parallel group clinical trial in which patients were stratified for sex and baseline pain." However, no detail given as to how patients were selected for each group
Allocation concealment (selection bias)	High risk	The drugs appear to have been similar in number and form but this was not clearly stated and no further details were given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was said to be "double blinded" but no other details were given
Incomplete outcome data (attrition bias) All outcomes	Low risk	210 patients participated and were included in statistical analysis. There were no drop-outs
Selective reporting (reporting bias)	Low risk	All adverse effects and outcomes reported as planned.

Hersh 2000 (*Continued*)

Other bias	High risk	Different methods of conscious sedation were used in addition to local anaesthetic. Quote: "most patients also received conscious sedation", this is not quantified

Mehlisch 1995

Methods	Double-blinded, double-dummy, parallel-group RCT. Single dose. Postoperative dosing.
Participants	Healthy male and female patients at least 15 years of age, who required surgical removal of 2 or more impacted (at least 1 partially embedded in bone) third molars. In order to be included, they had to experience moderate or severe pain associated with the surgical procedure (not specified as to how this was measured). Patients were excluded from the study if they received any analgesic within 4 hours or a long-acting analgesic within 12 hours of the study medication; received anaesthesia other than mepiva-Caine hydrochloride, fentanyl, or methohexital during the surgery; or were taking any concurrent medication that could confound the evaluation of analgesia or safety
Interventions	All patients had surgery performed under general anaesthetic with supplemental local anaesthetic 3 treatment groups. • Ibuprofen lysine 400 mg, 2x200 mg tablets (n = 99). • Acetaminophen 1000 mg, 2x500 mg tablets (n = 101). • Placebo (n = 99). Patients received a single dose of the test medication when the pain was moderate or severe (not specified as to how this was measured) Rescue medication (backup) was provided but not stated as to what the drug was. Patients were asked not to re-medicate during the first 1 hour period. If a patient did re-medicate within the trial period, the time was noted and no further efficacy evaluations were taken
Outcomes	A stopwatch was started when the study drug was administered and patients were instructed to stop the watch when they experienced meaningful pain relief. If they did not experience meaningful relief within 2 hours after dosing, use of the stopwatch was discontinued Response to treatment was evaluated by patient self rating of pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) and degree of pain relief (0 = none,1 = a little, 2 = some, 3 = a lot, 4 = complete) at 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 5, and 6 hours postdose. At the last evaluation time, the patient provided a global evaluation of the study drug (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent) Adverse clinical experiences were recorded by the study co-ordinator Data recorded for. • PID up to 6 hours. • Time to onset of analgesic effect. • Peak analgesic effect. • Overall analgesic effect. • Time to PID > 1.

Mehlisch 1995 (*Continued*)

	• Time to meaningful pain relief. • SPID at 6 hours. • TOTPAR at 6 hours. • Patient global evaluation. • Time to re-medication. • Number of re-medications.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned to one of three treatment groups... according to an allocation schedule of random numbers."
Allocation concealment (selection bias)	High risk	No details given.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was said to be a "double blind, double-dummy", however, no further details were given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"One of the patients in the ibuprofen lysine group had only one third molar removed and did not record efficacy evaluations; this patient was excluded from the efficacy analysis." Otherwise all participants accounted for.
Selective reporting (reporting bias)	Low risk	All adverse effects and outcomes reported as planned.
Other bias	High risk	No detail of distribution of study medications or if they were identifiable to the participant or operator

Mehlisch 2010

Methods	Randomised, double-blinded, placebo-controlled, parallel-group, 2-centre, modified factorial study Single dose. Postoperative dosing.
Participants	Healthy male or female outpatients were eligible for the study if they were aged 16 to 40 years, were scheduled to undergo surgical removal of 3 to 4 impacted molars 2 of which would be mandibular molars requiring bone removal Impaction scoring (1-4) was used to assess the molars.

	Exclusion criteria included a history of migraine headaches within the previous year; gastrointestinal disorders such as peptic or duodenal ulcer, dyspepsia, or heartburn; hypersensitivity to the study medications; and drug or alcohol abuse. Patients with a current history of significant disease, including psychotic illness or neurosis, were also excluded, as were those who had other painful conditions, were taking medications that might confound the assessment of pain relief, or were unable to refrain from smoking. Women who were pregnant or lactating were not eligible for enrolment
Interventions	Standard oral surgical procedures carried out under local anaesthetic and conscious sedation using nitrous oxide, diazepam, and methohexital (barbiturate drug). Following surgery, eligible patients were randomly assigned in a ratio of 2:1:2:1:1 to a single oral dose of the following • Ibuprofen 400 mg/paracetamol 1000 mg (n = 67). • Ibuprofen 200 mg/paracetamol 500 mg (n = 33). • Ibuprofen 400 mg alone (n = 69). • Paracetamol 1000 mg alone (n = 34). • Placebo (n = 31). Medication was given when postoperative pain intensity was rated at least moderate on the pain intensity categorical rating scale where 0 = none; 1 = mild; 2 = moderate; and 3 = severe and pain intensity was ≥ 50 mm on a 100-mm VAS Rescue medication was provided within the first 4 hours using tramadol 100 mg, and paracetamol 500 mg in combination with hydrocodone 5 mg or tramadol 100 mg after the first 4-hour period. All assessments completed after the patient had taken rescue medication were considered missing
Outcomes	Pain was assessed immediately after surgery (before dosing) and at specified intervals for up to 8 hours after dosing (15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes) Primary efficacy end point was the sum of pain relief and pain intensity differences from baseline (0 hours) to 8 hours postdosing (SPRID8). This measure was defined as the area under the curve (AUC) for the sum of the 2 measures (pain relief and PID) at each time point from 0 to 8 hours Secondary efficacy end points were: total pain relief from 0 to 8 hours (TOTPAR8), sum of pain intensity differences from 0 to 8 hours (SPID8), SPID on the VAS from 0 to 8 hours (SPID8 VAS), TOTPAR from 0 to 4 and from 0 to 6 hours (TOTPAR4, TOTPAR6), SPID4, SPID6, SPRID4, SPRID6, SPID4 VAS, SPID6 VAS, individual pain relief from 15 minutes to 8 hours, peak pain relief over 8 hours, individual PID from 15 minutes to 8 hours, PID VAS from 15 minutes to 8 hours, peak PID and peak PID VAS over 8 hours, time to PID ≥1, PRID, time to first perceptible pain relief, time to first confirmed perceptible pain relief, time to first meaningful pain relief, time to use of rescue medication, time to pain half gone, and patient's global assessment of pain relief on a 5-point scale (1 = poor; 2 = fair; 3 = good; 4 = very good; 5 = excellent) The 2-stopwatch method was also used to assess perceptible and meaningful pain relief (as in Daniels 2009). Patients were assessed 5-7 days postoperatively in relation to their surgery and to assess tolerability of the study medications
Notes	No reason given for 2:1:2:1:1 ratio used for allocating participants into different study groups

Mehlisch 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Upon study entry, patients at each site were stratified by sex and baseline pain intensity and given a unique number in sequence according to a predefined schedule. The block design for the randomisation schedule was in groups of 7
Allocation concealment (selection bias)	Low risk	The randomisation code was supplied to the investigator in a sealed envelope and only broken if necessary due to safety concerns
Blinding (performance bias and detection bias) All outcomes	Low risk	Unblinded study personnel were not involved in any part of the study other than the preparation and verification of doses. Identical medication was dispensed by blindfolded staff to blindfolded patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported on with intention-to-treat flow diagram presented in paper. All drop-outs accounted for
Selective reporting (reporting bias)	Low risk	All adverse effects and outcomes reported as planned. No obvious selective reporting of outcomes
Other bias	Low risk	Drop-outs, end points, adverse effects all documented.

Mehlisch 2010a	
Methods	Multicentre, 2-stage, randomised, double-blinded, parallel-group, placebo-controlled, factorial study. Related to Mehlisch 2010 but using an observation period of 72 hours and a 2-stage study design 3-dose trial. Postoperative dosing.
Participants	Male or female outpatients aged ≥ 16 years undergoing surgical removal of at least 3 impacted third molars (2 of which had to be mandibular impacted molars) Impaction scoring (1-4) was used to assess the molars. Same exclusion criteria as Mehlisch 2010.
Interventions	Stage 1: (first 8 hours). Patients randomly assigned to 1 of the following treatment groups

	• Ibuprofen 200 mg (n = 75). • Ibuprofen 400 mg (n = 74). • Paracetamol 500 mg (n = 76). • Paracetamol 1000 mg (n = 74). • Ibuprofen 100 mg/paracetamol 250 mg (n = 71). • Ibuprofen 200 mg/paracetamol 500 mg (n = 143). • Ibuprofen 400 mg/paracetamol 1000 mg (n = 149). • Placebo (n = 73). Stage 2: (72 hours). Patients who had been taking the combination drugs or placebo stayed on these, but those on monotherapy received the combination drugs incorporating the same dose of active monotherapy from phase 1 Medication was administered when postoperative pain intensity was rated at least moderate on the pain intensity categorical rating scale where 0 = none; 1 = mild; 2 = moderate; and 3 = severe and pain intensity was ≥ 50 mm on a 100-mm VAS. Medication had to be given within 6 hours of surgery but > 3 hours after fentanyl was last administered in order for the participant to be included In stage 2, patients were instructed to take their assigned study medication when at least 8 hours had elapsed since their previous dose of study medication during stage 1, when their pain VAS score was ≥ 30 mm, and provided that they had not consumed > 2 doses of first-line rescue medication in the previous 24 hours. As in stage 1, rescue medication was available as needed, but to ensure that the daily maximum dose of paracetamol was not exceeded, patients were allowed first-line rescue medication only twice in any 24-hour period. Patients who required > 2 doses of first-line rescue medication in any 24-hour period, in addition to the 3 doses of study medication, were considered treatment failures and were allowed to take tramadol 100 mg as second-line rescue medication Patients were given 6 tablets to take in stage 1 and 2 tablets in stage 2 to ensure adequate concealment Rescue medication was provided (hydrocodone 7.5 mg and paracetamol 500 mg) at any time after dosing, but any patient in stage 1 who required rescue medication in the first 60 minutes was considered a “drop-out” and any patient requiring > 2 doses in the first 24-hour period of stage 2 were considered treatment failures 735 patients initially randomised, 715 entered stage 2, 678 completed both stages Follow-up assessment was carried out 7-10 days postoperatively to assess vital signs and perform a physical examination, adverse events were also recorded
Outcomes	Stage 1. Same primary efficacy end points as in Mehlisch 2010 (SPRID8) along with (PRID) scores at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes The key secondary end point was the patient’s global assessment of the study medication, which was evaluated in response to the question ’How do you rate the study medication? ’; response choices were 1 = poor; 2 = fair; 3 = good; 4 = very good; and 5 = excellent. This was assessed at the end of 8 hours, or at the time of rescue medication if earlier than 8 hours. Other secondary end points included, among others, TOTPAR from 0 to 8 hours, SPID from 0 to 8 hours, SPID on the VAS (SPID VAS) from 0 to 8 hours, time to pain half gone, and duration of effect (time to first administration of rescue medication) The 2-stopwatch method was also used as described in the previous paper Tolerability of the study medications was also assessed at 8 hours after dosing in stage 1, at 72 hours in stage 2 and also at the follow-up visit

Mehlisch 2010a (*Continued*)

Notes	Does not state how the molars were removed and under what type of anaesthetic. Although fentanyl is mentioned in the patients and treatment section

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation tables were used. The patients were stratified by sex and severity of pain, then assigned a unique number following a predefined schedule
Allocation concealment (selection bias)	Low risk	The randomisation codes for each patient were supplied to the investigator in a sealed envelope
Blinding (performance bias and detection bias) All outcomes	Low risk	After preparation and checking, all tablets were deprinted and re-packaged to match the placebos
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported on with intention-to-treat flow diagram presented in paper. All drop-outs accounted for
Selective reporting (reporting bias)	Low risk	All adverse effects and outcomes reported as planned. No obvious selective reporting of outcomes
Other bias	Low risk	Drop-outs, end points, adverse effects all documented.

Olson 2001

Methods	Randomised, double-blinded, triple-dummy, parallel-group study Single centre. Single dose. Postoperative dosing.
Participants	Healthy ambulatory male or female subjects, ages 16 to 65 years, who experienced moderate or severe pain after undergoing the surgical removal of 1 or more impacted third molars, 1 of which must have been at least a partial bony mandibular impaction, were included in the study Pregnant females, nursing mothers, and subjects with known sensitivity to acetaminophen, ketoprofen, ibuprofen, or other NSAIDs were excluded from participating in the study. Subjects with a recent history of serious medical condition or presence of bleeding disorders were excluded from the investigation. Subjects were also excluded if they had prior use of any analgesic, sedative, or psychotropic agent within 5 half-

Olson 2001 (*Continued*)

	lives for that drug before taking the study medication (except for local anaesthesia for the procedure). Prior use of any antihistamines within 48 hours of study entry was also prohibited. Subjects with a history of chronic abuse of analgesics or alcohol or substance abuse and subjects receiving other investigational drugs within 30 days of the study
Interventions	All surgery performed under local anaesthetic (lignocaine), patients fasted from midnight the previous night The surgeon assessed the trauma rating of the procedure from mild to severe. Subjects remained at the study centre whilst medication was given and for 6 hours after receiving medication Treatment groups. • Liquigel ibuprofen 400 mg (n = 67). • Ketoprofen 25 mg (n = 67). • Paracetamol 1000 mg (n = 66). • Placebo (n = 39). Rescue medication provided but not specified as to what drug it was Patients were medicated when they scored at least moderate pain on a categorical scale and a VAS of > 50.
Outcomes	Pain severity was evaluated using the categorical pain scale at 15, 30, and 45 minutes and then at 1, 1.5, 2, 3, 4, 5, and 6 hours following study drug administration At each assessment, patients rated their pain intensity and pain relief using the following categorical rating scale for pain intensity: none = 0, slight = 1, moderate = 2, or severe = 3. For pain relief, the following were used: none = 0, a little = 1, some = 2, a lot = 3, or complete relief = 4 A stopwatch was used to describe meaningful pain relief time At the conclusion of the 6-hour evaluation period or at the time of re-medication (if it occurred before the 6th hour), each subject provided an overall evaluation of the study medication on a 5-point categorical scale (from poor = 0 to excellent = 4) If rescue medication was taken, no further measures were made. Time to rescue medication was also recorded
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Treatment assignments were determined by a randomisation schedule generated by the sponsor." This was independent of clinicians
Allocation concealment (selection bias)	Low risk	Randomisation was controlled by the sponsor and all unit doses were identical in appearance
Blinding (performance bias and detection bias)	Unclear risk	The study was said to be "double blinded", however, no details were given

Olson 2001 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	239 patients included, all data appear to have been reported
Selective reporting (reporting bias)	Low risk	All adverse effects and outcomes reported as planned. No obvious selective reporting of outcomes
Other bias	Low risk	Drop-outs, end points, adverse effects all documented.

NSAIDs = non-steroidal anti-inflammatory drugs; PI = pain intensity; PID = pain intensity difference; PRID = pain relief and pain intensity difference; RCT = randomised controlled trial; SPID = summed pain intensity difference; TOTPAR = total pain relief; VAS = visual analogue scale.

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

Study	Reason for exclusion
Bjornsson 2003	Multiple dose study, unable to extract reliable single dose data
Chopra 2009	Analgesic dosing continued for 7 days postoperatively and it was not possible to extract data from the study for the responses to the first dose
Dionne 1983	Multiple dose study, unable to extract reliable single dose data. Also included preoperative analgesic dosing
Ikeda 2002	This was not available as a full paper, only an abstract from the 2002 International Association for Dental Research (IADR) conference
Merry 2010	Multiple dose study, unable to extract reliable single dose data. Also included preoperative analgesic dosing
Ozkan 2010	Multiple dose study, unable to extract reliable single dose data. Also included preoperative analgesic dosing

DATA AND ANALYSES

Comparison 1. Ibuprofen versus paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours	6	926	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.31, 1.61]
1.1 Ibuprofen 200 mg versus paracetamol 1000 mg	1	92	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.90, 1.84]
1.2 Ibuprofen 400 mg versus paracetamol 1000 mg	5	646	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.28, 1.69]
1.3 Ibuprofen 400 mg versus paracetamol 600 mg	1	68	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.13, 5.16]
1.4 Ibuprofen 512 mg versus paracetamol 1000 mg	1	120	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.15, 1.78]
2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours	6	926	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.13, 1.46]
2.1 Ibuprofen 512 mg versus paracetamol 1000 mg	1	120	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.98, 1.67]
2.2 Ibuprofen 400 mg versus paracetamol 1000 mg	5	645	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.09, 1.55]
2.3 Ibuprofen 200 mg versus paracetamol 1000 mg	1	93	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.85, 1.41]
2.4 Ibuprofen 400 mg versus paracetamol 600 mg	1	68	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.96, 3.14]
3 Number of patients using rescue medication at 6 hours	5	823	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.26, 1.64]
3.1 Ibuprofen 200 mg versus paracetamol 1000 mg	1	93	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.94, 2.02]
3.2 Ibuprofen 400 mg versus paracetamol 1000 mg	4	542	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.25, 1.79]
3.3 Ibuprofen 512 mg versus paracetamol 1000 mg	1	120	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.86, 1.60]
3.4 Ibuprofen 400 mg versus paracetamol 600 mg	1	68	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.87, 4.30]
4 Number of patients using rescue medication at 8 hours	2	402	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.57, 2.60]
4.1 Ibuprofen 200 mg versus paracetamol 500 mg	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.31, 4.25]
4.2 Ibuprofen 400 mg versus paracetamol 500 mg	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [1.57, 4.89]
4.3 Ibuprofen 200 mg versus paracetamol 1000 mg	1	75	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.10, 3.17]
4.4 Ibuprofen 400 mg versus paracetamol 1000 mg	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.11, 2.48]

Comparison 2. Combined (ibuprofen and paracetamol) versus single drugs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of patients using rescue medication at 8 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg	2	467	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.36, 1.88]

Analysis 1.1. Comparison 1 Ibuprofen versus paracetamol, Outcome 1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 1 Ibuprofen versus paracetamol

Outcome: 1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours

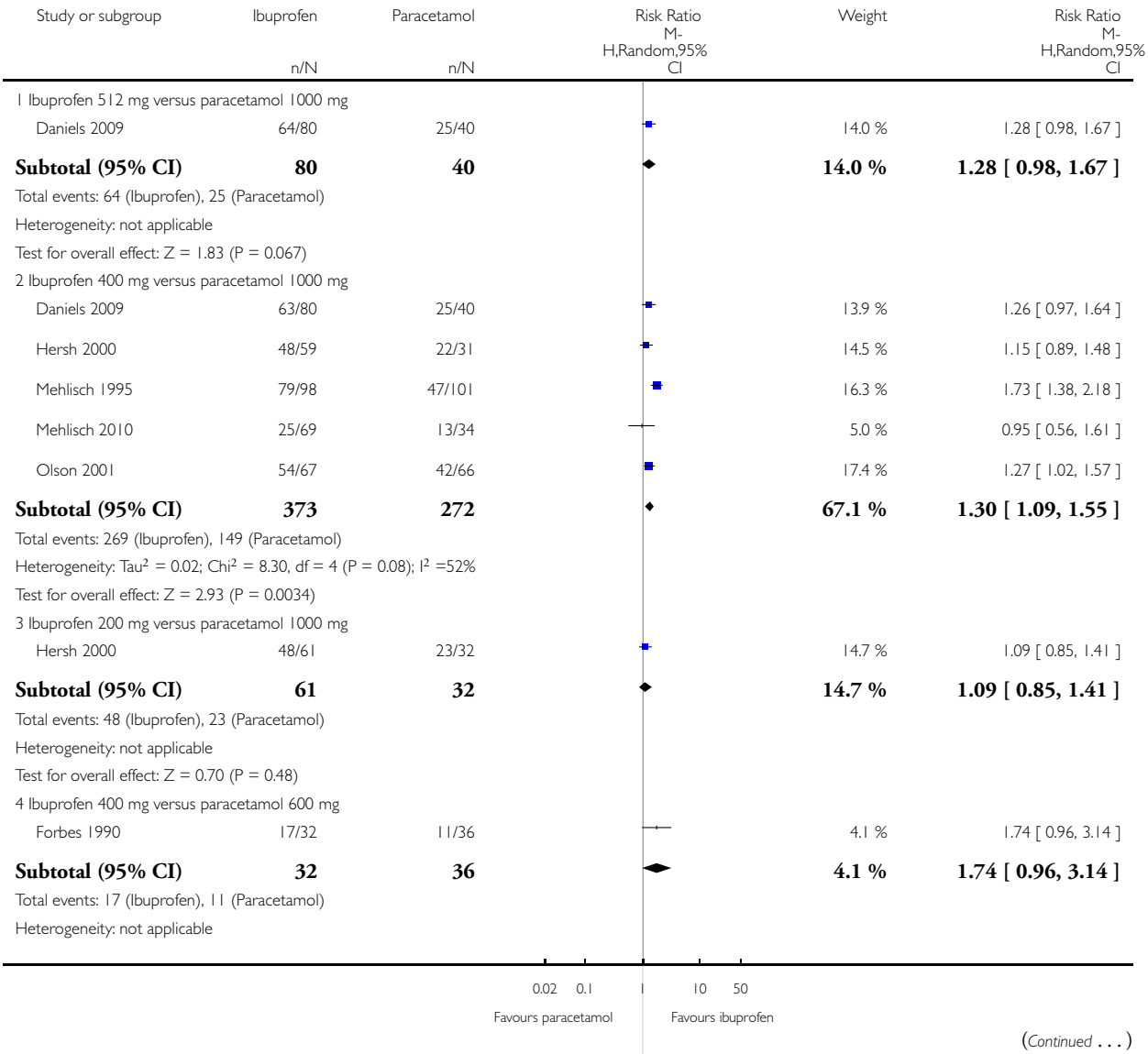
Study or subgroup	Ibuprofen n/N	Paracetamol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Ibuprofen 200 mg versus paracetamol 1000 mg					
Hersh 2000	43/61	17/31		8.1 %	1.29 [0.90, 1.84]
Subtotal (95% CI)	**61**	**31**		**8.1 %**	**1.29 [0.90, 1.84]**
Total events: 43 (Ibuprofen), 17 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 Ibuprofen 400 mg versus paracetamol 1000 mg					
Daniels 2009	78/80	28/40		23.4 %	1.39 [1.13, 1.71]
Hersh 2000	47/59	18/32		9.4 %	1.42 [1.02, 1.97]
Mehlisch 1995	67/98	35/101		11.4 %	1.97 [1.46, 2.66]
Mehlisch 2010	29/69	11/34		3.3 %	1.30 [0.74, 2.27]
Olson 2001	57/67	41/66		21.9 %	1.37 [1.11, 1.70]
Subtotal (95% CI)	**373**	**273**		**69.4 %**	**1.47 [1.28, 1.69]**
Total events: 278 (Ibuprofen), 133 (Paracetamol)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.91, df = 4 (P = 0.30); I^2 =19%					
Test for overall effect: Z = 5.48 (P < 0.00001)					
3 Ibuprofen 400 mg versus paracetamol 600 mg					
Forbes 1990	15/32	7/36		1.8 %	2.41 [1.13, 5.16]
Subtotal (95% CI)	**32**	**36**		**1.8 %**	**2.41 [1.13, 5.16]**
Total events: 15 (Ibuprofen), 7 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
4 Ibuprofen 512 mg versus paracetamol 1000 mg					
Daniels 2009	77/80	27/40		20.8 %	1.43 [1.15, 1.78]
Subtotal (95% CI)	**80**	**40**		**20.8 %**	**1.43 [1.15, 1.78]**
Total events: 77 (Ibuprofen), 27 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.17 (P = 0.0015)					
Total (95% CI)	**546**	**380**		**100.0 %**	**1.45 [1.31, 1.61]**
Total events: 413 (Ibuprofen), 184 (Paracetamol)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.23, df = 7 (P = 0.41); I^2 =3%					
Test for overall effect: Z = 7.15 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.21, df = 3 (P = 0.53), I^2 =0.0%					

Analysis 1.2. Comparison 1 Ibuprofen versus paracetamol, Outcome 2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 1 Ibuprofen versus paracetamol

Outcome: 2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours



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Study or subgroup	Ibuprofen n/N	Paracetamol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.84 (P = 0.066)					
Total (95% CI)	**546**	**380**	♦	**100.0 %**	**1.29 [1.13, 1.46]**
Total events: 398 (Ibuprofen), 208 (Paracetamol)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 11.23, df = 7 (P = 0.13); I^2 =38%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
Test for subgroup differences: Chi^2 = 2.47, df = 3 (P = 0.48), I^2 =0.0%					

0.02 0.1 1 10 50

Favours paracetamol Favours ibuprofen

Analysis 1.3. Comparison 1 Ibuprofen versus paracetamol, Outcome 3 Number of patients using rescue medication at 6 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 1 Ibuprofen versus paracetamol

Outcome: 3 Number of patients using rescue medication at 6 hours

Study or subgroup	Ibuprofen n/N	Paracetamol n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
1 Ibuprofen 200 mg versus paracetamol 1000 mg					
Hersh 2000	19/61	16/32		10.6 %	1.38 [0.94, 2.02]
Subtotal (95% CI)	**61**	**32**	◆	**10.6 %**	**1.38 [0.94, 2.02]**
Total events: 19 (Ibuprofen), 16 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.63 (P = 0.10)					
2 Ibuprofen 400 mg versus paracetamol 1000 mg					
Daniels 2009	18/80	18/40		15.8 %	1.41 [1.04, 1.91]
Hersh 2000	13/59	16/31		10.4 %	1.61 [1.09, 2.38]
Mehlisch 1995	25/98	60/101		19.9 %	1.83 [1.41, 2.39]
Olson 2001	14/67	25/66		25.1 %	1.27 [1.02, 1.59]

0.05 0.2 1 5 20

Favours paracetamol Favours ibuprofen

(*Continued* . . .)

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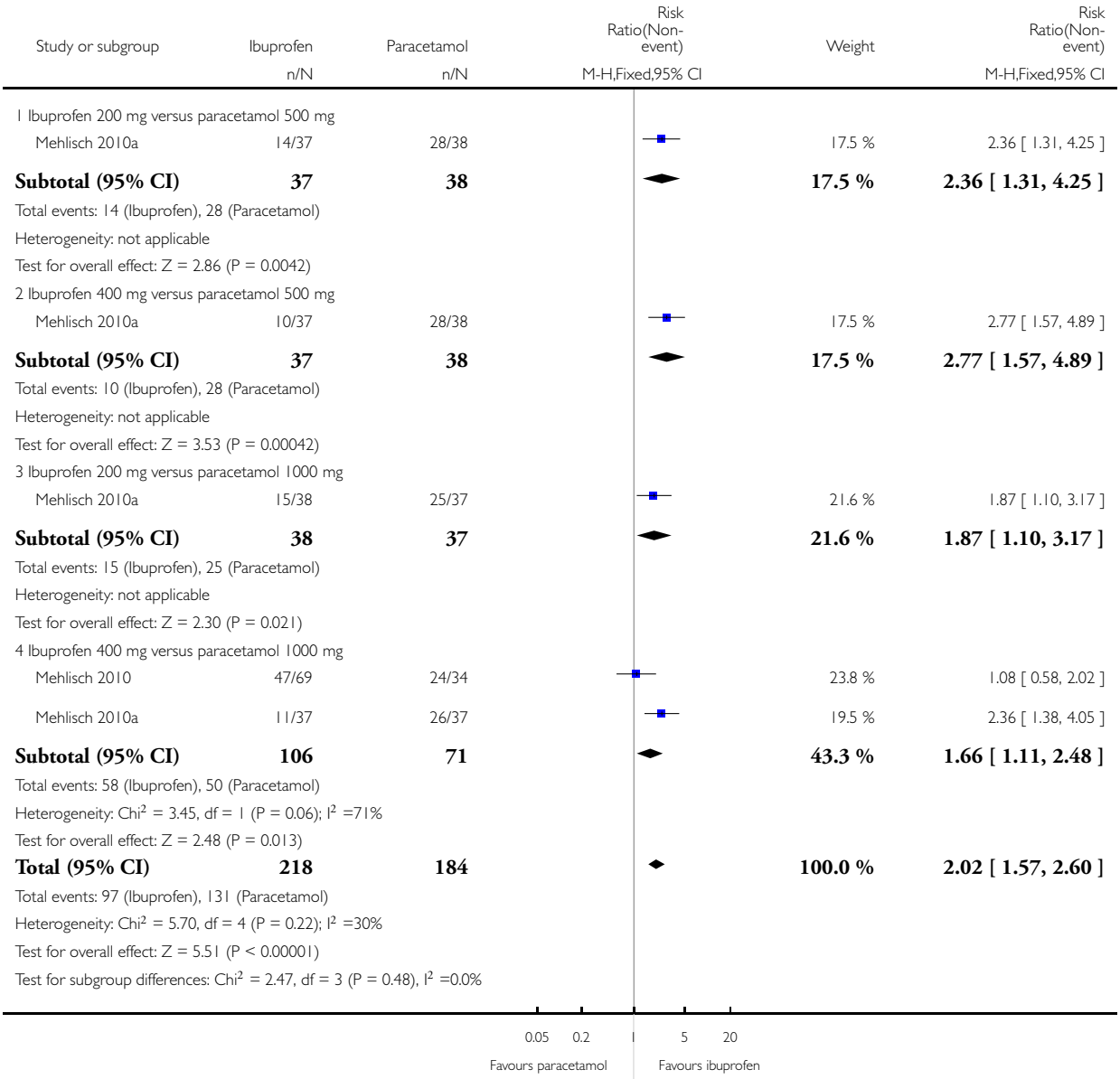
Study or subgroup	Ibuprofen n/N	Paracetamol n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
Subtotal (95% CI)	**304**	**238**	◆	**71.2 %**	**1.50 [1.25, 1.79]**
Total events: 70 (Ibuprofen), 119 (Paracetamol)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.73, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 4.42 (P < 0.00001)					
3 Ibuprofen 512 mg versus paracetamol 1000 mg					
Daniels 2009	26/80	17/40	■	15.6 %	1.17 [0.86, 1.60]
Subtotal (95% CI)	**80**	**40**	◆	**15.6 %**	**1.17 [0.86, 1.60]**
Total events: 26 (Ibuprofen), 17 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
4 Ibuprofen 400 mg versus paracetamol 600 mg					
Forbes 1990	20/32	29/36	◆	2.7 %	1.93 [0.87, 4.30]
Subtotal (95% CI)	**32**	**36**	◆	**2.7 %**	**1.93 [0.87, 4.30]**
Total events: 20 (Ibuprofen), 29 (Paracetamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**477**	**346**	◆	**100.0 %**	**1.44 [1.26, 1.64]**
Total events: 135 (Ibuprofen), 181 (Paracetamol)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.18, df = 6 (P = 0.30); I^2 =16%					
Test for overall effect: Z = 5.31 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.41, df = 3 (P = 0.49), I^2 =0.0%					

Analysis 1.4. Comparison 1 Ibuprofen versus paracetamol, Outcome 4 Number of patients using rescue medication at 8 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 1 Ibuprofen versus paracetamol

Outcome: 4 Number of patients using rescue medication at 8 hours



Analysis 2.1. Comparison 2 Combined (ibuprofen and paracetamol) versus single drugs, Outcome 1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 2 Combined (ibuprofen and paracetamol) versus single drugs

Outcome: 1 Proportion of patients with > 50% max pain relief (TOTPAR) over 6 hours

Study or subgroup	Combined n/N	Individual n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg				
Mehlisch 2010	45/67	39/103		1.77 [1.32, 2.39]

Analysis 2.2. Comparison 2 Combined (ibuprofen and paracetamol) versus single drugs, Outcome 2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 2 Combined (ibuprofen and paracetamol) versus single drugs

Outcome: 2 Proportion of patients with > 50% max pain relief (TOTPAR) over 2 hours

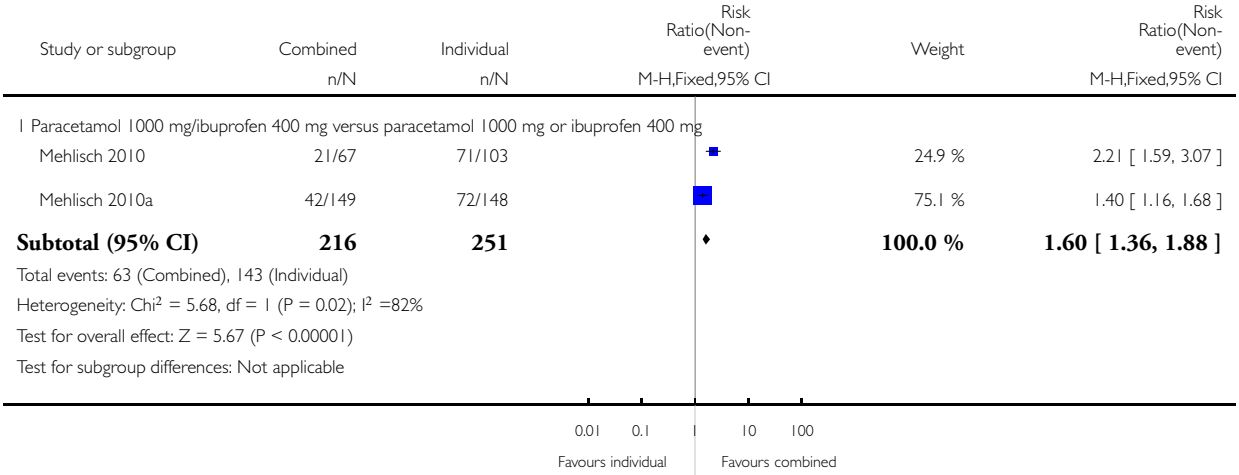
Study or subgroup	Combined n/N	Individual n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Paracetamol 1000 mg/ibuprofen 400 mg versus paracetamol 1000 mg or ibuprofen 400 mg				
Mehlisch 2010	32/67	38/103		1.29 [0.91, 1.85]

Analysis 2.3. Comparison 2 Combined (ibuprofen and paracetamol) versus single drugs, Outcome 3 Number of patients using rescue medication at 8 hours.

Review: Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth

Comparison: 2 Combined (ibuprofen and paracetamol) versus single drugs

Outcome: 3 Number of patients using rescue medication at 8 hours



ADDITIONAL TABLES

Table 1. Doses used in included studies

	Daniels 2009	Forbes 1990	Hersch 2000*	Mehlisch 1995	Mehlisch 2010	Mehlisch 2010a	Olson 2001*
Paracetamol 500 mg						√	
Paracetamol 600 mg		√					
Paracetamol 1000 mg	√		√	√	√	√	√
Ibuprofen 200 mg			√			√	

Table 1. Doses used in included studies (*Continued*)

Ibuprofen 400 mg	√	√	√	√	√	√	√
Ibuprofen 512 mg	√						
Paracetamol 250 mg/ ibuprofen 100 mg						√	
Paracetamol 500 mg/ ibuprofen 200 mg					√	√	
Paracetamol 1000 mg/ ibuprofen 400 mg					√	√	

*Liquigel formula.

Table 2. Use of rescue medication

Study	**Use of rescue medication (RM)**				
	Mean time to RM	Use of RM (%)	Use of RM (n)	Total	Observation period
Daniels 2009					6 hours
Paracetamol 1000		44	35	80	
Ibuprofen 400		23	18	80	
Ibuprofen 512		33	26	80	
Forbes 1990					6 hours
Paracetamol 600	3.89 hours	81	29	36	
Ibuprofen 400	4.63 hours	63	20	32	

Table 2. Use of rescue medication (*Continued*)

Hersch 2000					6 hours
Paracetamol 1000		51	32	63	
Ibuprofen 200		31	19	61	
Ibuprofen 400		22	13	59	
Mehlisch 1995					6 hours
Paracetamol 1000		60	60	101	
Ibuprofen 400		26	25	98	
Mehlisch 2010					8 hours
Paracetamol 1000	261 minutes	71	24	34	
Ibuprofen 400	296 minutes	68	47	69	
Paracetamol 1000/ ibuprofen 400	376 minutes	31	21	67	
Paracetamol 500/ ibuprofen 200	329 minutes	61	20	33	
Mehlisch 2010a					8 hours in phase 1
Paracetamol 500		74	56	76	
Paracetamol 1000		69	51	74	
Ibuprofen 200		39	29	75	
Ibuprofen 400		28	21	74	
Paracetamol 250/ ibuprofen 100		38	27	71	
Paracetamol 1000/ ibuprofen 400		28	42	149	
Paracetamol 500/ ibuprofen 200		22	31	143	
Olson 2001					6 hours
Paracetamol 1000		38	25	66	

Table 2. Use of rescue medication (*Continued*)

Ibuprofen 400		21	14	67	

Table 3. Adverse events

Study	**Adverse events (AE)**			
	Total AE (n)	Total AE %	Serious/Severe AE	Serious/Severe AE %
Daniels 2009				
Paracetamol 1000	25 (81)	31	3	12
Ibuprofen 400	19 (80)	24	1	3
Ibuprofen 512	24 (80)	30	2	6
Forbes 1990				
Paracetamol 600	5 (41)	12	Not specified	Not specified
Ibuprofen 400	8 (43)	19	Not specified	Not specified
Hersch 2000				
Paracetamol 1000	12 (63)	19	0	0
Ibuprofen 200	7 (61)	11	0	0
Ibuprofen 400	4 (59)	7	0	0
Mehlisch 1995				
Paracetamol 1000	17 (101)	17	0	0
Ibuprofen 400	12 (98)	12	0	0
Mehlisch 2010				
Paracetamol 1000	24 (34)	71	11	46
Ibuprofen 400	39 (69)	57	14	36
Paracetamol 1000/ ibuprofen 400	38 (67)	57	11	29
Paracetamol 500/ ibuprofen 200	14 (33)	42	6	43

Table 3. Adverse events (*Continued*)

Mehlisch 2010a				
Paracetamol 500	38 (76)	50	7	18
Paracetamol 1000	30 (74)	40	5	17
Ibuprofen 200	31 (75)	41	7	23
Ibuprofen 400	33 (74)	45	5	15
Paracetamol 250/ ibuprofen 100	22 (71)	31	8	36
Paracetamol 1000/ ibuprofen 400	44 (149)	30	15	34
Paracetamol 500/ ibuprofen 200	51 (143)	36	7	14
Olson 2001				
Paracetamol 1000	10 (66)	15	1	10
Ibuprofen 400	7 (67)	11	2	29

APPENDICES

Appendix 1. Cochrane Oral Health Group's Trials Register search strategy

(molar* or "wisdom tooth" or "wisdom teeth") AND (extract* or remov* or surgery or surgical) AND (ibuprofen or "anti inflammator*" or anti-inflammator* or antiinflammator* or NSAID or acetaminophen or paracetamol or acetominophen or acamol or acephen or acetaco or acetamidophenol or hydroxyacetanlide or algotropyl)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Molar, Third this term only
#2 ((third in All Text near/6 molar* in All Text) or (3rd in All Text near/6 molar* in All Text))
#3 ((wisdom in All Text near/6 tooth in All Text) or (wisdom in All Text near/6 teeth in All Text))
#4 (#1 or #2 or #3)
#5 MeSH descriptor Tooth extraction explode all trees
#6 (extract* in All Text or remov* in All Text or surgical in All Text or surgery in All Text)
#7 (#5 or #6)
#8 (#4 and #7)
#9 MeSH descriptor Ibuprofen this term only

#10 ibuprofen in All Text
#11 ("anti inflammator$" in All Text or anti-inflammator$ in All Text or antiinflammator$ in All Text)
#12 NSAID in All Text
#13 (#9 or #10 or #11 or #12)
#14 MeSH descriptor Acetaminophen this term only
#15 (paracetamol in All Text or acetaminophen in All Text or acetominophen in All Text or acamol in All Text or acephen in All Text or acetaco in All Text or acetamidophenol in All Text or hydroxyacetanlide in All Text or algotropyl in All Text)
#16 (#14 or #15)
#17 (#13 or #16)
#18 (#8 and #17)

Appendix 3. MEDLINE (OVID) search strategy

1. Third molar/
2. ((third adj6 molar$) or (3rd adj6 molar$)).mp.
3. ((wisdom adj6 tooth) or (wisdom adj6 teeth)).mp.
4. or/1-3
5. Tooth extraction/
6. (extract$ or remov$ or surgical or surgery).mp.
7. 5 or 6
8. 4 and 7
9. Ibuprofen/
10. ibuprofen.mp.
11. ("anti inflammator$" or anti-inflammator$ or antiinflammator$).mp.
12. NSAID.mp.
13. or/9-12
14. Acetaminophen/
15. (paracetamol or acetaminophen or acetominophen or acamol or acephen or acetaco or acetamidophenol or hydroxyacetanlide or algotropyl).mp.
16. 14 or 15
17. 8 and (13 or 16)

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the*Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 [updated March 2011].

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. EMBASE (OVID) search strategy

1. Molar tooth/
2. ((third adj6 molar$) or (3rd adj6 molar$)).mp.
3. ((wisdom adj6 tooth) or (wisdom adj6 teeth)).mp.
4. or/1-3
5. Tooth extraction/
6. (extract$ or remov$ or surgical or surgery).mp.
7. 5 or 6
8. 4 and 7
9. Ibuprofen/
10. ibuprofen.mp.
11. ("anti inflammator$" or anti-inflammator$ or antiinflammator$).mp.
12. NSAID.mp.
13. or/9-12
14. Acetaminophen/
15. (paracetamol or acetaminophen or acetominophen or acamol or acephen or acetaco or acetamidophenol or hydroxyacetanlide or algotropyl).mp.
16. 14 or 15
17. 8 and (13 or 16)

The above subject search was linked to the Cochrane Oral Health Group filter for identifying RCTs in EMBASE via OVID:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

Appendix 5. *meta*Register of Controlled Trials search strategy

(molar AND (paracetamol AND ibuprofen))

CONTRIBUTIONS OF AUTHORS

Background and original concept: Paul Coulthard (PC), Zahid Afzal (ZA), Edmund Bailey (EB).

Identification of included studies: EB, PC, Helen Worthington (HW).

Risk of bias: EB, Julian M Yates (JMY).

Data analysis: EB, HW, Arjen van Wijk (AvW).

Results and conclusions: EB, PC, HW.

DECLARATIONS OF INTEREST

Review authors have no interests to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was written focusing purely on the individual administration of ibuprofen versus paracetamol. Since publication of the protocol a new combination drug (marketed as Nuromol), containing both paracetamol and ibuprofen in the same tablet, was launched in the United Kingdom. This drug has shown promising results to date and we have chosen to also compare the combined drug with the single drugs using this model.

Quality assessment has been updated to reflect the change to risk of bias assessment.

The following subgroup analysis was removed as the review only focuses on postoperative pain relief: the time of administration of ibuprofen or paracetamol differs: preoperative versus postoperative.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*administration & dosage; adverse effects]; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage; adverse effects]; Drug Combinations; Drug Therapy, Combination [methods]; Ibuprofen [*administration & dosage; adverse effects]; Molar, Third [*surgery]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Salvage Therapy [methods]; Tooth Extraction [*adverse effects]

MeSH check words

Humans