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

Moore RA, Derry S, McQuay HJ, Wiffen PJ

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[Overview of Reviews]

Single dose oral analgesics for acute postoperative pain in adults

R Andrew Moore[1], Sheena Derry[1], Henry J McQuay[1], Philip J Wiffen[2]

[1]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [2]UK Cochrane Centre, Oxford, UK

Contact address: Maura Moore, Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LJ, UK. maura.moore@pru.ox.ac.uk.

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ABSTRACT

Background

Thirty-five Cochrane Reviews of randomised trials testing the analgesic efficacy of individual drug interventions in acute postoperative pain have been published. This overview brings together the results of all those reviews and assesses the reliability of available data.

Objectives

To summarise data from all Cochrane Reviews that have assessed the effects of pharmaceutical interventions for acute pain in adults with at least moderate pain following surgery, who have been given a single dose of oral analgesic taken alone.

Methods

We identified systematic reviews in *The Cochrane Library* through a simple search strategy. All reviews were overseen by a single Review Group, had a standard title, and had as their primary outcome numbers of participants with at least 50% pain relief over four to six hours compared with placebo. For individual reviews we extracted the number needed to treat (NNT) for this outcome for each drug/dose combination, and also the percentage of participants achieving at least 50% maximum pain relief, the mean of mean or median time to remedication, the percentage of participants remedicating by 6, 8, 12, or 24 hours, and results for participants experiencing at least one adverse event.

Main results

The overview included 35 separate Cochrane Reviews with 38 analyses of single dose oral analgesics tested in acute postoperative pain models, with results from about 45,000 participants studied in approximately 350 individual studies. The individual reviews included only high-quality trials of standardised design and outcome reporting. The reviews used standardised methods and reporting for both efficacy and harm. Event rates with placebo were consistent in larger data sets. No statistical comparison was undertaken.

There were reviews but no trial data were available for acemetacin, meloxicam, nabumetone, nefopam, sulindac, tenoxicam, and tiaprofenic acid. Inadequate amounts of data were available for dexibuprofen, dextropropoxyphene 130 mg, diflunisal 125 mg, etoricoxib 60 mg, fenbufen, and indometacin. Where there was adequate information for drug/dose combinations (at least 200 participants, in at least two studies), we defined the addition of four comparisons of typical size (400 participants in total) with zero effect as making the result potentially subject to publication bias and therefore unreliable. Reliable results were obtained for 46 drug/dose combinations in all painful postsurgical conditions; 45 in dental pain and 14 in other painful conditions.

NNTs varied from about 1.5 to 20 for at least 50% maximum pain relief over four to six hours compared with placebo. The proportion of participants achieving this level of benefit varied from about 30% to over 70%, and the time to remedication varied from two hours (placebo) to over 20 hours in the same pain condition. Participants reporting at least one adverse event were few and generally no different between active drug and placebo, with a few exceptions, principally for aspirin and opioids.

Drug/dose combinations with good (low) NNTs were ibuprofen 400 mg (2.5; 95% confidence interval (CI) 2.4 to 2.6), diclofenac 50 mg (2.7; 95% CI 2.4 to 3.0), etoricoxib 120 mg (1.9; 95% CI 1.7 to 2.1), codeine 60 mg + paracetamol 1000 mg (2.2; 95% CI 1.8 to 2.9), celecoxib 400 mg (2.5; 95% CI 2.2 to 2.9), and naproxen 500/550 mg (2.7; 95% CI 2.3 to 3.3). Long duration of action (≥ 8 hours) was found for etoricoxib 120 mg, diflunisal 500 mg, oxycodone 10 mg + paracetamol 650 mg, naproxen 500/550 mg, and celecoxib 400 mg.

Not all participants had good pain relief and for many drug/dose combinations 50% or more did not achieve at last 50% maximum pain relief over four to six hours.

Authors' conclusions

There is a wealth of reliable evidence on the analgesic efficacy of single dose oral analgesics. There is also important information on drugs for which there are no data, inadequate data, or where results are unreliable due to susceptibility to publication bias. This should inform choices by professionals and consumers.

PLAIN LANGUAGE SUMMARY

Comparing single doses of oral analgesics for acute pain in adults postoperation

All analgesic drugs (painkillers) are tested in standardised clinical studies of people with established pain following surgery, and often after removal of third molar (wisdom) teeth. In all these studies the participants have to have at least moderate pain in order for there to be a sensitive measure of pain-relieving properties. *The Cochrane Library* has 35 reviews of oral analgesic interventions, with 38 different drugs, at various doses involving 45,000 participants in about 350 studies. This overview sought to bring all this information together, and to report the results for those drugs with reliable evidence about how well they work or any harm they may do in single oral doses.

For some drugs there were no published trials, for some inadequate amounts of information, and for some adequate information but with results that would have been overturned by just a few unpublished studies with no effect. None of these could be regarded as reliable. However, amongst the data there were still 46 drug/dose combinations with reliable evidence.

No drug produced high levels of pain relief in all participants. The range of results with single-dose analgesics in participants with moderate or severe acute pain was from 70% achieving good pain relief with the best drug to about 30% with the worst drug. The period over which pain was relieved also varied, from about two hours to about 20 hours. Typically adverse event rates were no higher with analgesic drugs than with placebo, except often with opioids (for example, codeine, oxycodone) where more participants experienced them.

Commonly used analgesic drugs at the recommended or licensed doses produce good pain relief in some, but not all, patients with pain. The reasons for this are varied, but patients in pain should not be surprised if drugs they are given do not work for them. Alternatives analgesic drugs or procedures should be found that do work.

BACKGROUND

Description of the condition

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical

component of patient care and is important for cost-effective use of healthcare resources. Good postoperative pain management helps to achieve a satisfied patient who is in hospital or at home and unable to carry out normal activities for a minimal amount of time.

Description of the interventions

Analgesics used for relief of postoperative pain include so called 'mild' or step 1 (WHO 2010) analgesics, such as paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and celecoxib, 'moderate' or step 2 analgesics, which are weaker opioids such as codeine, and 'strong' or step 3 analgesics, which are strong opioids such as oxycodone and fentanyl.

Paracetamol has become one of the most used antipyretic and analgesic drugs worldwide, and is often also used in combination with other stronger analgesics. NSAIDs as a class are the most commonly prescribed analgesic medications worldwide and their efficacy for treating acute pain has been well demonstrated (Moore 2003). Opioids as a class have long been used to treat pain during and immediately after surgery, because they can be given parenterally, and because dose can be titrated to effect for immediate pain relief. Oral opioids are less often used alone, but are used in fixed-dose combination with drugs like paracetamol or ibuprofen (McQuay 1997).

This overview will consider only oral administration of analgesics. Parenteral administration by intravenous, intramuscular, or subcutaneous injections is useful for some drugs immediately following surgery, particularly for patients unable to swallow or where oral intake is not possible for other reasons (McQuay 1997). Most postoperative patients can swallow and oral administration is clearly the least technically demanding and cheapest method of drug delivery, especially when the benefits of injection over oral administration have not been demonstrated, as with NSAIDs (Tramer 1998).

Acute pain trials

Postoperative (after surgery) pain relief is part of a package of care that covers the preoperative (before surgery), perioperative (during surgery), and postoperative periods and involves using the best evidence at all times (Kehlet 1998). This overview involves only one aspect of one part of the patient journey, namely how well different oral drug interventions work to relieve pain. The choice of particular oral drug intervention depends on the clinical and operational circumstances and how any choice fits in with local care pathways. This overview only examined the efficacy of oral drugs: how to use them effectively in the relief of postoperative pain is a question not addressed here.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. To show that the analgesic is working, it is necessary to use placebo (McQuay 2005; McQuay 2006). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have acceptable pain relief. Approximately 18% of participants given placebo will have adequate pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. Therefore the use of additional or rescue analgesia is important for all participants in the trials.

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

Important characteristics of an analgesic include the proportion of patients who experience clinically useful levels of pain relief at a given dose, the duration of useful pain relief (which informs dosing intervals), and the drug's tolerability. Single dose studies can provide us with information on the number needed to treat (NNT) for at least 50% maximum pain relief over four to six hours compared with placebo and the proportions of participants achieving that outcome, the NNT to prevent (NNTp) use of rescue medication and the proportions needing rescue medication, the median (or mean) time to use of rescue medication, and the number needed to harm (NNH) for one or more adverse events, and the proportions experiencing adverse events. Additional information may also be available for the occurrence of serious adverse events and adverse event withdrawals, although the numbers of events captured in single dose trials are usually too few to allow statistical analysis.

How the intervention might work

Non-steroidal anti-inflammatory drugs

NSAIDs reversibly inhibit the enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX), now recognised to consist of two isoforms, COX-1 and COX-2, mediating production of prostaglandins and thromboxane A2 (Fitzgerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive (pain) processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Aspirin is a special case, in that it irreversibly blocks COX-1.

Paracetamol

Paracetamol lacks significant anti-inflammatory activity, implying a mode of action distinct from that of NSAIDs. Despite years of use and research, however, the mechanisms of action of paracetamol are not fully understood. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but has recently been considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis' wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002; PIC 2008) now has little credibility and a central mode action of paracetamol is thought to be likely (Graham 2005).

Opioids

Opioids bind to specific receptors in the central nervous system (CNS), causing reduced pain perception and reaction to pain, and increased pain tolerance. In addition to these desirable analgesic effects, binding to receptors in the CNS may cause adverse events such as drowsiness and respiratory depression, and binding to receptors elsewhere in the body (primarily the gastrointestinal tract) commonly causes nausea, vomiting, and constipation. In an effort to reduce the amount of opioid required for pain relief, and so reduce problematic adverse events, opioids are commonly combined with non-opioid analgesics, such as paracetamol.

Why it is important to do this overview

Knowing the relative efficacy of different analgesic drugs at various doses, under standard conditions, can be helpful. Choice of drug for an individual patient will depend on relative efficacy and a number of other factors including availability, cost, tolerability, and individual considerations, such as the patient's history and contraindications to a particular medication, and their ability to remedicate orally. A large number of systematic reviews of individual oral analgesics versus placebo in acute postoperative pain have been completed, using identical methods. An overview is required to facilitate indirect comparisons between individual analgesics, providing estimates of relative efficacy which can help to inform treatment choices.

OBJECTIVES

To provide an overview of the relative analgesic efficacy of oral analgesics that have been compared with placebo in acute postoperative pain in adults, and to report on adverse events associated with single doses of these analgesics. This will be done using a number of different outcomes and ways of expressing results, which have been set by informed discussions with various groups of healthcare professionals, and using reviews newly published or updated Cochrane Reviews that incorporate these methods to give the best presentation of results.

METHODS

Criteria for considering reviews for inclusion

All Cochrane Reviews of randomised controlled trials (RCTs) of single dose oral analgesics for acute postoperative pain in adults ($\geq$ 15 years).

Search methods for identification of reviews

We searched the *Cochrane Database of Systematic Reviews* for relevant reviews. See Appendix 1 for the search strategy. A series of Cochrane Reviews have been conducted by the same team, covering analgesics identified in the British National Formulary.

Data collection and analysis

Two review authors independently carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. Any disagreements were resolved by discussion, involving a third review author if necessary.

Selection of reviews

Included reviews assessed RCTs evaluating the effects of a single oral dose of analgesic given for relief of moderate to severe postoperative pain in adults, compared to placebo, and included:

- a clearly defined clinical question;
- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;
- patient-reported pain relief; and
- summary results for at least one desired outcome.

Data extraction and management

We extracted data from the included reviews using a standard data extraction form. We used original study reports only if specific data were missing.

We collected information on the following:

- number of included studies and participants;
- drug, dose, and formulation (if formulation is an issue);
- pain model (dental, other surgical).

We sought relative risk (RR) and numbers needed to treat to benefit (NNT), to prevent an event (NNTp), and to harm (NNH) or calculated these for the following outcomes:

- $\geq$ 50% maximum pain relief over four to six hours (patient-reported): this outcome encapsulates both degree of pain relief and duration of the effect, and is a dichotomous measure of success over a defined period following drug ingestion;
- use of rescue medication (or mean or median if appropriate, for example for time to remedication);
- patients suffering one or more adverse events; and
- withdrawal due to an adverse event.

We also sought information on the proportions of individuals with the outcomes listed above, and median or mean time to use of rescue medication. We collected information concerning serious adverse events if present.

Assessment of methodological quality of included reviews

Quality of included reviews

All included reviews were carried out according to a standard protocol which satisfied the criteria specified in the 'assessment of multiple systematic reviews' (AMSTAR) measurement tool (Shea 2007) for rigorous methodological quality.

Each review was required to:

1. provide an *a priori* design;
2. carry out duplicate study selection and data extraction;
3. carry out a comprehensive literature search;
4. include published and unpublished studies irrespective of language of publication;
5. provide a list of studies (included and excluded);
6. assess and document the scientific quality of the included studies;
7. use the scientific quality of the included studies appropriately in formulating conclusions;
8. use appropriate methods to combine the findings of studies; and
9. state conflicts of interests.

For each review we assessed the likelihood of publication bias by calculating the number of participants in studies with zero effect (relative benefit of one) that would be needed to give a NNT too high to be clinically relevant (Moore 2008). In this case we considered a NNT of $\geq$ 10 for the outcome 'at least 50% maximum pain relief over four to six hours' to be the cut-off for clinical relevance. We used this method because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Quality of evidence in included reviews

All included reviews used only primary studies that were both randomised and double-blind, so minimising the risk of bias from these items. All used patients with at least moderate pain intensity at baseline, providing a sensitive assay of analgesic efficacy. All used standard methods and reported standard outcomes, or provided data from which they could be calculated using validated methods. For studies in acute pain lasting up to six hours, it has been shown that use of last observation carried forward rather than baseline observation carried forward does not significantly influence results (Moore 2005).

We assessed the strength of evidence for each outcome according to the total number of participants contributing data and the methodological quality of, and degree of clinical heterogeneity (pain condition mix) in, the primary studies, as reported in the reviews. We also considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNT for at least 50% maximum pain relief to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number was less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable.

Data synthesis

We used information on the selected efficacy outcomesto draw up comparisons of analgesic efficacy, using indirect comparison of different drugs from almost identical clinical trial conditions, with placebo as a common comparator (Glenny 2005; Song 2003). The trials used in these reviews have a high level of clinical and methodological homogeneity, having, for more than 50 years, used consistent validated methods of measuring pain in patients with established pain of at least moderate severity, over at least four to six hours, and with placebo as a common comparator. Some of these data have been used to demonstrate the superiority of indirect over direct comparison in circumstances where there are large amounts of indirect data and small amounts of direct data

(Song 2003). The one potential source of clinical heterogeneity is the case mix, namely dental versus other surgery, and while this has previously been shown to have minimal effect on some descriptors, like NNT, it can result in differences in other descriptors, like percentage of participants obtaining an outcome (Barden 2004). This is addressed by examining results for dental and other surgery separately and together, where there are sufficient data. Any differences between different analgesics for harmful outcomes are highlighted, but single dose studies are not designed to reliably demonstrate such differences.

Comparative results are expressed as:

1. patients achieving at least 50% maximum pain relief, as a percentage and as NNT, compared with placebo;
2. duration of analgesia, as mean or median duration, and percentage remedicating by various times after dosing; and
3. adverse events - given the nature of the studies, especially their short duration, the outcome most often reported was percentage reporting at least one adverse event.

RESULTS

The overview included 35 separate Cochrane Reviews investigating 38 analgesics or analgesic combinations given as single oral doses in acute postoperative pain conditions (Aceclofenac 2009; Acemetacin 2009; Aspirin 1999; Celecoxib 2008; Codeine 2010; Dexibuprofen 2009; Dextropropoxyphene ± Paracetamol 1999; Diclofenac 2009; Diflunisal 2010; Dihydrocodeine 2000; Dipyrone 2010; Etodolac 2009; Etoricoxib 2009; Fenbufen 2009; Fenoprofen 2011; Flurbiprofen 2009; Gabapentin 2010; Ibuprofen 2009; Indometacin 2004; Ketoprofen and Dexketoprofen 2009; Lornoxicam 2009; Lumiracoxib 2010; Mefenamic acid 2011; Meloxicam 2009; Nabumetone 2009; Naproxen 2009; Nefopam 2009; Oxycodone ± Paracetamol 2009; Paracetamol + Codeine 2009; Paracetamol 2008; Piroxicam 2000; Rofecoxib 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009). In total there were 448 studies, combining the number of studies in the individual reviews. However, many studies had both placebo and active comparators; ibuprofen, for example, was used as an active comparator in many of them. The number of unique studies was probably closer to 350.

All of the reviews used the same methodological approach and the same primary outcome of NNT for at least 50% maximum pain relief over four to six hours compared with placebo. The sum of the number of participants in the reviews was 50,456, but there will have been double-counting of placebo participants both within reviews (comparison of different drug doses separately against placebo) and between reviews (drugs like ibuprofen are commonly used as an active comparator for new test analgesics and placebo arms will be counted in reviews of both analgesics). In these circumstances the number of unique participants is more likely to be of the order of 45,000.

Description of included reviews

Included reviews each had the same structure and organisation, and used identical methods based on criteria established by extensive analysis and validation, using individual patient data (see Table 1). They all used the same criteria and typically these were as follows.

Table 1. Characteristics of included reviews

Review	Date assessed as up to date	Population	Interventions	Comparison interventions	Outcomes for which data were reported	Review limitations
Aceclofenac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Acemetacin 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Aspirin 1999	2011 (update in progress)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Celecoxib 2008	2008	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Codeine 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dexibuprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Dextro-propoxyphene ± Paracetamol 1999	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Diclofenac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Diflunisal 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dihydrocodeine 2000	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Dipyrone 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Etodolac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Etoricoxib 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Fenbufen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Fenoprofen 2011	2011	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Flurbiprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Gabapentin 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Ibuprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Indometacin 2004	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	Limited numbers
Ketoprofen and Dexketoprofen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Lornoxicam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Lumiracoxib 2010	2010	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Mefenamic acid 2011	2011	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None

Table 1. Characteristics of included reviews (*Continued*)

Meloxicam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Nabumetone 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Naproxen 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Nefopam 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Oxycodone ± Paracetamol 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Paracetamol + Codeine 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Paracetamol 2008	2008	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Piroxicam 2000	2011 (additional searches)	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Rofecoxib 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	TOTPAR, SPID, remedication time, AE	None
Sulindac 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found
Tenoxicam 2009	2009	Adults with at least	Analgesic, various doses	Placebo	None	No studies found

Table 1. Characteristics of included reviews (*Continued*)

		moderate pain				
Tiaprofenic acid 2009	2009	Adults with at least moderate pain	Analgesic, various doses	Placebo	None	No studies found

AE = adverse event; SPID = summed pain intensity difference; TOTPAR = total pain relief

- Adult participants with established pain of at least moderate intensity (Collins 1997).
- Single dose oral administration of analgesic or placebo (with additional analgesia available, typically after 60 to 120 minutes).
- Randomised, double-blind studies.
- Pain assessed by patients using standard pain intensity and pain relief scales.
- Study duration of four hours or more.
- Searching included electronic searches, plus databases created by handsearching the older literature, now part of CENTRAL. Searching also included different retail names for drugs.
- No language restriction on included papers.
- Assessment of study quality according to established criteria and minimum criteria for inclusion.

Methodological quality of included reviews

All the reviews:

1. had *a priori* design;
2. performed duplicate study selection and data extraction;
3. had a comprehensive literature search;
4. used published and any unpublished studies included irrespective of language of publication, though not all reviews contacted companies or researchers for unpublished trial data;
5. provided a list of included and excluded studies;
6. provided characteristics of included studies;
7. assessed and documented the scientific quality of the included studies;
8. the scientific quality of the included studies was used appropriately in formulating conclusions, because only studies with minimal risk of bias were included (a particular issue was trial size, but conclusions were not drawn from inadequate data sets, based on previously established criteria (Moore 1998));
9. used appropriate methods to combine findings of studies and importantly provided analyses according to drug dose; and
10. conflict of interest statements were universal.

The reviews all used validated methods for conversion of mean to dichotomous data (Moore 1996; Moore 1997b; Moore 1997c), providing the number and proportion of participants with the clinically-relevant outcome of at least 50% maximum pain relief. Remedication is common within a few hours with placebo, therefore the method of imputing data after withdrawal is potentially of importance to the measurement of treatment effect. In the case of the primary outcome of the reviews, that of NNT for at least 50% maximum pain relief compared with placebo over four to six hours, the imputation method had been shown not to make any appreciable difference (Moore 2005), though use of last observation carried forward tended to overestimate treatment effect compared with baseline observation carried forward over longer periods (Moore 2005).

Effect of interventions

To assess the effects of interventions, we used a four-step process.

1. Note drugs for which no acute pain data could be found.
2. Note drug/dose combinations with inadequate amounts of information, where inadequate is defined as fewer than two studies and 200 participants - with limited flexibility around 200 participant limit).
3. Note drug/dose combinations with data but no evidence of effect, or with evidence of no effect.
4. Note drug/dose combinations with high susceptibility to publication bias, as defined in the Methods section.

Any remaining results would be of effective drug/dose combinations, backed by high-quality data not subject to bias, of sufficient size for random chance effects to be unimportant, and not susceptible to publication bias.

All extracted information on all reviews is available in Table 1.

1. Drugs for which Cochrane Reviews found no information

No clinical trial information was available for seven drugs (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009).

2. Drugs for which Cochrane Reviews found inadequate information (< 200 patients in comparisons, in at least two studies)

We found only limited information for six drugs, namely:

- Dexibuprofen 200 and 400 mg (176 participants with the two doses in one study) (Dexibuprofen 2009).
- Dextropropoxyphene 130 mg (50 participants in one study) (Dextropropoxyphene ± Paracetamol 1999).
- Diflunisal 125 mg (120 participants in two studies) (Diflunisal 2010).
- Etoricoxib 60 mg (124 participants in one study) (Etoricoxib 2009).
- Fenbufen 400 mg and 800 mg (46 participants with the two doses in one study) (Fenbufen 2009).
- Indometacin 50 mg (94 participants in one study) (Indometacin 2004).

3. Drugs for which Cochrane Reviews found no evidence of effect or evidence of no effect

There was evidence for lack of effect for three drug/dose combinations, with no difference between active drug and placebo:

- Aceclofenac 150 mg (217 participants in one study) (Aceclofenac 2009).
- Aspirin 500 mg (213 participants in two studies) (Aspirin 1999).
- Oxycodone 5 mg (317 participants in three studies) (Oxycodone ± Paracetamol 2009).

4. Drug/dose combinations for which Cochrane Reviews found evidence of effect, but where results were potentially subject to publication bias

Summary table A shows the drug/dose combinations in all types of surgery, and in dental and other postoperative pain situations separately, where our judgement was of high susceptibility to publication bias. These tended to have larger (less effective) NNTs, small numbers of participants, or both. The appropriateness or otherwise of this categorisation is discussed below, but these results are the least reliable of those available from the reviews. For gabapentin, the NNT was above 10, and based on a relatively small number of participants.

Summary table A: Results potentially subject to publication bias

				At least 50% maximum pain relief over 4 to 6 hours						
		Number of		Number with outcome/total		Percent with outcome				
Drug	Dose (mg)	Studies	Participants	Active	Placebo	Active	Placebo	Relative benefit (95% CI)	NNT (95% CI)	Susceptibility to publication bias
All types of surgery										
Codeine + paracetamol	30/300	6	690	123/379	56/311	32	18	1.9 (1.4 to 2.5)	6.9 (4.8 to 12)	310
Dextropropoxyph	65	6	440	85/214	60/226	40	27	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)	131
Diflunisal	250	3	195	49/98	16/97	47	16	2.9 (1.8 to 4.6)	3.3 (2.3 to 5.5)	396
Dihydrocodeine	30	3	194	31/97	19/97	32	20	1.6 (1.01 to 2.5)	8.1 (4.1 to 540)	46

(*Continued*)

Etodolac	50	4	360	44/154	34/206	29	17	1.7(1.1 to 2.6)	8.3 (4.8 to 30)	74
Gabapentir	250	3	327	26/177	8/150	15	5	2.5 (1.2 to 5.0)	11 (6.4 to 35)	NNT over 10
Ibuprofen	50	3	316	50/159	16/157	31	10	3.2 (1.9 to 5.1)	4.7 (3.3 to 8.0)	356
Mefenamic acid	500	2	256	60/126	29/130	48	22	2.1 (1.5 to 3.1)	4.0 (2.7 to 7.1)	384
Naproxen	200/220	2	202	54/120	13/82	45	16	2.9 (1.6 to 5.1)	3.4 (2.4 to 5.8)	392
Oxycodone	15	3	228	61/113	37/115	54	32	1.7 (1.2 to 2.3)	4.6 (2.9 to 11)	268
Oxycodone + paracetamol	5/325	3	388	60/221	14/167	27	8	3.6 (2.1 to 6.3)	5.4 (3.9 to 8.8)	331
Dental pain only										
Etodolac	50	4	360	44/154	34/206	29	17	1.7 (1.1 to 2.6)	8.3 (4.8 to 30)	74
Flurbiprofen	25	2	145	24/70	5/75	34	7	5.2 (2.1 to 13)	3.6 (2.5 to 6.6)	258
Lornoxicam	4	2	151	29/73	13/78	40	17	2.4 (1.3 to 4.1)	4.3 (2.7 to 11)	200
Other postoperative only										
Codeine	60	18	1265	232/626	157/639	37	25	1.5 (1.3 to 1.8)	8.0 (5.7 to 13)	316
Dexketoprofen	10/12.5	2	201	43/99	21/102	43	21	2.1 (1.4 to 3.3)	4.4 (2.8 to 9.7)	256
Dexketoprofen	10/12.5	2	201	47/99	21/102	47	21	2.3 (1.6 to 3.5)	3.7 (2.5 to 7.0)	342
Dextropropoxyph	65	5	410	77/199	54/211	39	26	1.5 (1.1 to 2.0)	7.7 (4.5 to 24)	122

(*Continued*)

Ketoprofen	50	5	434	90/216	50/218	42	23	1.8 (1.4 to 2.4)	5.3 (3.7 to 9.9)	385
Naproxen	500/550	4	372	83/195	45/187	43	24	1.8 (1.3 to 2.4)	5.4 (3.6 to 11)	317
Rofecoxib	50	3	628	127/346	62/282	37	22	1.7 (1.3 to 2.2)	6.8 (4.6 to 13)	296

5. Drug/dose combinations for which Cochrane Reviews found evidence of effect, where results were reliable and not subject to potential publication bias

Reliable results are presented by pain condition for the primary outcome of NNT compared with placebo for at least 50% maximum pain relief over four to six hours: firstly all types of surgery together, then dental pain only, and finally by other painful conditions. The results contain all available data. Some of the data are from doses of drugs not typically used clinically, such as 180/240 mg etoricoxib or ibuprofen 100 mg, or from drugs not commonly available in many parts of the world, like rofecoxib. All data are presented so that readers can use that which is relevant for them.

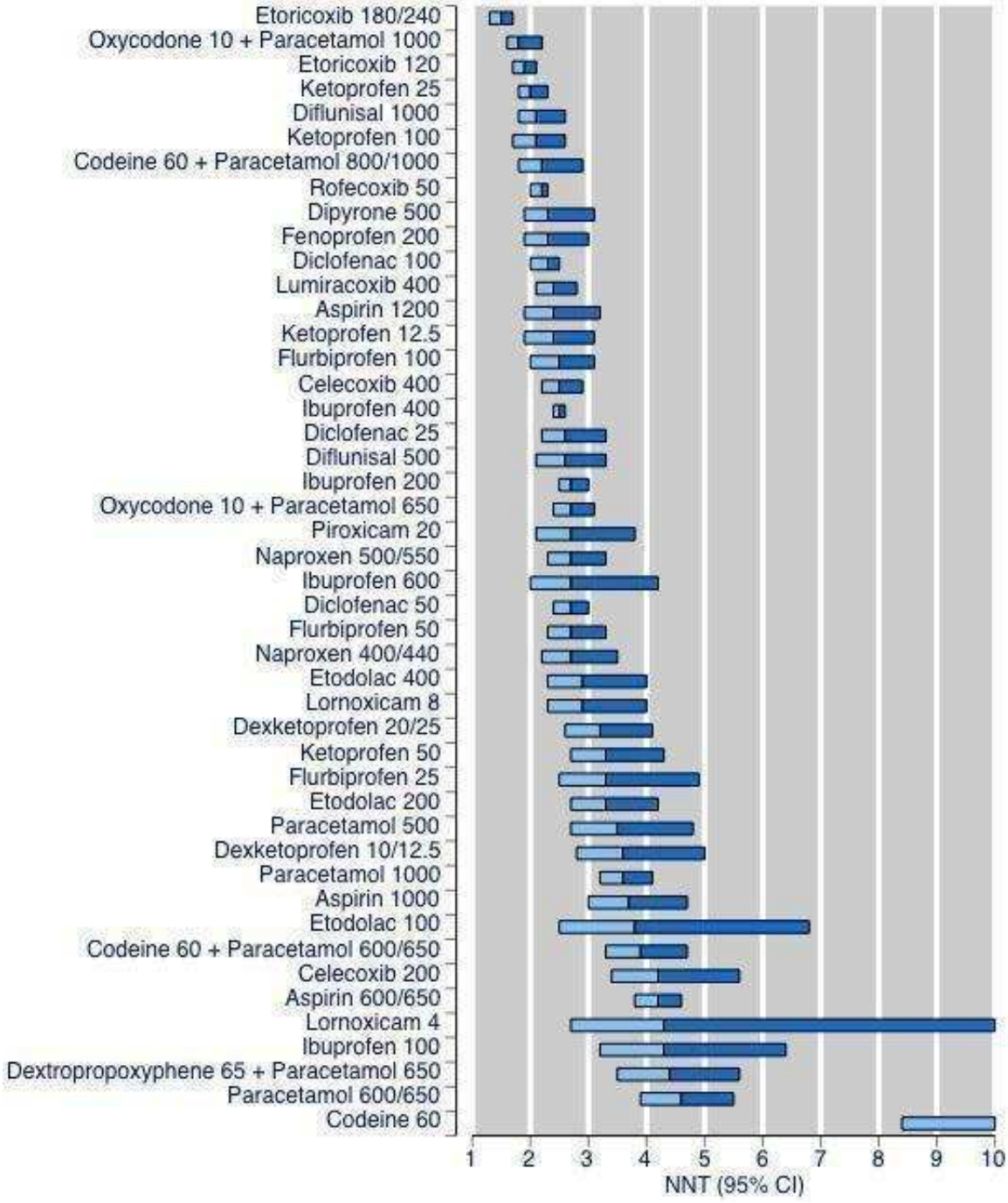
All types of surgery

For all types of surgery, the results judged to be reliable are shown in Summary table B. Overall, about 45,000 participants contributed data. For lornoxicam 4 mg only 151 participants from two studies provided data, but more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was that this result was on the borderline of being reliable. For codeine 60 mg, although the NNT was above 10, it was based on over 2400 participants and we deemed that a reliable result.

The number of participants was high (above 2000) with ibuprofen 400 mg and 200 mg, aspirin 600/650 mg, paracetamol 975/1000 mg, and rofecoxib 50 mg. Results with high numbers of participants and low (good) NNTs were particularly robust, with almost 20,000 participants needed in zero effect studies to overturn the result for ibuprofen 400 mg and over 13,000 to overturn that for rofecoxib 50 mg.

NNTs varied from as low as 1.5 for high doses of etoricoxib, to as high as 12 for codeine 60 mg. The majority of drug/dose combinations had NNTs below 3. A listing by rank order is shown in Figure 1. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol.

Figure 1. All types of surgery: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Summary table B: Results judged to be reliable in all types of surgery

				At least 50% maximum pain relief over 4 to 6 hours						
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	65	4965	983/2496	379/2469	39	15	2.5 (2.3 to 2.8)	4.2 (3.8 to 4.6)	6856
Aspirin	1000	8	770	178/416	55/354	43	16	2.7 (2.1 to 3.5)	3.7 (3.0 to 4.7)	1311
Aspirin	1200	3	249	85/140	25/109	62	19	3.3 (1.8 to 6.3)	2.4 (1.9 to 3.2)	789
Celecoxib	200	4	705	149/423	32/282	35	11	3.5 (2.4 to 5.1)	4.2 (3.4 to 5.6)	974
Celecoxib	400	4	620	184/415	9/205	34	4	11 (5.9 to 22)	2.5 (2.2 to 2.9)	1860
Codeine	60	33	2411	311/1199	209/1212	26	17	1.5 (1.3 to 1.7)	12 (8.4 to 18)	NNT above 10
Codeine + paracetamol	60 + 600/650	17	1413	370/857	96/556	43	17	2.6 (2.2 to 3.2)	3.9 (3.3 to 4.7)	2210
Codeine + paracetamol	60 + 800/1000	3	192	64/121	5/71	53	7	6.3 (2.9 to 14)	2.2 (1.8 to 2.9)	681
Dexketoprofen	10/12.5	5	452	104/230	38/222	45	17	2.7 (2.0 to 3.7)	3.6 (2.8 to 5.0)	804
Dexketoprofen	20/25	6	523	129/225	38/248	47	15	3.3 (2.4 to 4.5)	3.2 (2.6 to 4.1)	1111
Dextropropoxyphe + paracetamol	65 + 650	6	963	184/478	74/485	38	15	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)	1226

(*Continued*)

Diclofenac	25	4	502	131/248	37/254	53	15	3.6 (2.6 to 5.0)	2.6 (2.2 to 3.3)	1429
Diclofenac	50	11	1325	441/780	102/545	57	19	3.0 (2.5 to 3.6)	2.7 (2.4 to 3.0)	3582
Diclofenac	100	7	787	231/416	44/371	56	12	4.8 (3.6 to 6.4)	2.3 (2.0 to 2.5)	2635
Diflunisal	500	6	391	104/198	27/193	53	14	3.8 (2.6 to 5.4)	2.6 (2.1 to 3.3)	1113
Diflunisal	1000	5	357	112/182	26/175	62	15	4.1 (2.9 to 6.0)	2.1 (1.8 to 2.6)	1343
Dipyrone	500	5	288	106/143	45/145	74	31	2.4 (1.8 to 3.1)	2.3 (1.9 to 3.1)	964
Etodolac	100	5	498	103/251	50/247	41	20	2.0 (1.5 to 2.7)	4.8 (3.5 to 7.8)	540
Etodolac	200	7	670	145/333	44/337	44	13	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	3	222	52/134	4/88	39	5	9.0 (3.4 to 24)	2.9 (2.3 to 4.0)	544
Etoricoxib	120	5	655	259/406	26/249	64	11	6.1 (4.1 to 9.0)	1.9 (1.7 to 2.1)	2792
Etoricoxib	180/240	2	199	129/150	6/49	79	12	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Fenoprofen	200	4	287	83/146	19/141	57	13	4.2 (2.7 to 6.4)	2.3 (1.9 to 3.0)	961
Flurbiprofen	25	3	208	36/102	5/106	35	5	7.0 (2.9 to 16)	3.3 (2.5 to 4.9)	422
Flurbiprofen	50	10	692	245/353	108/339	69	32	2.2 (1.9 to 2.6)	2.7 (2.3 to 3.3)	1871
Flurbiprofen	100	7	416	139/215	48/201	65	24	2.8 (2.2 to 3.6)	2.5 (2.0 to 3.1)	1248
Ibuprofen	100	4	396	60/192	16/204	31	8	3.7 (2.3 to 5.9)	4.3 3.2 to 6.4)	525

(*Continued*)

Ibuprofen	200	20	2690	718/1572	101/1118	46	9	4.6 (3.9 to 5.6)	2.7 (2.5 to 3.0)	7273
Ibuprofen	400	61	6475	2013/3728	375/2747	54	14	3.9 (3.6 to 4.4)	2.5 (2.4 to 2.6)	19425
Ibuprofen	600	3	203	88/114	36/89	77	40	2.0 (1.5 to 2.6)	2.7 (2.0 to 4.2)	549
Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	8	535	175/281	31/254	62	12	4.9 (3.5 to 6.9)	2.0 (1.8 to 2.3)	2140
Ketoprofen	50	8	624	151/314	56/310	48	18	2.7 (2.0 to 3.5)	3.3 (2.7 to 4.3)	1267
Ketoprofen	100	5	321	106/161	28/160	66	18	3.6 (2.5 to 5.1)	2.1 (1.7 to 2.6)	1208
Lornoxicam	4	2	151	29/73	13/78	40	17	2.4 (1.3 to 4.1)	4.3 (2.7 to 11)	478
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Lumiracoxib	400	4	578	183/366	17/212	50	8	6.9 (4.1 to 11)	2.4 (2.1 to 2.8)	1830
Naproxen	400/440	3	334	103/210	14/124	49	11	4.8 (2.8 to 8.4)	2.7 (2.2 to 3.5)	903
Naproxen	500/550	9	784	200/394	59/390	52	15	3.4 (2.6 to 4.4)	2.7 (2.3 to 3.3)	2120
Oxycodone + paracetamol	10/650	10	1043	346/680	49/363	51	14	3.9 (2.9 to 5.2)	2.7 (2.4 to 3.1)	2820
Oxycodone + paracetamol	10/1000	2	289	100/147	19/142	68	13	4.9 (3.2 to 7.6)	1.8 (1.6 to 2.2)	1317
Paracetamol	500	6	561	176/290	86/271	61	32	1.9 (1.6 to 2.3)	3.5 (2.7 to 4.8)	1042

(*Continued*)

Paracetamol	600/650	19	1886	358/954	145/932	38	16	2.4 (2.0 to 2.8)	4.6 (3.9 to 5.5)	2214
Paracetamol	975/1000	28	3232	876/1906	241/1329	46	18	2.7 (2.4 to 3.0)	3.6 (3.2 to 4.1)	5746
Piroxicam	20	3	280	89/141	36/139	63	26	2.5 (1.8 to 3.3)	2.7 (2.1 to 3.8)	757
Rofecoxib	50	25	3688	1458/2519	134/1169	58	11	5.1 (4.3 to 6.1)	2.2 (2.0 to 2.3)	13076

Dental conditions

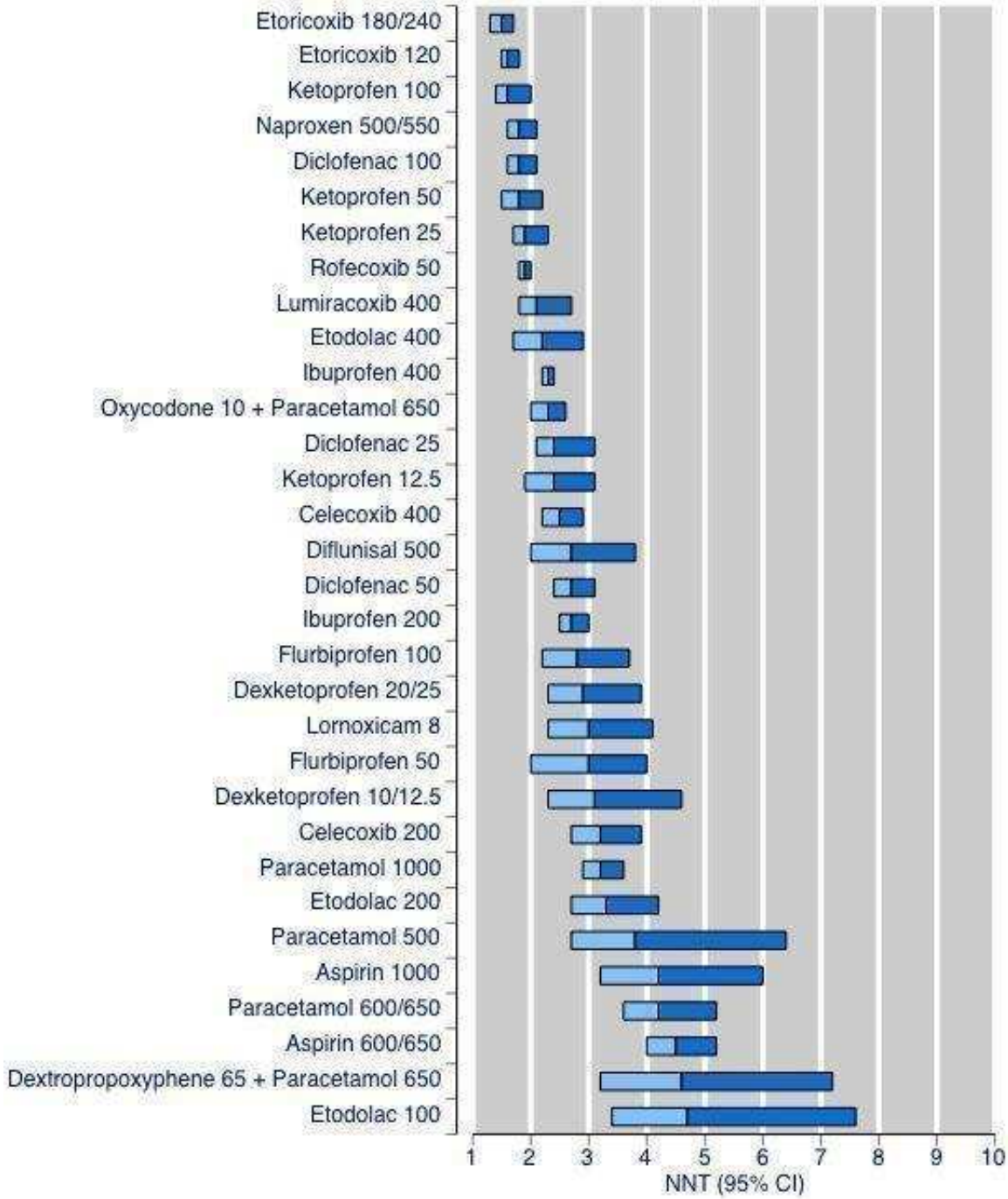
In practice this means almost exclusively the third molar extraction model, with minor differences in the number of teeth removed, and the extent of any bone involvement during surgery. Results judged to be reliable are shown in Summary table C; overall, about 29,000 participants contributed data.

For etodolac 400 mg, and ketoprofen 50 and 100 mg, fewer than 200 participants provided data, but many more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was that this result was on the borderline of being reliable. For codeine 60 mg, although the NNT was above 10, it was based on over 1146 participants and we deemed that a reliable result.

The number of participants was high (above 2000) with ibuprofen 400 mg and 200 mg, aspirin 600/650 mg, paracetamol 975/1000 mg, and rofecoxib 50 mg. Results with high numbers of participants and low (good) NNTs were particularly robust, with about 18,000 participants needed in zero effect studies to overturn the result for ibuprofen 400 mg, and over 13,000 to overturn that for rofecoxib 50 mg.

NNTs varied from as low as 1.5 for high doses of etoricoxib to as high as 21 for codeine 60 mg. The majority of drug/dose combinations had NNTs below 3. A listing by rank order is shown in Figure 2. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol.

Figure 2. Dental pain: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Both Summary of results C and Figure 2 give all results for a particular dose of a particular drug, irrespective of drug formulation. There can be important differences between formulations, and examples of this are shown in Summary table C for sodium and potassium salts of diclofenac, and soluble and standard formulations of ibuprofen. These results show that, based on reasonable and reliable evidence, formulation has a major impact on efficacy in acute pain for diclofenac (Diclofenac 2009) and ibuprofen (Ibuprofen 2009).

Summary table C: Results judged to be reliable in painful dental conditions

		At least 50% maximum pain relief over 4 to 6 hours								
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	45	3581	634/1763	251/1818	36	14	2.6 (2.3 to 2.9)	4.5 (4.0 to 5.2)	4377
Aspirin	1000	4	436	87/250	20/186	35	11	2.8 (1.9 to 4.3)	4.2 (3.2 to 6.0)	602
Celecoxib	200	3	423	94/282	2/141	41	1	16 (5.1 to 49)	3.2 (2.7 to 3.9)	899
Celecoxib	400	4	620	184/415	9/205	34	4	11 (5.9 to 22)	2.5 (2.2 to 2.9)	1860
Codeine	60	15	1146	79/573	52/573	14	9	1.5 (1.1 to 2.1)	21 (12 to 96)	NNT above 10
Dexketoprofen	10/12.5	3	251	61/131	17/120	47	14	3.3 (2.0 to 5.3)	3.1 (2.3 to 4.6)	559
Dexketoprofen	20/25	4	322	82/176	17/146	47	12	4.5 (2.8 to 7.2)	2.9 (2.3 to 3.9)	788
Dextropropoxyph + paracetamol	65 + 650	3	353	61/173	23/180	35	13	2.8 (1.8 to 4.2)	4.6 (3.2 to 7.2)	414

(*Continued*)

Diclofenac	25	3	398	99/196	22/202	51	11	4.7 (3.1 to 7.1)	2.5 (2.1 to 3.2)	1194
Diclofenac	50	9	1119	378/678	82/441	56	19	3.0 (2.4 to 3.7)	2.7 (2.4 to 3.1)	3025
Diclofenac	100	4	413	151/228	19/185	66	10	6.6 (4.3 to 10)	1.8 (1.6 to 2.1)	1881
Diflunisal	500	3	220	62/112	19/108	55	18	3.1 (2.0 to 4.8)	2.7 (2.0 to 3.8)	595
Etodolac	100	4	418	80/211	34/207	38	16	2.3 (1.6 to 3.3)	4.7 (3.4 to 7.6)	471
Etodolac	200	7	670	145/333	44/337	44	13	3.3 (2.5 to 4.5)	3.3 (2.7 to 4.2)	1360
Etodolac	400	2	149	43/85	3/64	51	5	11 (3.5 to 18)	2.2 (1.7 to 2.9)	528
Etoricoxib	120	4	500	233/326	16/174	71	9	8.0 (5.0 to 13.0)	1.6 (1.5 to 1.8)	2625
Etoricoxib	180/240	2	199	129/150	6/49	79	12	6.4 (3.1 to 14)	1.5 (1.3 to 1.7)	1128
Flurbiprofen	50	7	473	161/245	74/228	66	32	2.1 (1.7 to 2.5)	3.0 (2.0 to 4.0)	1104
Flurbiprofen	100	6	354	119/184	48/170	65	29	2.4 (1.9 to 3.1)	2.8 (2.2 to 3.7)	910
Ibuprofen	200	18	2470	680/1462	100/1008	47	10	4.5 (3.7 to 5.4)	2.7 (2.5 to 3.0)	6678
Ibuprofen	400	49	5428	1746/3148	271/2280	55	12	4.3 (3.8 to 4.9)	2.3 (2.2 to 2.4)	18172
Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2 (2.7 to 6.6)	2.4 (1.9 to 3.1)	868
Ketoprofen	25	6	452	153/239	26/213	64	12	5.2 (3.6 to 7.5)	1.9 (1.7 to 2.3)	1927
Ketoprofen	50	3	190	61/98	6/92	62	6	9.0 (4.2 to 19)	1.8 (1.5 to 2.2)	866

(*Continued*)

Ketoprofen	100	3	195	79/97	10/98	72	10	7.3 (4.0 to 13)	1.6 (1.4 to 2.0)	1024
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7 (2.7 to 8.1)	2.9 (2.3 to 4.0)	668
Lumiracoxib	400	3	460	163/307	7/153	53	2	9.7 (4.3 to 2.2)	2.1 (1.8 to 2.7)	1730
Naproxen	500/550	5	402	122/199	14/203	61	7	8.7 (5.2 to 14)	1.8 (1.6 to 2.1)	1831
Oxycodone + paracetamol	10/650	6	673	252/496	11/177	51	6	6.8 (3.9 to 12)	2.3 (2.0 to 2.6)	2253
Paracetamol	500	3	305	84/150	46/155	56	30	1.9 (1.4 to 2.5)	3.8 (2.7 to 6.4)	498
Paracetamol	600/650	10	1276	225/638	74/638	35	12	3.1 (2.4 to 3.8)	4.2 (3.6 to 5.2)	1762
Paracetamol	975/1000	19	2157	545/1335	82/822	41	10	4.1 (3.3 to 5.2)	3.2 (2.9 to 3.6)	4584
Rofecoxib	50	22	3060	1332/2173	73/887	61	8	7.3 (5.9 to 9.2)	1.9 (1.8 to 2.0)	13045
Formulation comparisons										
Diclofenac sodium	50	3	313	58/193	18/120	30	15	2.0 (1.3 to 3.3)	6.7 (4.2 to 17)	154
Diclofenac potassium	50	5	622	237/367	40/255	65	16	3.8 (2.8 to 5.0)	2.1 (1.9 to 2.4)	2340
Diclofenac sodium	100	2	211	30/114	4/97	26	4	5.3 (1.9 to 15)	4.5 (3.2 to 7.6)	258
Diclofenac potassium	100	6	591	200/302	39/289	66	13	5.0 (3.7 to 6.8)	1.9 (1.7 to 2.2)	2520

(*Continued*)

Ibuprofen	200 soluble	7	828	270/478	34/350	56	10	5.7 (4.2 to 7.9)	2.1 (1.9 to 2.4)	3115
Ibuprofen	200 standard	15	1883	406/984	62/899	41	7	5.9 (4.7 to 7.6)	2.9 (2.6 to 3.2)	4610
Ibuprofen	400 soluble	9	959	361/550	41/409	66	10	6.5 (4.8 to 8.9)	1.8 (1.7 to 2.0)	4369
Ibuprofen	400 standard	46	4772	1385/2598	230/2174	53	11	5.2 (4.6 to 5.9)	2.3 (2.2 to 2.5)	15,976

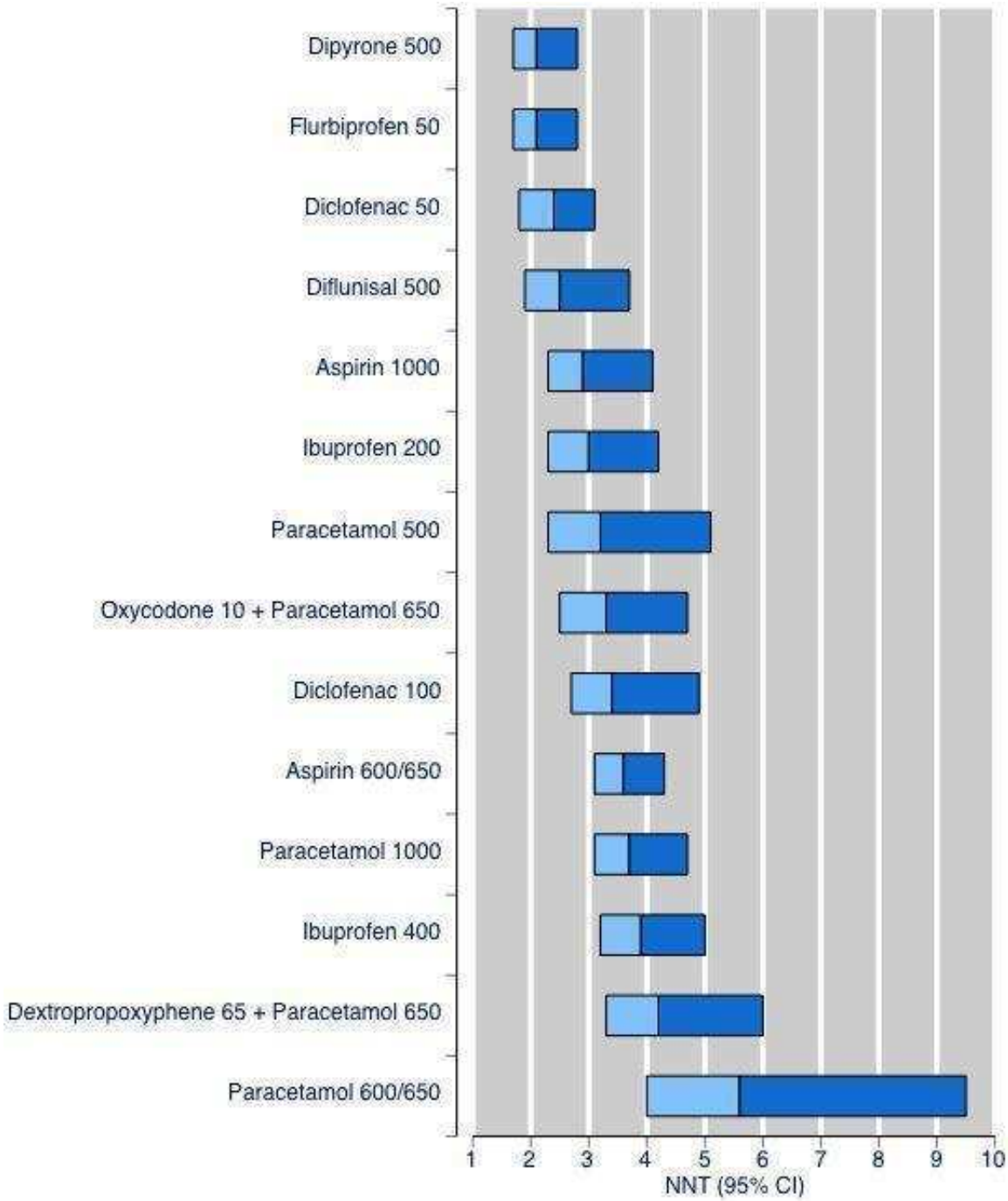
Other painful conditions

This grouping included all acute postoperative pain that is not dental; it includes conditions like episiotomy, orthopaedic, and abdominal surgery, where the pain is of at least moderate in intensity and oral analgesics are indicated. There were insufficient data to allow further subgrouping according to type of surgery. Results judged to be reliable are shown in Summary table D; overall, about 7000 participants contributed data.

For diflunisal 500 mg fewer than 200 participants provided data, but more than 400 participants would have been needed in zero effect studies to overturn the result; our judgement was this result was on the borderline of being reliable.

The number of participants was above 1000 with aspirin 600/650 mg, ibuprofen 400 mg, and paracetamol 975/1000 mg. NNTs varied from as low as 2.1 for dipyrone 500 mg and flurbiprofen 50 mg to as high as 5.6 with paracetamol 1000. A listing by rank order is shown in Figure 3. Higher doses of the same drug tended to have lower (better) NNTs, though this was not particularly evident with paracetamol or ibuprofen.

Figure 3. Other painful conditions: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.



Summary table D: Results judged to be reliable in other painful conditions

				At least 50% maximum pain relief over 4 to 6 hours						
		Number of		Number with outcome/total		Percent with outcome				
Drug	**Dose (mg)**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Aspirin	600/650	19	1384	349/733	128/651	48	20	2.4 (2.0 to 2.8)	3.6 (3.1 to 4.3)	2460
Aspirin	1000	4	334	91/166	35/168	55	21	2.6 (1.9 to 3.6)	2.9 (2.3 to 4.1)	818
Dextropropoxyphe + paracetamol	65 + 650	3	610	123/305	51/305	40	15	2.4 (1.8 to 3.2)	4.2 (3.3 to 6.0)	842
Diclofenac	50	2	206	63/102	20/104	62	19	3.2 (2.1 to 4.9)	2.4 (1.8 to 3.3)	652
Diclofenac	100	3	374	79/188	24/186	42	13	3.3 (2.2 to 4.9)	3.4 (2.7 to 4.9)	726
Diflunisal	500	3	171	42/86	8/85	49	9	5.3 (2.7 to 10)	2.5 (1.9 to 3.7)	513
Dipyrone	500	4	210	78/104	29/106	75	27	2.7 (2.0 to 3.8)	2.1 (1.7 to 2.8)	790
Flurbiprofen	50	3	219	84/108	34/111	78	31	2.5 (1.9 to 3.3)	2.1 (1.7 to 2.8)	824
Ibuprofen	200	2	220	42/110	5/110	38	5	7.7 (3.2 to 18)	3.0 (2.3 to 4.2)	513
Ibuprofen	400	12	1047	277/580	103/467	48	22	2.2 (1.8 to 2.6)	3.9 (3.2 to 5.0)	1638
Oxycodone + paracetamol	10/650	4	370	93/184	37/186	51	20	2.5 (1.9 to 3.4)	3.3 (2.5 to 4.7)	751

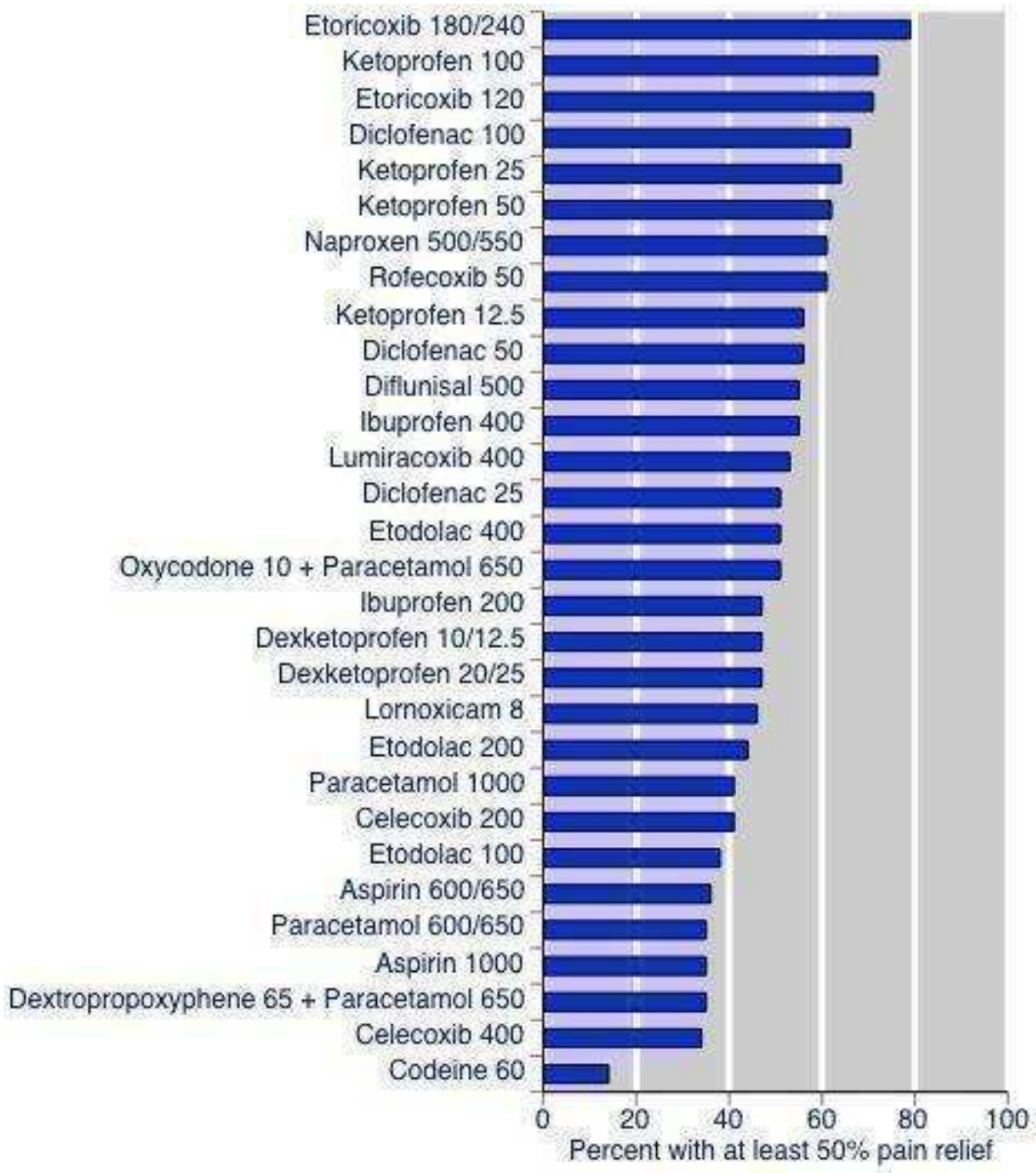
(*Continued*)

Paracetamol	500	3	256	92/140	40/116	66	34	1.9 (1.5 to 2.5)	3.2 (2.3 to 5.1)	544
Paracetamol	600/650	9	610	136/316	74/294	43	25	1.8 (1.4 to 2.3)	5.6 (4.0 to 9.5)	479
Paracetamol	975/1000	10	1075	333/568	161/507	59	32	1.7 (1.5 to 2.0)	3.7 (3.1 to 4.7)	1830

6. Percentage of patients achieving target of at least 50% maximum pain relief

These results are described in Summary tables B, C, and D for each drug/dose combination. There was very wide variation between drugs even in the same painful condition, and where there were consistent responses with placebo. Figure 4 shows that in dental pain, while some drugs achieved a high level of pain relief in over 60 to 70% of participants, in others it was as low as about 30%. The response with placebo in dental pain averages about 10% to 15%, but tends to be higher in other surgical conditions.

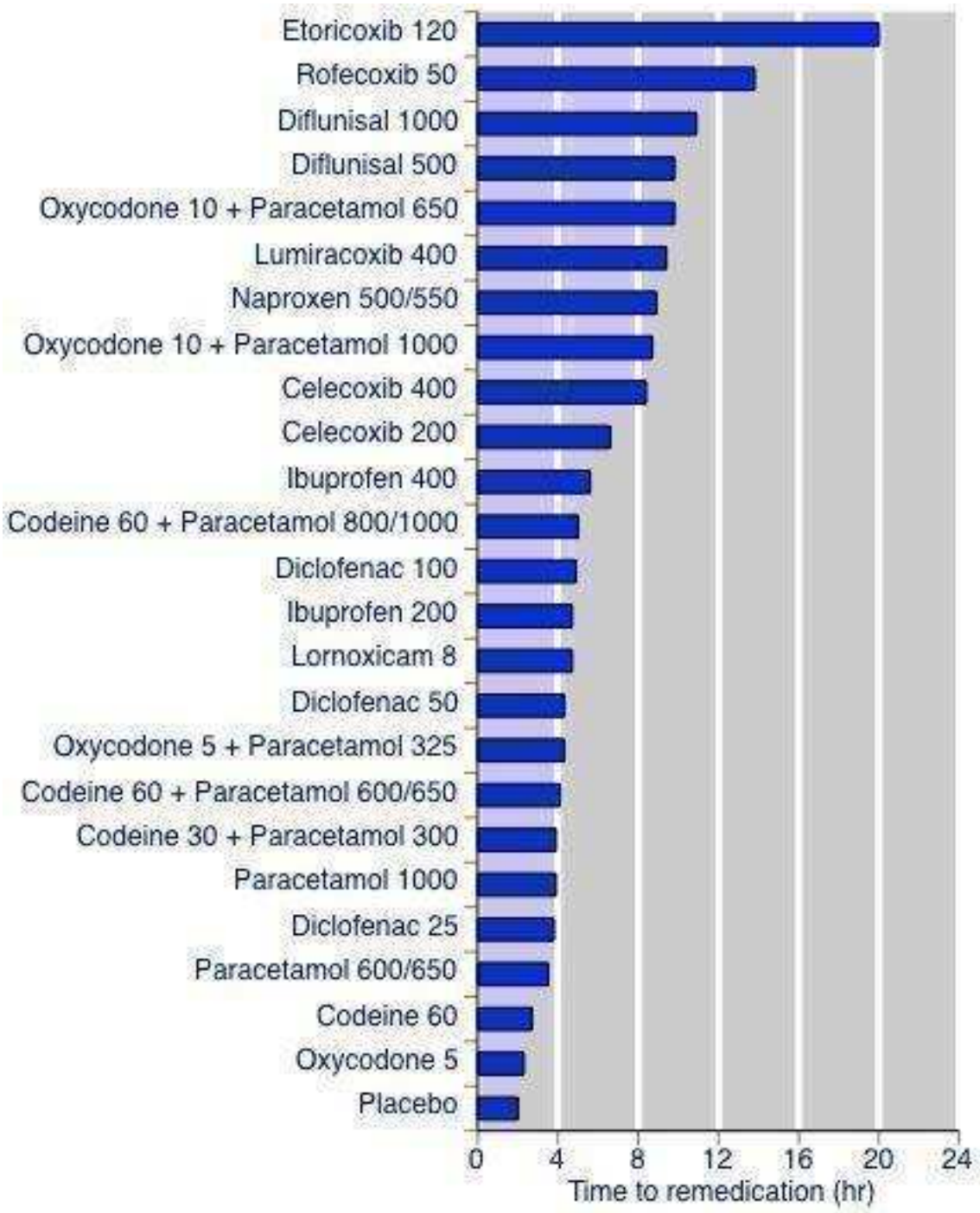
Figure 4. Percentage of patients achieving at least 50% maximum pain relief (dental pain).



7. Time to remedication

A number of reviews reported the mean of the mean or median time to remedication, a useful secondary outcome indicating the duration of effective analgesia before the pain intensifies to the point where additional analgesia is required. For placebo, averaging over all reviews, the mean time to remedication is two hours; trials typically have a one to two-hour period before which additional analgesia is not allowed, to allow time for any analgesic to work. For active drugs in dental pain, the mean duration varied between below three hours for codeine 60 mg and oxycodone 5 mg, up to 20 hours for etoricoxib 120 mg (Figure 5; Appendix 3).

Figure 5. Mean time to remedication in painful dental conditions.



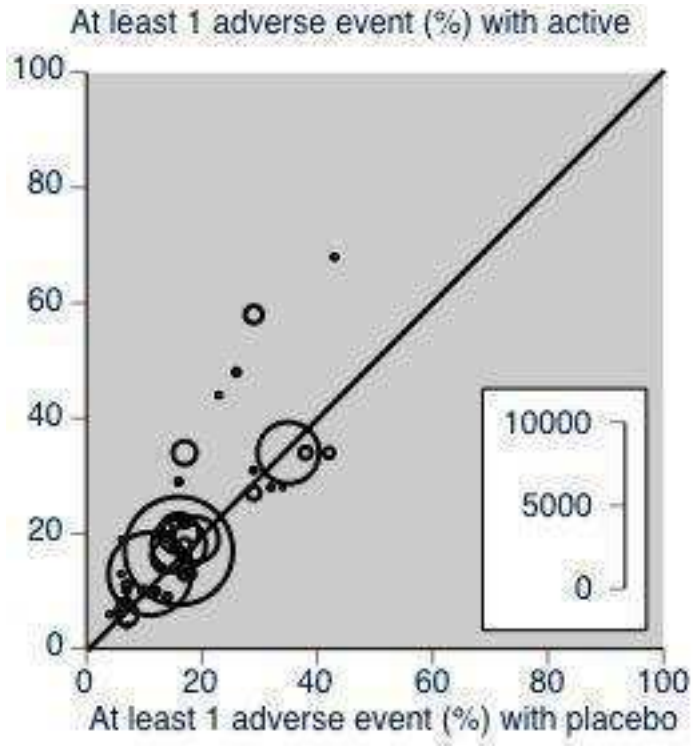
8. Percentage remedicated with time

We collected information on the percentage of patients who had remedicated with active treatment and placebo at various times after the start of therapy and this is reported in Appendix 3. This was sparsely reported in a small subsection of studies. In brief, typically 70% to 90% of participants given placebo had used rescue medication by six hours, and this tended to increase further at longer durations, though it never reached 100%. With analgesics, the numbers remedicating at six hours were always lower than with placebo.

9. Experience of adverse events

Adverse event reporting in acute pain studies is known to be heavily influenced by the methods used (Edwards 2002). Most reviews reported no serious adverse events and the only common report was that of participants experiencing at least one adverse event during the period of the study. These results are shown in Summary table E. The usual finding was no difference in adverse event rates between active and placebo groups (Figure 6). Statistical differences were found only for aspirin 600/650 mg (NNH 44), codeine + paracetamol 60/650 mg (NNH 6.0), diflunisal 1000 mg (NNH 7.7), dihydrocodeine 30 mg (NNH 7.4), and oxycodone ± paracetamol combinations (NNH 3.5 to 4.5).

Figure 6. Plot of percentage of participants reporting at least one adverse event with active drug and placebo. Each symbol represents results from one drug/dose combination, and the size of the size of the symbol is proportional to the number of participants (inset scale).



Summary table E: Participants experiencing at least one adverse event (AE)

		At least one AE							
		Number of		Number on		Percent with outcome			
Drug	**Dose (mg)**	**Studies**	**Patients**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative risk (95% CI)**	**NNH (95% CI)**
Aspirin	600/650	64	4965	19/76	20/88	13	11	1.2 (1.0 to 1.4)	44 (23 to 345)
Celecoxib	200	4	705	64/406	44/263	16	17	0.90 (0.63 to 1.28)	
Celecoxib	400	4	620	107/315	87/206	34	42	1.05 (0.85 to 1.3)	
Codeine	60	33	2411	81/399	63/399	20	16	1.3 (0.9 to 1.7)	
Codeine + paracetamol	60 + 600/650	17	1413	266/779	83/479	34	17	1.6 (1.3 to 1.9)	6.0 (4.6 to 8.3)
Dexketoprofen	10/12.5	5	452	12/132	18/126	9	14	0.6 (0.3 to 1.3)	
Dexketoprofen	20/25	6	523	43/220	26/193	20	13	1.3 (0.8 to 2.1)	
Diclofenac	25	4	502	20/248	18/254	8	7	1.2 (0.6 to 2.1)	
Diclofenac	50	11	1325	41/643	34/473	6	7	1.0 (0.7 to 1.5)	
Diclofenac	100	7	787	18/419	64/373	18	17	1.0 (0.8 to 1.4)	
Diflunisal	250	3	195	4/98	7/97	4	7	0.6 (0.2 to 1.8)	
Diflunisal	500	6	391	38/235	33/227	18	15	1.3 (0.8 to 1.9)	
Diflunisal	1000	5	357	61/208	34/209	29	16	1.8 (1.2 to 2.6)	7.7 (4.8 to 20)

(*Continued*)

Dihydrocodeine	30	3	194	13/67	4/69	19	6	3.4 (1.2 to 9.8)	7.4 (4.1 to 38)
Etodolac	50	4	360	10/132	12/188	8	6	1.4 (0.6 to 3.2)	
Etodolac	100	5	498	26/230	16/229	11	7	1.6 (0.9 to 2.8)	
Etodolac	200	7	670	67/314	54/319	22	17	1.2 (0.9 to 1.7)	
Etodolac	400	3	222	43/154	37/109	28	34	0.8 (0.6 to 1.2)	
Etoricoxib	120/180/240	5	725	190/551	67/174	34	38	0.9 (0.7 to 1.1)	
Fenoprofen	200	4	287	9/146	9/141	6	6	0.94 (0.4 to 2.1)	
Flurbiprofen	25	3	208	15/109	17/112	14	16	0.95 (0.5 to 1.7)	
Flurbiprofen	50	10	692	37/284	50/290	13	17	0.75 (0.5 to 1.1)	
Flurbiprofen	100	7	416	20/200	24/203	10	12	0.86 (0.5 to 1.5)	
Gabapentin	250	3	327	49/177	49/152	28	32	0.9 (0.7 to 1.3)	
Ibuprofen	50	3	316	11/114	8/111	10	7	1.3 (0.6 to 3.0)	
Ibuprofen	100	4	396	22/152	20/158	14	13	1.2 (0.7 to 2.1)	
Ibuprofen	200	20	2690	208/1102	137/706	19	19	0.9 (0.7 to 1.02)	
Ibuprofen	400	61	6475	476/2870	326/1997	17	16	0.9 (0.8 to 1.04)	
Ketoprofen	12.5	3	274	8/138	6/136	6	4	1.3 (0.5 to 3.6)	

(*Continued*)

Ketoprofen	25	8	535	27/259	22/231	10	10	1.2 (0.7 to 2.0)	
Ketoprofen	50	8	624	29/141	18/137	21	14	1.6 (0.9 to 2.6)	
Ketoprofen	100	5	321	19/86	16/89	22	18	1.2 (0.7 to 2.2)	
Lornoxicam	8	3	273	84/190	16/70	44	23	1.4 (0.9 to 2.2)	
Lumiracoxib	400	4	578	40/307	28/153	13	18	0.7 (0.4 to 1.3)	
Mefenamic acid	500	2	256	7/53	3/53	13	6	2.2 (0.7 to 7.2)	
Naproxen	400/440	3	334	38/173	14/84	22	17	1.3 (0.8 to 2.2)	
Naproxen	500/550	9	784	80/291	83/290	27	29	0.96 (0.7 to 1.2)	
Oxycodone	5	3	317	48/157	46/160	31	29	1.1 (0.8 to 1.6)	
Oxycodone + paracetamol	5/325	3	388	107/221	44/167	48	26	1.6 (1.2 to 2.1)	4.5 (3.2 to 7.9)
Oxycodone + paracetamol	10/650	10	1043	199/343	61/209	58	29	1.8 (1.4 to 2.3)	3.5 (2.7 to 4.8)
Oxycodone + paracetamol	10/1000	2	289	100/147	61/141	68	43	1.6 (1.3 to 2.0)	4.0 (2.8 to 7.3)
Paracetamol	500	6	561	10/158	12/161	7	6	0.9 (0.4 to 1.9)	
Paracetamol	600/650	19	1886	121/775	102/747	16	14	1.2 (0.9 to 1.5)	

(*Continued*)

Paracetamol	975/1000	28	3232	259/1423	145/919	18	16	1.1 (0.9 to 1.3)	
Rofecoxib	50	25	3688	750/2236	409/1168	34	35	0.96 (0.87 to 1.1)	

DISCUSSION

Summary of main results

We have reliable efficacy estimates of 46 drug/dose combinations in all types of surgery: 45 in painful dental conditions (overwhelmingly following third molar extraction) and 14 in other postoperative conditions. These estimates of efficacy have all been obtained using essentially the same clinical trial methods since they were first set out (Beecher 1957), and both trial and review methods have been standardised based on good evidence. The original philosophy concerning acute pain trials has been tested subsequently in a number of analyses using individual patient data (Moore 1997a; Moore 2005; Moore 2011) and those and other analyses also underpin the trials and reviews. This makes the results of studies comparable and that has previously included finding no significant difference between different pain models (Barden 2004).

We also know that there are a number of drugs for which there are no available trial data on how effective they are in acute pain (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009), as well as drug/dose combinations with inadequate evidence of benefit, or definite evidence of no benefit.

Placebo responses in the different meta-analyses - the percentage achieving at least 50% maximum pain relief with placebo over four to six hours - were consistent, with most falling between 5% and 15%, especially with larger numbers of participants given placebo for dental conditions (Figure 7) and all postoperative conditions (Figure 8). For other postoperative conditions the numbers of participants given placebo tended to be small and the range of responses somewhat higher (Figure 9). The degree of variability is what is expected by the random play of chance (Moore 1998).

Figure 7. Plot of percent with outcome with placebo versus number of participants given placebo - dental only.

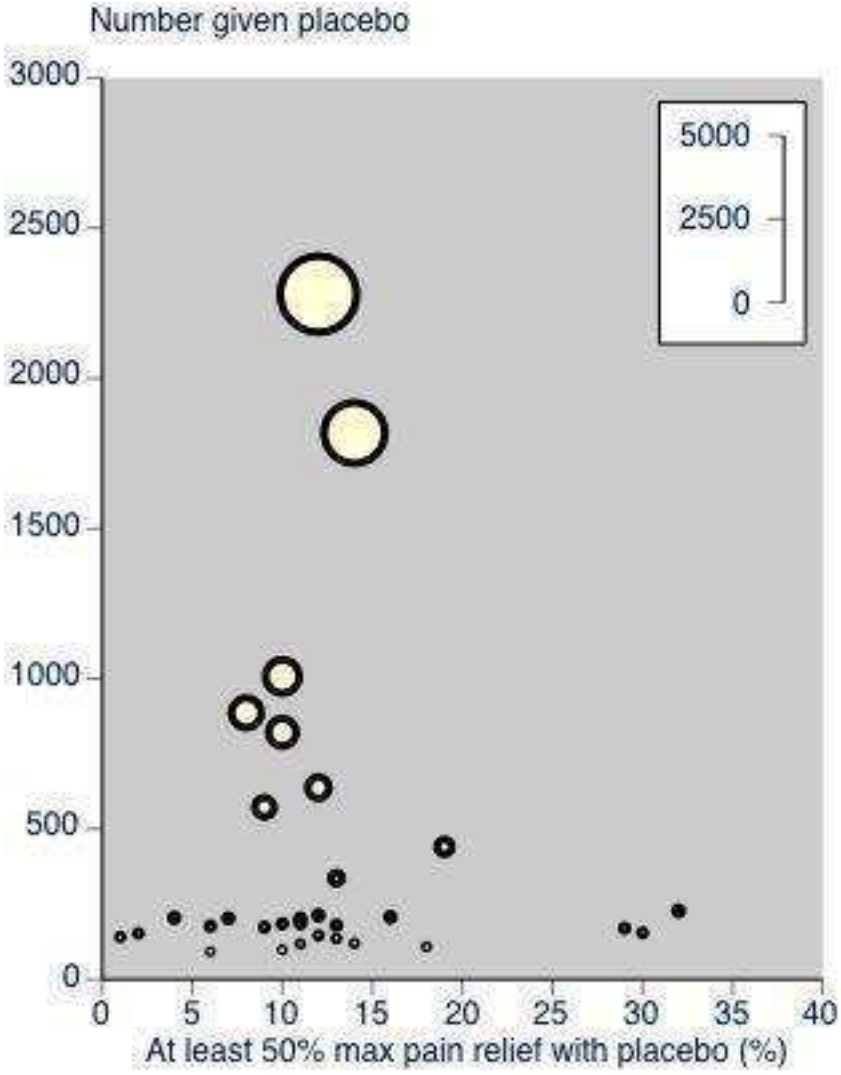


Figure 8. Plot of percent with outcome with placebo versus number of participants given placebo - other conditions only.

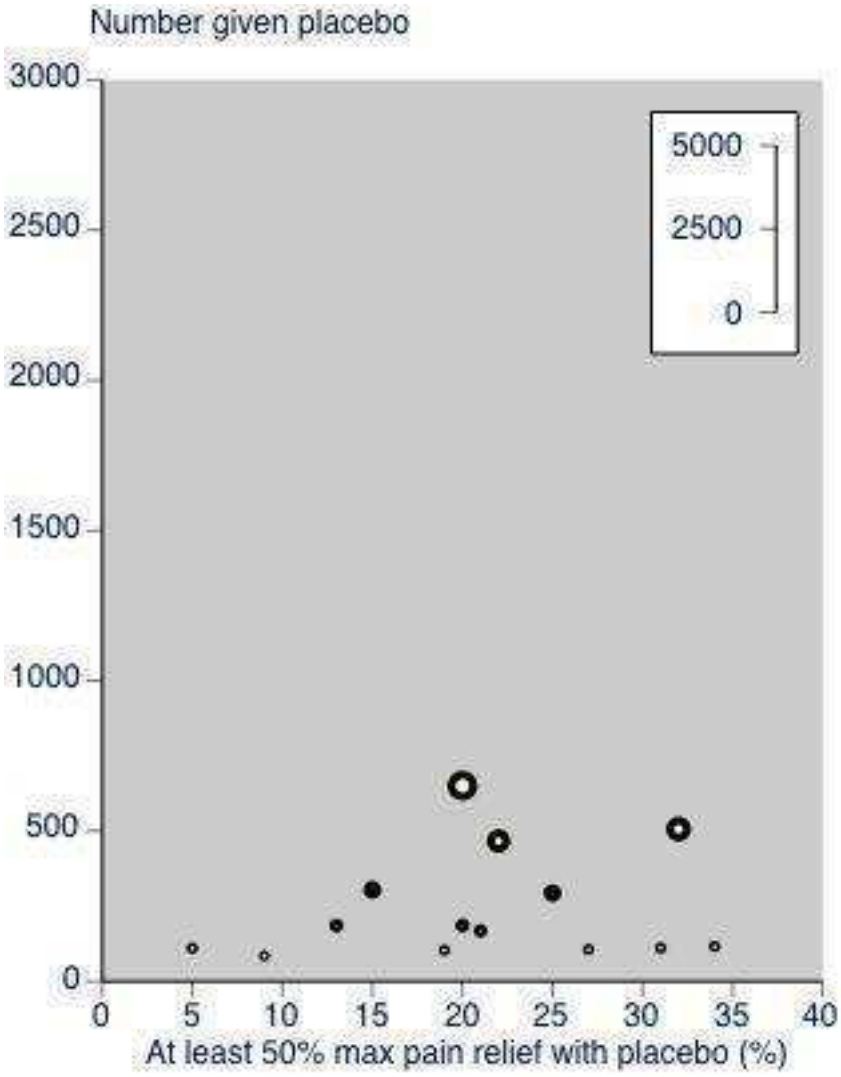
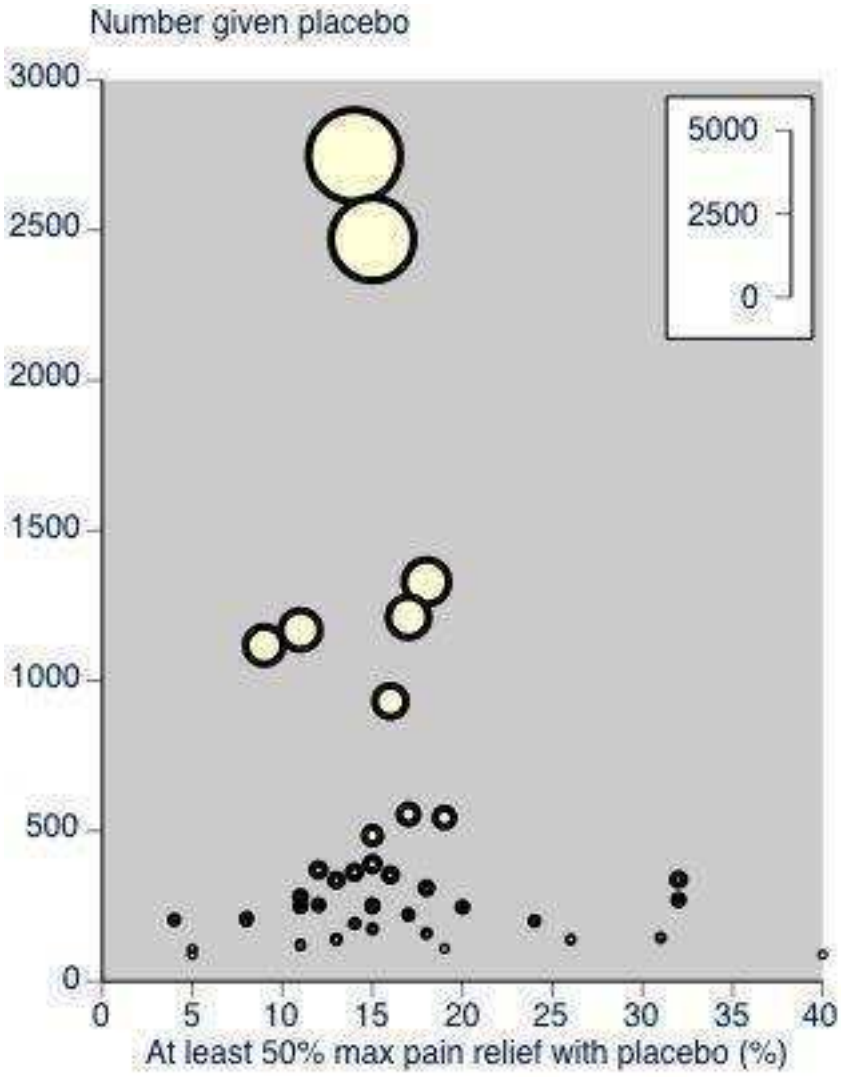


Figure 9. Plot of percent with outcome with placebo versus number of participants given placebo - all types of surgery.

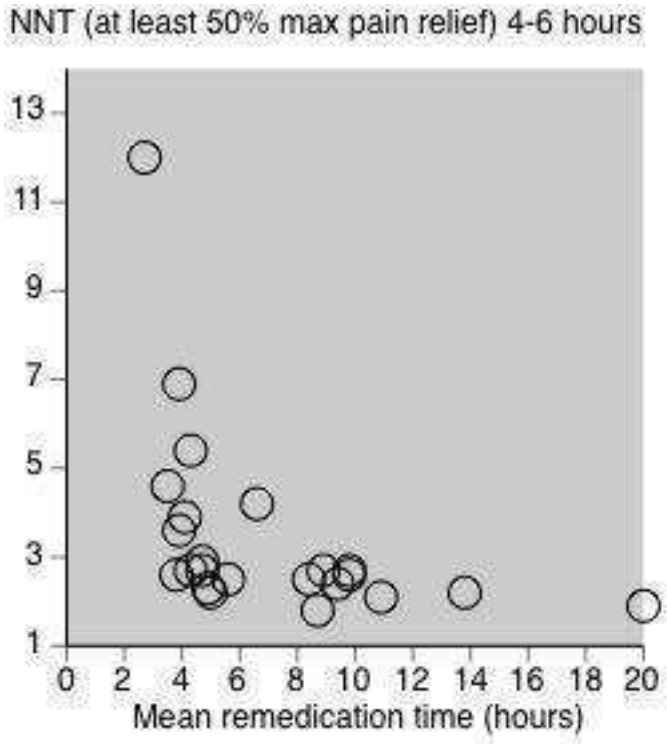


The efficacy results with adequate evidence show a range of values, whether measured relative to placebo in terms of a number needed to treat (NNT) for at least 50% maximum pain relief over four to six hours, in terms of the percentage of participants obtaining this level of benefit, or in terms of time before additional analgesia is required. Some drugs could be shown to not have any beneficial effects at some doses. Adverse events in these short-duration studies were generally not different between active drug and placebo, with a few exceptions, principally opioids.

The results also show clearly that even the most effective drugs fail to deliver good analgesia to a proportion of patients, meaning that a degree of analgesic failure is to be expected. Figure 4 shows that with many interventions, it is to be expected in more than half of patients treated.

There was also an interesting relationship between efficacy over four to six hours and duration of analgesia measured by mean time to remedication (Figure 10). Drugs with short duration of action tended to have higher (worse) NNTs, while drugs with longer duration of action had universally lower (better) NNTs, typically of two or below in those where mean remedication time was eight hours or longer. While not unexpected, this relationship implies that drugs with longer effects are likely to be more useful and effective in clinical practice.

Figure 10. Plot of NNT over four to six hours versus mean time to remedication.



Overall completeness and applicability of evidence

The 35 Cochrane Reviews cover almost all oral analgesics, although throughout the world many different combination analgesics can be found, typically without any published clinical trials. The review found that for seven drugs there were no clinical trial data and for a further six drugs there was inadequate information for any reliable basis of efficacy. In both these cases there are probably unpublished clinical trials. The authors' (unpublished) experience is that obtaining clinical trial data for older drugs is difficult and often impossible - though not always, as the eventual publication of 14 unpublished clinical trials of tramadol in a meta-analysis demonstrated (Moore 1997a). None of the drugs or doses for which this was a concern are used commonly in treating acute pain.

Some reviews appear not to be recent; all had been updated since 2008, but without finding any new studies and so they have kept their original citation dates (Aspirin 1999; Dextropropoxyphene ± Paracetamol 1999; Dihydrocodeine 2000; Piroxicam 2000). Additional searches for these drugs revealed no new studies since the reviews were completed. For other drugs, like etoricoxib, one or two additional studies have very recently been published, but do not materially change the conclusions.

There are no Cochrane Reviews for some commonly used drugs. These include tramadol, though there is an extant protocol for this, tramadol + paracetamol, and the combination of ibuprofen + paracetamol, a recently released combination, and one where these commonly-available drugs are frequently taken together. Non-Cochrane reviews are available for these (Edwards 2002; Moore 1997a; Moore 2011), which used the same methods and standards as the Cochrane Reviews, but results of these have not been included in the comparative figures. For completeness, results for these non-Cochrane reviews are shown in Summary table F.

The results for tramadol 50 mg in dental pain and for tramadol 100 mg in other painful conditions are clearly not reliable, as they are subject to potential publication bias. Results for higher doses of tramadol, tramadol and paracetamol, and ibuprofen and paracetamol are reliable. It is worth noting that reviews of tramadol indicated high rates of adverse events, though they were not reported in ways comparable to Cochrane Reviews (Edwards 2002; Moore 1997a).

Summary table F: Data from non-Cochrane reviews

					At least 50% maximum pain relief over 4 to 6 hours						
			Number of		Number on		Percent with outcome				
Drug	**Dose (mg)**	**Pain condition**	**Studies**	**Participants**	**Active**	**Placebo**	**Active**	**Placebo**	**Relative benefit (95% CI)**	**NNT (95% CI)**	**Susceptibility to publication bias**
Tramadol	50	Dental	6	471	41/246	13/225	17	6	2.9 (1.6 to 5.2)	9.1 (6.1 to 19)	47
Tramadol	100	Dental	7	578	89/300	22/278	30	8	3.8 (2.4 to 5.8)	4.6 (3.6 to 6.4)	679
Tramadol	100	Other	4	304	51/168	13/136	30	10	3.2 (1.8 to 5.6)	4.8 (3.4 to 8.2)	329
Tramadol	150	Other	5	371	106/184	31/187	60	17	3.5 (2.4 to 4.9)	2.4 (2.0 to 3.1)	1175
Tramadol + paracetamol	75/650	Dental	5	659	128/340	11/339	40	3	12 (6.4 to 21)	2.9 (2.5 to 3.5)	1613
Ibuprofen + paracetamol	200/500	Dental	2	280	130/176	10/104	74	10	7.7 (4.2 to 14)	1.6 (1.4 to 1.8)	1470

Adverse events

Acute pain studies using a single dose of analgesic and with limited duration represent a poor test of adverse events, which can also often be complicated by proximity to anaesthesia. They are particularly limited in speaking to serious adverse events that might occur following long-term use of any of the drugs in this review. Moreover, the populations of postoperative patients participating in these studies will have tended to be younger and without many of the comorbid conditions that can occur. The aim of the studies was solely to test whether the drugs were analgesics.

Quality of the evidence

The quality of the evidence was good, using standard reviews examining standard clinical trials designed to measure the analgesic efficacy of drugs in sensitive assays in acute painful conditions. The overview process further removed any results likely to be the object of potential publication bias, so that only reliable results remained. This leaves a very large body of efficacy results presented both by all types of surgery, and split by the main painful conditions of dental pain and other (non-dental) painful conditions.

These results report a clinically useful level of pain relief over a sensible period, and with the common comparator of placebo. Though indirect comparisons are often criticised, this is one circumstance where indirect comparison can be justified because of the clinical homogeneity of trials and outcomes, and because data

like these have been tested and indirect comparison found to be a reasonable approach (Song 2003).

Potential biases in the overview process

No obvious biases in the overview process exist, for the reasons given above. One possible concern would be if placebo responses varied extensively, as that would indicate a lack of clinical homogeneity, and some potential biases with high placebo responses in some studies or reviews limiting the measurement of efficacy of NNT, which measures absolute risk difference (Moore 2011). Figure 7, Figure 8 and Figure 9 show the placebo responses according to review and number of participants given placebo for dental studies, other postoperative studies, and all combined.

Small data sets are clearly more variable than larger, as would be expected (Moore 1998). However, with few exceptions placebo response rates were within limited ranges, typically between 5% and 20% for dental pain and 15% to 30% for other painful conditions.

Most studies in the individual reviews will have been sponsored or conducted by manufacturers. This is not likely to be a source of any bias, since specific analyses have been conducted on some of the larger data sets to demonstrate that no industry bias exists in like-for-like comparisons (Barden 2006).

Agreements and disagreements with other studies or reviews

The only other overview of this type known to exist for acute pain studies is a non-Cochrane overview in dental pain (Barden 2004). The general methods used were similar and there were no major differences.

Other important issues

This overview has brought together information on a very large number of participants and studies that have had one single aim, namely to test whether a particular drug at a particular dose had analgesic properties. The basic design of the individual studies was developed in the 1950s and 1960s, and rigorously tested at the time when randomised and double-blind studies were needed for objective assessment of analgesic efficacy (Houde 1960). Even the earliest studies emphasised large individual variability, and the variability in treatment groups of small size (Keats 1950).

These methods of analgesic testing have, with little change, become the standard way of demonstrating that a drug is an analgesic, and are typically performed early in the development of any new pain-relieving drug. A number of relatively recent individual patient analyses have examined various aspects of their design, conduct, and reporting (Barden 2004; Barden 2006; Moore 2005; Moore 1997a; Moore 2011). All of these investigations confirmed the success of the model, though adverse event reporting was inadequate (Edwards 1999). Other individual patient analyses of the postoperative period have demonstrated that patient satisfaction is highly correlated with good pain relief, showing the value of the outcome of at least 50% maximum pain relief (Mhuircheartaigh 2009).

While the reviews in this overview provide an excellent assessment of analgesic efficacy, both in the fact of the effects and often in its magnitude, there remains a distinction between measurement in trials and effectiveness in the clinic, and for different types of acute pain. Relative efficacy is, however, maintained between different painful conditions. For example, in dental pain ibuprofen 400 mg (NNT 2.3) is better than paracetamol 1000 mg (3.2) and aspirin 1000 mg (4.2). In migraine the same pattern is seen (Derry 2010; Kirthi 2010; Rabbie 2010), while NSAIDs are better than paracetamol for osteoarthritis (Towheed 2006). Information about analgesic efficacy from individual systematic reviews and overviews can be incorporated into schema for effective management of acute pain (Frampton 2009), or into other acute painful conditions.

It is the case that many of the individual studies used both a placebo and an active comparator. However, the actual drug and dose of active comparator varied so widely that useful direct comparisons between any two drugs was not available. Despite the fact that indirect comparisons have been shown to be reliable where sufficient high-quality data existed (Song 2003), one further step might be taken. That step would involve the use of network meta-analysis to confirm the assessment of relative efficacy in the overview, and to explore further methodological issues in this highly standardised and homogeneous data set (Caldwell 2005; Salanti 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The major implication for practice is the knowledge that there is a body of reliable evidence about the efficacy of 46 drug/dose combinations in acute pain. These results include information of immediate practical relevance including the percentage of patients likely to benefit in the short term, and comparative information about the likely duration of effect - a matter of pragmatic importance. However, not every patient will achieve good pain relief even with the most effective drugs, and analgesic failure is to be expected with a single dose, or perhaps with particular drugs in particular patients. Failure to achieve good pain relief should be actively and regularly sought and rectified.

Acute pain treatment is often part of a complex of interactions between patient, condition, and desired outcome; the overview helps by presenting evidence from which rational choices and decisions can be made. The evidence linking short-term benefit with longer duration of action is particularly important in this regard.

The overview also, and importantly, demonstrates where there are major absences of evidence. Where there is no evidence of efficacy, the drugs in question should probably not be used to treat acute pain.

Implications for research

Possibly the main implication for research is methodological. There will be few circumstances where such a body of information exists in such a clinically homogenous data set and it might appear to be an ideal opportunity to test new methods in meta-analysis, like network meta-analysis.

ACKNOWLEDGEMENTS

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REFERENCES

References to included reviews

Moore RA, Derry S, McQuay HJ. Single dose oral aceclofenac for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007588.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral acemetacin for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007589.pub2]

Rees J, Oldman A, Smith LA, Collins S, Carroll D, Wiffen PJ, et al.Single dose oral aspirin for acute pain. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD002067]

Derry S, Barden J, McQuay HJ, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004233.pub2]

Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008099.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007550.pub2]

Moore RA, Collins S, Rees J, Derry S, McQuay HJ. Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: 10.1002/14651858.CD001440]

Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004768.pub2]

Wasey JO, Derry S, Moore RA, McQuay HJ. Single dose oral diflunisal for acute postoperative pain in adults.. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD007440.pub2]

Moore RA, Rees J, Derry S, McQuay HJ. Single dose oral dihydrocodeine for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002760]

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrone for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2010, Issue 9. Art. No.: CD003227. [DOI: 10.1002/14651858.CD003227.pub2]

Tirunagari SK, Derry S, Moore RA, McQuay HJ. Single dose oral etodolac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007357.pub2]

Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD004309. [DOI: 10.1002/14651858.CD004309.pub2]

Moore RA, Derry S, McQuay HJ. Single dose oral fenbufen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007547.pub2]

Traa MX, Derry S, Moore RA. Single dose oral fenoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD007556.pub2]

Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007358.pub2]

Straube S, Derry S, Moore RA, Wiffen PJ, McQuay HJ. Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD008183.pub2]

Derry C, 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]

Moore RA, Derry S, Mason L, McQuay HJ, Rees J. Single dose oral indometacin for the treatment of acute postoperative pain. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004308.pub2]

Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007355.pub2]

Hall PE, Derry S, Moore RA, McQuay HJ. Single dose

oral lornoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007441.pub2]
Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD006865.pub2]
Moll R, Derry S, Moore RA, McQuay HJ. Single dose oral mefenamic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD007553.pub2]
Moore RA, Derry S, McQuay HJ. Single dose oral meloxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007552.pub2]
Moore RA, Derry S, Moore M, McQuay HJ. Single dose oral nabumetone for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007548.pub2]
Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004234.pub3]
Kakkar M, Derry S, Moore RA, McQuay HJ. Single dose oral nefopam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007442.pub2]
Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002763.pub2]
Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD001547.pub2]
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]
Moore RA, Rees J, Loke Y, Derry S, McQuay HJ. Single dose oral piroxicam for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002762]
Bulley S, Derry S, Moore RA, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD004604.pub3]
Moore RA, Derry S, McQuay HJ. Single dose oral sulindac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007540.pub2]
Moore OA, McIntyre M, Moore RA, Derry S, McQuay HJ. Single dose oral tenoxicam for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD007591.pub2]
Moore RA, Derry S, MooreM, McQuay HJ. Single dose oral tiaprofenic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007542.pub2]

Additional references

Barden 2004
Barden J, Edwards JE, McQuay HJ, Andrew Moore R. Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain* 2004;**107**(1-2):86–90. [DOI: 10.1016/j.pain.2003.09.021]

Barden 2006
Barden J, Derry S, McQuay HJ, Moore RA. Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain* 2006;**121**(3):207–18. [DOI: doi:10.1016/j.pain.2005.12.011]

Beecher 1957
Beecher HK. The measurement of pain; prototype for the quantitative study of subjective responses. *Pharmacology Reviews* 1957;**9**:59–209.

Botting 2000
Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3?. *Clinical Infectious Diseases* 2000; **31**(5):S203–10. [DOI: 10.1086/317520]

Caldwell 2005
Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;**331**:897–900. [DOI: 10.1136/bmj.331.7521.897]

Chandrasekharan 2002
Chandrasekharan NV. 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 of the United States of America* 2002;**99**:13926–31. [DOI: 10.1073/pnas.162468699]

Collins 1997
Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres?. *Pain* 1997;**72**:95–7.

Derry 2010
Derry S, Moore RA, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD008040.pub2]

Edwards 1999
Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *Journal of Pain and Symptom Management* 1999;**18**(6):427–37. [DOI: 10.1093/bja/aep300]

Edwards 2002
Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis

of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *Journal of Pain Symptom Management* 2002;**23**:121–30. [DOI: 10.1002/14651858.CD002067]

Fitzgerald 2001
FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine* 2001;**345**(6):433–42. [PUBMED: 11496855]

Flower 1972
Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature* 1972;**240**:410–1.

Frampton 2009
Frampton C, Quinlan J. Evidence for the use of non-steroidal anti-inflammatory drugs for acute pain in the post anaesthesia care unit. *Journal of Perioperative Practice* 2009; **19**(12):418–23.

Glenny 2005
Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al.International Stroke Trial Collaborative Group. Indirect comparisons of competing interventions. *Health Technology Assessment* 2005;**9**(26):1-134, iii-iv.

Graham 2005
Graham GG, Scott KF. Mechanism of action of paracetamol. *American Journal of Therapeutics* 2005;**12**(1):46–55. [ISSN: 1075–2765]

Hawkey 1999
Hawkey CJ. Cox-2 inhibitors. *Lancet* 1999;**353**(9149): 307–14.

Hinz 2008
Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB Journal* 2008;**22**(2):383–90. [DOI: 10.1096/fj.07-8506com]

Houde 1960
Houde RW, Wallenstein Sl, Rogers A. Clinical pharmacology of analgesics. 1. A method of assaying analgesic effect. *Clinical Pharmacology and Therapeutics* 1960;**1**:163–74.

Keats 1950
Keats AS, Beecher HK, Mosteller FC. Measurement of pathological pain in distinction to experimental pain. *Journal of Applied Physiology* 1950;**3**(1):35–44.

Kehlet 1998
Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Annals of Surgery* 2008; **248**(2):189–98. [DOI: 10.1097/SLA.0b013e31817f2c1a]

Kirthi 2010
Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008040.pub2]

McQuay 1997
McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997;**314**(7093):1531–5.

McQuay 2005
McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005;**81**:155–60. [DOI: 10.1136/pgmj.2004.024737]

McQuay 2006
McQuay HJ, Moore A. Methods of therapeutic trials. In: McMahon SB, Koltzenburg M editor(s). *Textbook of Pain*. Fifth. Churchill Livingstone, 2006:415–26.

Mhuircheartaigh 2009
Mhuircheartaigh RJ, Moore RA, McQuay HJ. Analysis of individual patient data from clinical trials: epidural morphine for postoperative pain. *British Journal of Anaesthesia* 2009;**103**(6):871–81. [DOI: 10.1093/bja/aep300]

Moore 1996
Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996;**66**:229–37. [DOI: 10.1016/0304-3959(96)03032-1]

Moore 1997a
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. [DOI: 10.1016/S0304-3959(96)03291-5]

Moore 1997b
Moore A, 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. [DOI: 10.1016/S0304-3959(96)03251-4]

Moore 1997c
Moore A, 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**:311–15. [DOI: 10.1016/S0304-3959(96)03306-4]

Moore 1998
Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**:209–16. [DOI: 10.1016/S0304-3959(98)00140-7]

Moore 2003
Moore RA, Edwards J, Barden J, McQuay HJ. *Bandolier's Little Book of Pain*. Oxford: Oxford University Press, 2003. [DOI: 0-19-263247-7]

Moore 2005
Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 2005;**116**(3):322–31. [DOI: 10.1016/j.pain.2005.05.001]

Moore 2006
Moore A, McQuay H. *Bandolier's Little Book of Making Sense of the Medical Evidence*. Oxford: Oxford University Press, 2006. [ISBN: 0–19–856604–2]

Moore 2008
Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic reviews in pain research: methodology refined*. Seattle: IASP Press, 2008:15–23. [ISBN: 978–0–931092–69–5]

Moore 2011
Moore RA, Straube S, Paine J, Derry S, McQuay HJ. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;**152**(5):982–9.

PIC 2008
Paracetamol Information Centre. www.pharmweb.net (accessed 16 February 2010).

Rabbie 2010
Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD008039.pub2]

Salanti 2008
Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Statistical Methods in Medical Research* 2008;**17**(3):279–301. [DOI: 10.1177/0962280207080643]

Schwab 2003
Schwab JM, Schluesener HJ, Laufer S. COX-3: just another COX or the solitary elusive target of paracetamol? . *Lancet* 2003;**361**:981–2. [DOI: 10.1016/S0140-6736(03)12841-3]

Shea 2007
Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al.Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10. [DOI: 10.1186/1471-2288-7-10]

Song 2003
Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;**326**(7387):472. [DOI: 10.1136/bmj.326.7387.472]

Thornton 2000
Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000;**53**(2):207–16. [DOI: 10.1016/S0895-4356(99)00161-4]

Towheed 2006
Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004257.pub2]

Tramer 1998
Tramèr MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiologica Scandinavica* 1998;**42**(1):71–9. [PUBMED: 9527748]

WHO 2010
WHO. Pain ladder. www.who.int/cancer/palliative/painladder/en/. Accessed 12 July 2011.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy for Cochrane Reviews

1. (postoperative):ti,ab,kw or (post NEXT operative):ti,ab,kw
2. (pain):ti,ab,kw or (painful):ti,ab,kw or (analgesi*):ti,ab,kw
3. (1 AND 2) in Cochrane Database of Systematic Reviews

Appendix 2. Results for remedication in individual reviews

			Remedication time				Percent remedicated by:							
			Number of		Median/Mean time to remedication (hours)		6 hours		8 hours		12 hours		24 hours	
Drug	**Dose**	**Condition**	**Studies**	**Patients**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Celecoxib	200	All	5	805	6.6	2.6								
		Dental	4	523	6.1	1.5							74	94
		Other												
	400	All	4	620	8.4	1.6							63	91
		Dental	4	620	8.4	1.6							63	91
		Other												
Codeine	60	All	4	275	2.7	2	38	46						
		Dental												
		Other												
Codeine + Paracetamol	30/300	All	5	455	3.9	2.9	48	57						
		Dental												
		Other												
	60/600/650	All	10	995	4.1	2.4	59	80						

(*Continued*)

		Dental											
		Other											
	60/800/1000	All	2	127	5	2.3							
		Dental											
		Other											
Dexketoprofen	10/12.5	All					54	74					
		Dental											
		Other											
	20/25	All					52	75					
		Dental	2		4.2	2.2							
		Other											
Diclofenac	25	All	4	502	3.8	1.5	51	71					
		Dental											
		Other											
	50	All	5	457	4.3	2	35	68					
		Dental											
		Other											
	100	All	6	683	4.9	1.9	37	73					
		Dental											

(*Continued*)

		Other											
Diflu-nisal	125	All											
	250	All											
	500	All			9.8	3.2	27	66			53	87		
		Den-tal											
		Other											
	1000	All			10.9	3.2	23	75			43	88		
Etodola	50	All											
		Den-tal											
		Other											
	100	All											
		Den-tal											
		Other											
	200	All					61	77						
		Den-tal					64	88						
		Other												
	400	All					63	77						
		Den-tal					59	88						
		Other												
Etori-coxib	60	All												
		Den-tal												

(*Continued*)

		Other											
	120	All			20	2	50	92					
		Dental			>24	2							
		Other											
	180/240	All											
		Dental											
		Other											
Flurbiprofen	25	All					35	70					
		Dental											
		Other											
	50	All					25	66					
		Dental											
		Other											
	100	All					16	68					
		Dental											
		Other											
Gabapen	250	All	3	327	2.4	2.1	69	86					
		Dental											
		Other											
Ibupro-	50	All					29	50					

(*Continued*)

fen														
		Dental												
		Other												
	100	All					38	64						
		Dental					59	80						
		Other												
	200	All	10	1807	4.7	2.1	48	76						
		Dental					53	83						
	200 soluble	Dental												
	200 standard	Dental												
		Other												
	400	All	31	3548	5.6	1.9	42	79						
		Dental					41	80						
	200 soluble	Dental												
	200 standard	Dental												
		Other												
	600	All												
		Dental												
		Other												

(*Continued*)

	800	All											
		Dental											
		Other											
Ketoprofen	12.5	All					80	98					
		Dental											
		Other											
	25	All					46	79					
		Dental											
		Other											
	50	All					48	81					
		Dental											
		Other											
	100	All					43	85					
		Dental											
		Other											
Lornoxicam	4	All											
		Dental											
		Other											
	8	All	2		4.7	1.4							
		Dental											

(*Continued*)

		Other												
Lumiracoxib	400	All	4	548	9.4	1.7					64	91		
		Dental												
		Other												
Mefenamic acid	500	All					47	62						
		Dental												
		Other												
Naproxe	200/220	All												
		Dental												
		Other												
	400/440	All												
		Dental												
		Other												
	500/550	All	8	711	8.9	2					67	82		
		Dental											56	96
		Other												
Oxycodone	5	All	2	237	2.3	2.1	83	88						
		Dental												

(*Continued*)

		Other											
	15	All											
		Dental											
		Other											
Oxycodone + paracetamol	5/325	All			4.3	2	66	85					
		Dental											
		Other											
	10/650	All			9.8	1.5	55	83	86	88			
		Dental											
		Other											
	10/1000	All			8.7	1.1						67	87
		Dental											
		Other											
Paracetamol	500	All					35	63					
		Dental											
		Other											
	600/650	All	7	461	3.5	2.4	52	65					

(*Continued*)

		Dental												
		Other												
	975/1000	All	16	1540	3.9	1.7	53	72						
		Dental												
		Other												
Rofecoxib	50	All	20	3182	13.8	1.9			27	74				
		Dental	18	2872	16.2	1.7			20	79	32	89	52	87
		Other												

Note that empty cells indicate absence of data

HISTORY

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CONTRIBUTIONS OF AUTHORS

SD and RAM carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. HJM and PW acted as arbitrators. All authors were involved in discussing the results writing and approving the overview.

RAM/SD will be responsible for updating the overview.

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