Cochrane
Library

Cochrane Database of Systematic Reviews

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

Derry S, Wiffen PJ, Moore RA

Derry S, Wiffen PJ, Moore RA.
Single dose oral diclofenac for acute postoperative pain in adults.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD004768.
DOI: [10.1002/14651858.CD004768.pub3](https://doi.org/10.1002/14651858.CD004768.pub3).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	12
DISCUSSION	15
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	19
REFERENCES	20
CHARACTERISTICS OF STUDIES	23
DATA AND ANALYSES	41
Analysis 1.1. Comparison 1 Diclofenac fast-acting versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours.	42
Analysis 1.2. Comparison 1 Diclofenac fast-acting versus placebo, Outcome 2 Remedication within 6 or 8 hours.	42
Analysis 2.1. Comparison 2 Diclofenac potassium versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours.	43
Analysis 2.2. Comparison 2 Diclofenac potassium versus placebo, Outcome 2 Remedication within 6 or 8 hours.	44
Analysis 3.1. Comparison 3 Diclofenac sodium versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours. ..	45
Analysis 3.2. Comparison 3 Diclofenac sodium versus placebo, Outcome 2 Remedication within 6 or 8 hours.	46
Analysis 4.1. Comparison 4 Adverse events - diclofenac versus placebo, Outcome 1 Adverse events within 24 hours.	46
APPENDICES	47
WHAT'S NEW	54
HISTORY	55
CONTRIBUTIONS OF AUTHORS	55
DECLARATIONS OF INTEREST	56
SOURCES OF SUPPORT	56
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	56
INDEX TERMS	56

[Intervention Review]

Single dose oral diclofenac for acute postoperative pain in adults

Sheena Derry¹, Philip J Wiffen², R Andrew Moore³¹Oxford, UK. ²Thame, UK. ³Plymouth, UK**Contact:** Sheena Derry, Oxford, Oxfordshire, UK. sheena.derry@retired.ox.ac.uk.**Editorial group:** Cochrane Pain, Palliative and Supportive Care Group.**Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 5, 2019.**Citation:** Derry S, Wiffen PJ, Moore RA. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD004768. DOI: [10.1002/14651858.CD004768.pub3](https://doi.org/10.1002/14651858.CD004768.pub3).

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Diclofenac is a nonsteroidal anti-inflammatory drug, available as a potassium salt (immediate release) or sodium salt (enteric coated to suppress dissolution in the stomach). This review updates an earlier review published in the Cochrane Database of Systematic Reviews (Issue 2, 2009) entitled 'Single dose oral diclofenac for acute postoperative pain in adults'.

Objectives

To assess the analgesic efficacy and adverse effects of a single oral dose of diclofenac for moderate to severe postoperative pain, using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Oxford Pain Relief Database, two clinical trial registries, and the reference lists of articles. The date of the most recent search was 9 March 2015.

Selection criteria

Randomised, double-blind, placebo-controlled clinical trials of single dose, oral diclofenac (sodium or potassium) for acute postoperative pain in adults.

Data collection and analysis

Two review authors independently considered studies for inclusion in the review, assessed risk of bias, and extracted data. We used the area under the pain relief versus time curve to derive the proportion of participants with at least 50% pain relief over six hours prescribed either diclofenac or placebo. We calculated the risk ratio (RR) and number needed to treat to benefit (NNT). We used information on the use of rescue medication to calculate the proportion of participants requiring rescue medication and the weighted mean of the median time to use. We also collected information on adverse effects.

Main results

This update included three new studies, providing a 26% increase in participants in comparisons between diclofenac and placebo. We included 18 studies involving 3714 participants, 1902 treated with diclofenac and 1007 with placebo. This update has also changed the focus of the review, examining the effects of formulation in more detail than previously. This is a result of increased understanding of the importance of speed of onset in determining analgesic efficacy in acute pain.

The largest body of information, for diclofenac potassium 50 mg, in seven studies, produced an NNT for at least 50% of maximum pain relief compared with placebo of 2.1 (95% confidence interval (CI) 1.9 to 2.5) (high quality evidence). There was a graded improvement in efficacy as doses rose from 25 mg to 100 mg, both for participants achieving at least 50% maximum pain relief, and for remedication within 6 to 8 hours. Fast-acting formulations (dispersible products, solutions, and softgel formulations) had a similar efficacy for a 50 mg dose,

with an NNT of 2.4 (2.0 to 3.0). Diclofenac sodium in a small number of studies produced a lesser effect, with an NNT of 6.6 (4.1 to 17) for the 50 mg dose.

Adverse event rates were low in these single dose studies, with no difference between diclofenac and placebo (moderate quality evidence).

Authors' conclusions

Diclofenac potassium provides good pain relief at 25 mg, 50 mg, and 100 mg doses. Diclofenac sodium has limited efficacy and should probably not be used in acute pain.

PLAIN LANGUAGE SUMMARY

Single dose oral diclofenac for acute postoperative pain in adults

Acute pain is often felt soon after injury. Most people who have surgery have moderate or severe pain afterwards. Painkillers are tested in people with pain, often following a painful condition such as the removal of wisdom teeth. This pain is usually treated with painkillers taken by mouth. We believe these results can be applied to other acute painful conditions.

A series of Cochrane reviews looks at how good painkillers are. We know that in some circumstances, fast-dissolving and absorbed painkillers provide better pain relief than those that are absorbed slowly. This review examined how good different formulations of diclofenac were in relieving moderate or severe pain after surgery.

This is an update of a review published in 2009. New searches in March 2015 identified three new studies, making 18 studies with 3714 participants altogether, 1902 of whom were treated with diclofenac and 1007 with placebo. Diclofenac potassium is a rapidly absorbed formulation, and the 50 mg dose provided the largest amount on information. With this dose of this formulation, more than 6 in 10 (64%) participants had effective pain relief, compared with fewer than 2 in 10 (17%) with placebo (high quality evidence).

Adverse events occurred at similar rates with diclofenac and placebo in these single dose studies (moderate quality evidence). There were few serious adverse events or withdrawals due to adverse events.

Diclofenac potassium represents a useful option in controlling acute pain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Diclofenac potassium compared with placebo for moderate to severe acute pain in adults

Patient or population: Adults with acute pain

Settings: Hospital or community

Intervention: Oral diclofenac potassium 50 mg

Comparison: Oral placebo

Outcomes	Probable outcome with		Relative effect and NNT or NNH (95% CI)	Number of studies, participants, events	Quality of the evidence (GRADE)	Comments
	Comparator	Intervention				
At least 50% of maximum pain relief over 4 to 6 hours	170 in 1000	640 in 1000	RR 3.7 (2.9 to 4.7) NNT 2.1 (1.9 to 2.5)	7 studies 757 participants 313 events	High	Number of events above 200
Participants remedicing within 8 hours	690 in 1000	360 in 1000	RR 0.5 (0.45 to 0.6) NNTp 3.0 (2.5 to 3.8)	7 studies 757 participants 392 events	High	Number of events above 200
Participants with at least 1 adverse event (all diclofenac potassium doses, 25 mg to 100 mg)	70 in 1000	80 in 1000	RR 1.0 (0.7 to 1.6) NNH not calculated	7 studies 1090 participants 84 events	Moderate	Number of events below 200
Participants with a serious adverse event (whole data set)	1 reported	0 reported		18 studies 2830 participants	Low	Studies under-powered to detect these events

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

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

CI: confidence interval; NNT: number needed to treat to benefit; NNH: number needed to treat to harm or cause one event; NNTp: number needed to treat to prevent one event;
RR: risk ratio

BACKGROUND

This review updates an earlier review published in the Cochrane Database of Systematic Reviews (Issue 2, 2009) entitled 'Single dose oral diclofenac for acute postoperative pain in adults' (Derry 2009a). We carried out additional searches in 2011 that identified no new studies, and therefore planned a full update for 2015.

This is one of a series of reviews whose aim is to increase awareness of the range of analgesics that are potentially available, and to present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy making at the local level. The series covers all analgesics licensed for acute postoperative pain in Europe and North America, and dipyrrone, which is commonly used in Spain, Portugal, and Latin American countries. The results have been examined in an overview (Moore 2011a), and important individual reviews include ibuprofen (Derry 2009b), codeine (Derry 2010), paracetamol (Toms 2008), and etoricoxib (Clarke 2012), and combinations of ibuprofen with paracetamol (Derry 2013a), codeine (Derry 2013b), and oxycodone (Derry 2013c). Knowing the relative efficacy of different analgesic drugs at various doses can be helpful.

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 or nerve injury, or both. The management of postoperative pain and inflammation is a critical component of patient care.

Description of the intervention

Acute pain trials

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are small, allowing no reliable conclusions to be drawn about safety. To show that the analgesic is working, it is necessary to use placebo (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is hence important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years (McQuay 2012). 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 4 to 6 hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Pain relief of half the maximum possible pain

relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication, it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Diclofenac

Diclofenac is a benzene acetic acid derivative used to treat the pain and swelling associated with rheumatic disorders since 1974 (Fineschi 1997). It is one of the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) in the world, especially outside the USA. The most common daily doses are 75 mg and 150 mg, given as divided doses.

Diclofenac is available in two different salts in a number of different formulations. Diclofenac sodium is usually distributed in enteric-coated tablets, which resist dissolution in low pH gastric environments and release contents in the duodenum (Olson 1997); this tends to produce slow absorption into blood. Diclofenac potassium is formulated to be released and absorbed in the stomach, and references to pharmaceutical company data indicate that peak plasma concentrations occur by about 45 minutes (Bakshi 1992). Fast-acting formulations may involve diclofenac sodium or potassium, but are designed to dissolve diclofenac in the stomach contents and promote rapid uptake, with peak plasma concentrations at 30 minutes or so. We could not find a systematic review of diclofenac absorption kinetics with these different formulations.

Of the two salts, diclofenac potassium and diclofenac sodium, the sodium salt is used much more frequently (98% of the 2.3 million prescriptions in England in 2013 were of the sodium salt; PCA 2014). Diclofenac potassium is the formulation usually available at lower doses without prescription.

Fast-acting formulations not only produce more rapid plasma concentrations and pain relief, but better overall results and a longer duration of action, at least for ibuprofen (Moore 2014; Moore 2015a). There is no similar comprehensive review of effects of formulation for diclofenac, but the evidence is now strong that fast-acting formulations are likely to have different effects from standard formulations. Taking drugs with food reduces and delays absorption of NSAIDs, including diclofenac, and may impair analgesic efficacy (Moore 2015b). Where drugs are taken for a short time, adverse events in single dose studies are not generally different from placebo (Moore 2011a).

Diclofenac potassium formulations were recently withdrawn from non-prescription sale in the UK due to concerns over potential cardiovascular risk.

How the intervention might work

Clinicians prescribe NSAIDs on a routine basis for a range of mild to moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. 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). Since NSAIDs do not depress respiration and do not impair gastrointestinal motility as opioids do, they are clinically useful for treating pain after minor surgery and day surgery, and have an opioid-sparing effect after more major surgery (Grahame-Smith 2002).

A major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site (because of the inhibition of platelet aggregation) (Forrest 2002), and from the upper gastrointestinal tract (especially in patients stressed by surgery, the elderly, frail, or dehydrated). Other potentially serious adverse events include acute liver injury, acute renal injury, heart failure, and adverse reproductive outcomes (Hernández-Díaz 2001). Research has also implicated diclofenac in haematological abnormalities (Martindale 2015). However, such complications are more likely to occur with chronic use, and NSAIDs generally present fewer risks with short term use, as in the treatment of postoperative pain (Rapoport 1999).

Why it is important to do this review

The original version of this review included both ibuprofen and diclofenac, and was an update of a previous non-Cochrane review (Collins 1998). A 2004 update of diclofenac included only included seven studies in which 581 participants were treated with diclofenac and 364 with placebo (Barden 2004). A further updated review included 15 studies, with 1512 participants treated with diclofenac and 793 with placebo (Derry 2009a).

Since 2011, new clinical trials have been published, and the importance of formulation has been recognised. Taken together these factors meant that results of the previous reviews needed to be revisited.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of a single oral dose of diclofenac for moderate to severe postoperative pain, using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blind studies of single dose oral diclofenac compared with placebo for the treatment of moderate to severe

postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. We included multiple dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first arm were presented separately.

We excluded:

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

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

Types of participants

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

Types of interventions

Orally administered diclofenac sodium or potassium with matched placebo administered as a single oral dose for postoperative pain.

Types of outcome measures

We collected the following data where available.

- Participant characteristics.
- Participant-reported pain at baseline (we did not include physician-, nurse-, or carer-reported pain in the analysis).
- Participant-reported pain relief expressed at least hourly over four to six hours using validated pain scales (pain intensity or pain relief in the form of VAS or categorical scales, or both).
- Patient global assessment of efficacy (PGE), using a standard categorical scale.
- Time to use of rescue medication.
- Number of participants using rescue medication.
- Number of participants with one or more adverse events.
- Number of participants with serious adverse events.
- Number of withdrawals (all-cause, adverse events).

Primary outcomes

Participants achieving at least 50% pain relief over four to six hours (Moore 2011b).

Secondary outcomes

1. Median (or mean) time to use of rescue medication.
2. Participants using rescue medication.
3. Participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event.

4. Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication).

Search methods for identification of studies

Electronic searches

We searched the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library Issue 4, 2008 for the earlier version, and via Cochrane Register of Studies Online (CRSO) to 9 March 2015 for this update.
- MEDLINE (via Ovid) from inception to December 2008 for the earlier versions, and 2008 to 9 March 2015 for this update.
- EMBASE (via Ovid) from inception to December 2008 for the earlier versions, and 2008 to 9 March 2015 for this update.
- The Oxford Pain Relief Database ([Jadad 1996a](#)) for the earlier version. This database is no longer being updated.

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

Searching other resources

We searched for additional studies in reference lists of retrieved articles and reviews. We also searched the ClinicalTrials database (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for otherwise unpublished trial results and information about ongoing studies.

Merck provided details of two unpublished studies for the original review, but we did not contact manufacturers for this update.

Data collection and analysis

Selection of studies

Two review authors independently assessed the search results and agreed on the studies to be included in the review. Disagreements would have been resolved by consensus or referral to a third review author, but this was not necessary.

Data extraction and management

Two review authors extracted data and recorded them on a standard data extraction form. One review author entered data suitable for pooling into RevMan 5.3 ([RevMan 2014](#)).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for study inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum ([Jadad 1996b](#)).

We also completed a 'Risk of bias' table using methods adapted from those described by the Cochrane Pregnancy and Childbirth Group. Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, resolving any disagreements by discussion ([Higgins 2011](#)). We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation

sequence as: low risk of bias (any truly random process: random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (odd or even date of birth; hospital or clinic record number), which were therefore at high risk of bias.

2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (open list), which were therefore at high risk of bias.
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding: identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind and therefore at high risk of bias.
4. Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised ([Dechartres 2013](#); [Nüesch 2010](#)). We considered studies to be at low risk of bias if they had 200 participants or more, at unclear risk if they had 50 to 200 participants, and at high risk of bias if they had fewer than 50 participants.

Measures of treatment effect

We used risk ratio (or relative risk, RR) to establish statistical difference, and numbers needed to treat to benefit (NNT) and pooled percentages as absolute measures of benefit or harm.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with treatment than with control (placebo or active), we used the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with treatment compared with control (placebo or active), we used the term the number needed to treat to harm or cause one event (NNH).

Unit of analysis issues

We accepted only randomisation of the individual participant.

Dealing with missing data

The only likely issue with missing data in these studies was from imputation using last observation carried forward when a patient requested rescue medication. We have previously shown that this does not affect results for up to six hours after taking study medication ([Moore 2005](#)).

Assessment of heterogeneity

We examined heterogeneity using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies.

Assessment of reporting biases

We assessed the number of trials of average size amongst the included studies, with a RR of 1 (no effect), that would be needed to reduce any statistically significant result to one that fails to meet statistical significance (following Moore 2008).

Data synthesis

For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used the number of participants randomised to each treatment group who took the study medication. We analysed results for different doses separately.

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

We accepted the following pain measures for the calculation of TOTPAR or SPID (in order of priority; see Appendix 4).

- Five-point categorical pain relief scales with comparable wording to 'none, slight, moderate, good, or complete'.
- Four-point categorical pain intensity scales with comparable wording to 'none, mild, moderate, severe'.
- VAS for pain relief.
- VAS for pain intensity.

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

For each treatment group we extracted the number of participants reporting treatment-emergent adverse effects and calculated relative benefit and risk estimates with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). We calculated NNT and NNH with 95% CIs from the pooled number of events using the method of Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR did not include the number one.

Subgroup analysis and investigation of heterogeneity

We planned to report results according to formulation, and within a formulation the dose of diclofenac. The three formulations used were:

1. any fast-acting formulation (gel capsule, effervescent or other solution, or other formulation declared to be fast-acting). Both salts were allowed for this analysis;
2. diclofenac potassium; and
3. diclofenac sodium.

In this update, we include any formulation tested.

A minimum of two studies and 200 participants had to be available in any subgroup analysis (Moore 1998), which was restricted to the primary outcome (50% pain relief over 4 to 6 hours) and the dose with the greatest amount of data. We determined significant differences between NNT, NNTp, or NNH for different groups in subgroup and sensitivity analyses using the z test (Tramèr 1997).

Sensitivity analysis

No sensitivity analyses were planned.

RESULTS

Description of studies

Results of the search

The 2009 review included 15 studies (Ahlstrom 1993; Bakshi 1992; Bakshi 1994; Chang 2002; Cooper 1996; Desjardins 2004; Herbertson 1995; Hersh 2004; Hofele 2006; Kubitzek 2003; Mehlisch 1995; Nelson 1994; Olson 1997; Torres 2004; Zuniga 2004). Searches run for this update identified six other candidate publications (Daniels 2012; Manvelian 2012a; NCT01462435; Riff 2009; Zuniga 2010; Zuniga 2011).

One of these is an ongoing study (NCT01462435); details are in the Characteristics of studies awaiting classification table. Two others were pooled analyses of various outcomes from two randomised trials already included (Daniels 2012; Zuniga 2011).

Figure 1 shows the results of the searches.

Figure 1. Study flow diagram.

Included studies

The 18 included studies enrolled 3714 participants. Treatments tested are shown in Table A. Active comparators included aspirin,

ibuprofen, rofecoxib, and valdecoxib, but there were no more than two studies for any one.

Table A: Treatments tested

Drug	Diclofenac dose (mg)	Number treated
Fast-acting diclofenac	25	165
	50	254
	100	92
Diclofenac K	25	248
	50	395
	100	302
Diclofenac Na	50	193
	75	68
	100	85
Diclofenac nanoparticles	18 and 36	100
Placebo		1007
Active comparators		805

Thirteen studies were in participants with dental pain following surgical extraction of one or more impacted third molars (Ahlstrom 1993; Bakshi 1992; Bakshi 1994; Chang 2002; Cooper 1996; Hersh 2004; Hofele 2006; Kubitzek 2003; Manvelian 2012a; Mehlich 1995; Nelson 1994; Zuniga 2004; Zuniga 2010). Two studies involved pain following bunionectomy (Desjardins 2004; Riff 2009). Others involved general gynaecological surgery (Herbertson 1995), post-episiotomy pain (Olson 1997), and inguinal hernia (Torres 2004). Details of the included studies are in [Characteristics of included studies](#).

Excluded studies

Details of excluded studies are in [Characteristics of excluded studies](#).

Risk of bias in included studies

All included studies were both randomised and double-blind. On the Oxford Quality Scale, we gave five studies a quality score of five (Chang 2002; Desjardins 2004; Hersh 2004; Hofele 2006; Zuniga 2004), eight a score of four (Ahlstrom 1993; Bakshi 1994; Kubitzek 2003; Nelson 1994; Mehlich 1995; Olson 1997; Riff 2009; Zuniga 2010), and five a score of three (Bakshi 1992; Cooper 1996; Herbertson 1995; Manvelian 2012a; Torres 2004).

Allocation

All studies reported that they were randomised, and six adequately described the method used to generate the random sequence. The method used to conceal the random allocation was not generally described. For one study, allocation concealment was suspected possibly not to be adequate (Zuniga 2004) (Figure 2 and Figure 3).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Size
Ahlstrom 1993	?	?	+	-
Bakshi 1992	?	?	?	-
Bakshi 1994	?	?	+	?
Chang 2002	+	?	+	?
Cooper 1996	?	?	?	-
Desjardins 2004	+	?	+	?
Herbertson 1995	?	?	?	?
Hersh 2004	+	?	+	?
Hofele 2006	+	?	?	?
Kubitsek 2003	?	?	+	?
Manvelian 2012a	?	?	?	?
Mehlich 1995	?	?	+	?
Nelson 1994	?	?	?	-
Olson 1997	+	?	+	?
Riff 2009	?	?	?	?
Torres 2004	?	?	?	?
Zuniga 2004	+	-	?	-
Zuniga 2010	?	?	?	?

Blinding

Few studies adequately described the method of double-blinding (Figure 2 and Figure 3).

Other potential sources of bias

Small size was an issue in 5 of the 18 studies (Figure 2 and Figure 3).

Effects of interventions

See: [Summary of findings for the main comparison](#)

Efficacy outcomes were at least 50% of maximum pain relief over six hours, and remedication rates within six or eight hours. We have provided these by formulation, and within each formulation by dose of diclofenac. For adverse events we used all events reported within 24 hours of dosing, and pooled data for all doses together for different formulations. We did not carry out analyses on a small pilot study of a nanoparticle formulation (Manvelian 2012a), or a study using a 75 mg dose of diclofenac sodium (Torres 2004).

Results for individual studies are in [Appendix 5](#) (analgesia and use of rescue medication) and [Appendix 6](#) (adverse events and withdrawals).

Participants with at least 50% pain relief

Fast-acting diclofenac formulations

Fast-acting formulations included dispersible tablets (Ahlstrom 1993; Bakshi 1994), soluble diclofenac in a sachet (Hofele 2006), and softgel formulations (Riff 2009; Zuniga 2004; Zuniga 2010).

Diclofenac 25 mg versus placebo

Two studies (325 participants) included comparisons of fast-acting diclofenac 25 mg with placebo (Riff 2009; Zuniga 2010).

- The proportion of participants with at least 50% pain relief with fast-acting diclofenac 25 mg was 22% (36/165, range 21% to 24%).
- The proportion of participants with at least 50% pain relief with placebo was 3% (4/160, range 2% to 3%).
- The relative benefit of treatment compared with placebo was 8.7 (95% CI 3.2 to 24); the NNT for one additional participant to benefit compared with placebo was 5.2 (3.8 to 8.0) (Analysis 1.1).

Diclofenac 50 mg versus placebo

Four studies (486 participants) included comparisons of fast-acting diclofenac 50 mg with placebo (Ahlstrom 1993; Bakshi 1994; Hofele 2006; Zuniga 2010).

- The proportion of participants with at least 50% pain relief with fast-acting diclofenac 50 mg was 61% (156/254, range 29% to 75%).
- The proportion of participants with at least 50% pain relief with placebo was 20% (46/232, range 2% to 38%).
- The relative benefit of treatment compared with placebo was 2.9 (2.2 to 3.8); the NNT for one additional participant to benefit compared with placebo was 2.4 (2.0 to 3.0) (Analysis 1.1).

Diclofenac 100 mg versus placebo

Two studies (168 participants) included comparisons of fast-acting diclofenac 100 mg with placebo (Zuniga 2004; Zuniga 2010). This

was below our threshold of 200 participants for any subgroup analysis, but was included here for completeness.

- The proportion of participants with at least 50% pain relief with fast-acting diclofenac 100 mg was 38% (35/92, range 30% to 55%).
- The proportion of participants with at least 50% pain relief with placebo was 1% (1/76, range 0% to 2%).
- The relative benefit of treatment compared with placebo was 18 (3.6 to 91); the NNT for one additional participant to benefit compared with placebo was 2.7 (2.1 to 3.8) (Analysis 1.1).

Diclofenac potassium

Diclofenac 25 mg versus placebo

Four studies (502 participants) included comparisons of diclofenac potassium 25 mg with placebo (Hersh 2004; Kubitzek 2003; Nelson 1994; Olson 1997).

- The proportion of participants with at least 50% pain relief with diclofenac potassium 25 mg was 56% (140/248, range 46% to 68%).
- The proportion of participants with at least 50% pain relief with placebo was 15% (37/254, range 8% to 29%).
- The relative benefit of treatment compared with placebo was 3.9 (2.8 to 5.3); the NNT for one additional participant to benefit compared with placebo was 2.4 (2.0 to 2.9) (Analysis 2.1).

Diclofenac 50 mg versus placebo

Seven studies (757 participants) included comparisons of diclofenac potassium 50 mg with placebo (Bakshi 1992; Herbertson 1995; Hersh 2004; Hofele 2006; Mehlich 1995; Nelson 1994; Olson 1997).

- The proportion of participants with at least 50% pain relief with diclofenac potassium 50 mg was 64% (253/398, range 53% to 74%).
- The proportion of participants with at least 50% pain relief with placebo was 17% (60/359, range 8% to 29%).
- The relative benefit of treatment compared with placebo was 3.7 (2.9 to 4.7); the NNT for one additional participant to benefit compared with placebo was 2.1 (1.9 to 2.5) (Analysis 2.1).

Diclofenac 100 mg versus placebo

Six studies (594 participants) included comparisons of diclofenac potassium 100 mg with placebo (Herbertson 1995; Hersh 2004; Mehlich 1995; Nelson 1994; Olson 1997; Zuniga 2004).

- The proportion of participants with at least 50% pain relief with diclofenac potassium 100 mg was 65% (196/305, range 45% to 73%).
- The proportion of participants with at least 50% pain relief with placebo was 13% (39/289, range 0% to 29%).
- The relative benefit of treatment compared with placebo was 4.8 (3.6 to 6.5); the NNT for one additional participant to benefit compared with placebo was 1.9 (1.7 to 2.3) (Analysis 2.1).

Diclofenac sodium

Diclofenac 50 mg versus placebo

Three studies (284 participants) included comparisons of diclofenac sodium 50 mg with placebo (Bakshi 1992; Chang 2002; Cooper 1996).

- The proportion of participants with at least 50% pain relief with diclofenac sodium 50 mg was 30% (58/193, range 26% to 56%).
- The proportion of participants with at least 50% pain relief with placebo was 15% (18/120, range 0% to 22%).
- The relative benefit of treatment compared with placebo was 2.0 (1.3 to 3.3); the NNTp for one additional participant to benefit compared with placebo was 6.6 (4.1 to 17) (Analysis 3.1).

Time to remedication

This outcome examined the time from taking study medication to use of rescue medication. Most studies asked participants to wait one or two hours after taking study medication before taking rescue medication. Short times indicate large numbers of participants with inadequate pain relief (treatment failures), and longer times indicate the duration of analgesia. Not all studies reported relevant data; of those that did, most reported median times to remedication, and a few reported mean times.

Fast-acting diclofenac formulations

For the 50 mg dose, the mean time to use of rescue medication was 7.6 hours for diclofenac and 3.8 hours for placebo (two studies, 349 participants; Bakshi 1994; Hofele 2006).

Diclofenac potassium

For the 25 mg dose, the median time to use of rescue medication was 3.1 hours for diclofenac and 1.2 hours for placebo (5 studies, 625 participants; Hersh 2004; Kubitzek 2003; Nelson 1994; Olson 1997; Zuniga 2010).

For the 50 mg dose, the median time to use of rescue medication was 4.5 hours for diclofenac and 1.7 hours for placebo (5 studies, 566 participants; Hersh 2004; Mehlich 1995; Nelson 1994; Olson 1997; Zuniga 2010).

For the 100 mg dose, the median time to use of rescue medication was 6.3 hours for diclofenac and 2.0 hours for placebo (6 studies, 611 participants; Hersh 2004; Mehlich 1995; Nelson 1994; Olson 1997; Zuniga 2004; Zuniga 2010).

Diclofenac sodium

One study using a 50 mg dose in dental pain reported a median time to use of rescue medication of 1.6 hours for both diclofenac and placebo (105 participants; Chang 2002). Another study reported a mean time to use of rescue medication of 4.7 hours for diclofenac and 2.1 hours for placebo (70 participants; Cooper 1996).

One study using a 100 mg dose in bunionectomy pain reported a median time to use of rescue medication of 2.1 hours for diclofenac and 1.4 hours for placebo (252 participants; Desjardins 2004).

Participants remedication within six to eight hours

This outcome examined the need for additional analgesia in the period immediately after taking the test medications.

Fast-acting diclofenac formulation

Diclofenac 50 mg versus placebo

Four studies (486 participants) included comparisons of fast-acting diclofenac 50 mg with placebo (Ahlstrom 1993; Bakshi 1994; Hofele 2006; Zuniga 2010).

- The proportion of participants remedication with fast-acting diclofenac 50 mg was 33% (83/254, range 24% to 40%).
- The proportion of participants remedication with placebo was 71% (164/232, range 65% to 78%).
- The relative benefit of treatment compared with placebo was 0.46 (0.38 to 0.56); the NNTp for one additional participant not to need to remedicate compared with placebo was 2.6 (2.2 to 3.4) (Analysis 1.2).

Diclofenac 100 mg versus placebo

Two studies (168 participants) included comparisons of fast-acting diclofenac 100 mg with placebo (Zuniga 2004; Zuniga 2010).

- The proportion of participants remedication with fast-acting diclofenac 100 mg was 50% (46/92, range 40% to 72%).
- The proportion of participants remedication with placebo was 78% (59/76, range 72% to 100%).
- The relative benefit of treatment compared with placebo was 0.61 (0.48 to 0.77); the NNTp for one additional participant not to need to remedicate compared with placebo was 3.6 (2.4 to 7.3) (Analysis 1.2).

Diclofenac potassium

Diclofenac 25 mg versus placebo

Four studies (502 participants) included comparisons of diclofenac potassium 25 mg with placebo (Riff 2009; Zuniga 2010).

- The proportion of participants remedication with diclofenac potassium 25 mg was 51% (127/248, range 4% to 77%).
- The proportion of participants remedication with placebo was 71% (181/254, range 37% to 89%).
- The relative benefit of treatment compared with placebo was 0.72 (0.63 to 0.82); the NNTp for one additional participant not to need to remedicate compared with placebo was 5.0 (3.5 to 8.5) (Analysis 2.2).

Diclofenac 50 mg versus placebo

Seven studies (757 participants) included comparisons of diclofenac potassium 50 mg with placebo (Bakshi 1992; Herbertson 1995; Hersh 2004; Hofele 2006; Mehlich 1995; Nelson 1994; Olson 1997).

- The proportion of participants remedication with diclofenac potassium 50 mg was 36% (144/398, range 8% to 50%).
- The proportion of participants remedication with placebo was 69% (248/359, range 37% to 83%).
- The relative benefit of treatment compared with placebo was 0.52 (0.45 to 0.60); the NNTp for one additional participant not to need to remedicate compared with placebo was 3.0 (2.5 to 3.8) (Analysis 2.2).

Diclofenac 100 mg versus placebo

Six studies (589 participants) included comparisons of diclofenac potassium 100 mg with placebo ([Herbertson 1995](#); [Hersh 2004](#); [Mehlich 1995](#); [Nelson 1994](#); [Olson 1997](#); [Zuniga 2004](#)).

- The proportion of participants remedivating with diclofenac potassium 100 mg was 34% (103/300, range 0% to 76%).
- The proportion of participants remedivating with placebo was 72% (208/289, range 37% to 100%).
- The relative benefit of treatment compared with placebo was 0.45 (0.38 to 0.54); the NNTp for one additional participant not to need to remedicate compared with placebo was 2.6 (2.2 to 3.3) ([Analysis 2.2](#)).

Diclofenac sodium

Diclofenac 50 mg versus placebo

Two studies (284 participants) included comparisons of diclofenac sodium 50 mg with placebo ([Bakshi 1992](#); [Chang 2002](#)).

- The proportion of participants remedivating with diclofenac sodium 50 mg was 59% (103/175, range 41% to 67%).
- The proportion of participants remedivating with placebo was 69% (75/109, range 59% to 76%).
- The relative benefit of treatment compared with placebo was 0.82 (95% CI 0.69 to 0.98); the NNTp for one additional participant not to need to remedicate compared with placebo was not calculated because of the bare statistical significance ([Analysis 3.2](#)).

Adverse events

Not all studies reported the number of participants experiencing any adverse event in the 24 hours after dosing.

Fast-acting diclofenac formulations

Five studies (636 participants) included comparisons of fast-acting diclofenac formulations with placebo ([Ahlstrom 1993](#); [Bakshi 1994](#); [Hofele 2006](#); [Zuniga 2004](#); [Zuniga 2010](#)).

- The proportion of participants reporting an adverse event with fast-acting diclofenac formulations was 8% (34/409, range 3% to 17%).
- The proportion of participants reporting an adverse event with placebo was 7% (17/227, range 5% to 11%).
- The relative benefit of treatment compared with placebo was 1.0 (0.60 to 1.8); the NNH was not calculated ([Analysis 4.1](#)).

Diclofenac potassium

Seven studies (1090 participants) included comparisons of diclofenac potassium with placebo ([Bakshi 1992](#); [Herbertson 1995](#); [Hersh 2004](#); [Hofele 2006](#); [Nelson 1994](#); [Olson 1997](#); [Zuniga 2004](#)).

- The proportion of participants reporting an adverse event with diclofenac potassium was 8% (60/765, range 1% to 16%).
- The proportion of participants reporting an adverse event with placebo was 7% (24/325, range 2% to 15%).
- The relative benefit of treatment compared with placebo was 1.0 (0.66 to 1.6); the NNH was not calculated ([Analysis 4.1](#)).

Diclofenac sodium

Only one study reported adverse events; 3/51 and 3/46 participants reported treatment-related adverse events with diclofenac 50 mg and placebo, respectively ([Bakshi 1992](#)).

Serious adverse events

No study reported any serious adverse events with single dose treatment. One study reported a serious event (asthma flare) in a participant given placebo ([Chang 2002](#)), but it is not clear whether this occurred during the single or multiple dose phase.

Withdrawals

Three studies reported withdrawals due to adverse events. [Chang 2002](#) reported withdrawal of one placebo-treated participant due to an asthma flare (see 'Serious adverse events', above). [Desjardins 2004](#) reported withdrawal of one participant treated with diclofenac 100 mg and three participants treated with placebo, but did not provide specific details. [Herbertson 1995](#) reported withdrawal of eight participants in total, one of whom was treated with diclofenac 100 mg and experienced nausea and vomiting.

DISCUSSION

The original version of this review included seven studies, in which 581 participants were treated with diclofenac and 364 with placebo ([Barden 2004](#)). An updated review included 15 studies, with 1512 participants treated with diclofenac and 793 with placebo ([Derry 2009a](#)). This further update included 18 studies, with 1902 participants treated with diclofenac and 1007 with placebo, representing a 26% increase in participants in comparisons between diclofenac and placebo.

In addition to including more studies and participants, this update also changed the focus of the review, examining the effects of formulation in more detail than previously. This is a result of increased understanding of the importance of speed of onset in determining analgesic efficacy in acute pain ([Moore 2014](#); [Moore 2015a](#)). Fast-acting diclofenac formulations, fast-acting gelatin capsules, or nanoparticles produce maximum plasma concentrations at about 15 to 40 minutes ([Chen 2015](#); [Manvelian 2012b](#); [Scallion 2009](#)), similar to diclofenac potassium, at around 30 to 40 minutes ([Chen 2015](#)), but much faster than diclofenac sodium, where maximum plasma concentrations are reported to be longer than 2 hours ([Willis 1979](#)).

These results relate to absorption in the fasted state. Taking drugs with food can have very significant effects on the absorption of drugs. For rapidly absorbed analgesics, maximum plasma concentrations are typically delayed and reduced in extent in the fed compared with the fasting state ([Moore 2015b](#)). This may not always be the case, as with some formulations of diclofenac ([Chen 2015](#); [Manvelian 2012b](#)). The complexity of taking analgesics in the fed state does not impinge on the analgesic results in this (and other) acute pain reviews, as participants are almost universally fasted when taking the analgesics.

Summary of main results

The formulation with results from the largest number of studies and participants was diclofenac potassium. It demonstrated a graded improvement in efficacy as doses rose from 25 mg to 100 mg, both for participants achieving at least 50% maximum pain relief (which

is what patients say they want from treatment; [Moore 2013](#)), and for remedication within 6 to 8 hours (see 'Summary of results A' below). The largest body of information, for diclofenac potassium 50 mg, in seven studies, produced a NNT for at least 50% of maximum pain relief compared with placebo of 2.1 (1.9 to 2.5), which is amongst the better results found in acute pain studies ([Moore 2011a](#)).

Fast-acting diclofenac preparations, of which there were various forms, were less frequently studied. A 50 mg dose, in four studies, produced a similar NNT to diclofenac potassium, of 2.4 (2.0 to 3.0). The results for the 100 mg dose derive from only 168 participants and therefore should be interpreted with caution. We have included this analysis, despite having fewer than 200 participants, for indicative purposes only.

We found few data for diclofenac sodium, and the NNT compared with placebo was high, at 6.6 (4.1 to 17). This probably reflects its much slower absorption than diclofenac potassium or fast-acting formulations.

Adverse events rates for all formulations were very similar to those with placebo. Serious adverse events were not reported, or did not occur.

Summary of results A

Percent with outcome							
Formulation	Dose (mg)	Number of studies	Participants	Diclofenac	Placebo	RR (95% CI)	NNT (95% CI)
At least 50% maximum pain relief over 6 hours							
Fast acting	25	2	325	22	3	8.7 (3.2 to 24)	5.2 (3.8 to 8.0)
	50	4	486	61	20	2.9 (2.2 to 3.8)	2.4 (2.0 to 3.0)
	100	2	168	38	1	18 (3.6 to 91)	2.7 (2.1 to 3.8)
Diclofenac potassium	25	4	502	56	15	3.9 (2.8 to 5.3)	2.4 (2.0 to 2.9)
	50	7	757	64	17	3.7 (2.9 to 4.7)	2.1 (1.9 to 2.5)
	100	6	594	67	13	5.1 (3.7 to 6.8)	1.9 (1.7 to 2.1)
Diclofenac sodium	50	3	313	30	15	2.0 (1.3 to 3.3)	6.6 (4.1 to 17)
Remedication within 6 to 8 hours							
							NNTp (95% CI)
Fast acting	50	4	486	33	71	0.46 (0.38 to 0.56)	2.6 (2.2 to 3.4)
	100	2	168	50	78	0.61 (0.48 to 0.77)	3.6 (2.4 to 7.3)
Diclofenac potassium	25	4	502	51	71	0.72 (0.63 to 0.82)	5.0 (3.5 to 8.5)
	50	7	757	36	69	0.52 (0.45 to 0.60)	3.0 (2.5 to 3.8)
	100	6	594	34	72	0.45 (0.38 to 0.54)	2.6 (2.2 to 3.3)
Diclofenac sodium	50	2	284	59	69	0.82 (0.69 to 0.98)	not calculated

Overall completeness and applicability of evidence

The main limitation of the review was the small number of studies and participants for most analyses. The limited number of studies and participants did not allow for any sensible assessment of common or rare adverse events, although diclofenac is widely studied in other conditions, particularly chronic musculoskeletal pain, such as occurs with osteoarthritis.

Some important outcomes, such as those concerning duration of pain relief, were very poorly reported. Some results were available, but studies frequently did not report median time to duration, or percentages of participants who needed additional analgesia by particular times, or by the end of the study.

Quality of the evidence

The studies themselves were of high quality, but sample sizes were somewhat limited. The biggest problem was that studies did not report key methodological information about randomisation and blinding, though our experience is that these studies are usually done impeccably. This lack of methodological detail was true even for the most recent studies, and reflects a lack of awareness by authors, journals, and sponsors, about how clinical trials should be reported.

Potential biases in the review process

We carried out extensive searches to identify relevant studies, but there always remains the possibility of unidentified studies. For the largest data set, diclofenac potassium 50 mg, a very large amount of null effect data would be required to reduce the analgesic effect to a clinically irrelevant value of 8 (Moore 2008); over 2100 participants would be needed in null effect studies to do this. It is unlikely that such a body of evidence exists. That would not be the case for fast-acting formulations, where the amount of data for any one formulation is small, and particularly for diclofenac sodium, where analgesic efficacy is modest and the data available very few.

Agreements and disagreements with other studies or reviews

Previous versions of this review, and other reviews, have not reported results according to formulation, as done here, making comparison difficult. The overall estimate of efficacy for 50 mg diclofenac for at least 50% maximum pain relief in the previous version of this review was 2.7 (2.4 to 3.0). This compares with a NNT of 2.1 (1.9 to 2.5) for 50 mg diclofenac potassium in this review, a significantly better result ($z = 2.28$, $P = 0.023$). Including slower-acting formulations like diclofenac sodium in previous reviews probably erroneously underestimated analgesic efficacy possible with some forms of the drug.

AUTHORS' CONCLUSIONS

Implications for practice

For people with moderate to severe acute pain

Diclofenac potassium provides good pain relief at 25 mg, 50 mg, and 100 mg doses. Choice of dose may depend on the situation. Diclofenac sodium has limited efficacy and should probably not be used in acute pain.

For clinicians

Diclofenac potassium provides good pain relief at 25 mg, 50 mg, and 100 mg doses. Choice of dose may depend on the situation. Diclofenac sodium has limited efficacy and should probably not be used in acute pain.

For policy makers

Diclofenac sodium has limited efficacy and should probably not be used in acute pain. It is not clear if this is widely recognised. Diclofenac potassium is among the most effective analgesics in acute pain.

For Funders

Diclofenac sodium has limited efficacy and should probably not be used in acute pain. Diclofenac potassium is among the most effective analgesics in acute pain.

Implications for research

General

This review confirms other research indicating that rapidly dispersible and absorbed analgesics provide good pain relief, and that slow absorption results in poor pain relief in acute pain. Formulation is therefore of major consequence, and while the evidence on this is growing, there remain considerable gaps in our knowledge. These include direct linking of pharmacokinetics and pharmacodynamics in acute pain, something readily amenable to test in relatively inexpensive clinical trials.

Research could, and probably should, include effects of fasting and fed states for acute pain and headache, especially in situations where many over-the-counter drugs are taken. The effects of food on drug absorption and analgesics efficacy are not well understood, but they are significant.

Design

The current design of acute pain studies is well understood, and has proven to be robust.

Measurement (endpoints)

Endpoints in these studies have been extensively validated, as have standard pain scoring systems. The main outcome used is one valued by people with pain, and has economic benefits in most circumstances.

Comparison between active treatments

The standardised nature of the study design means that indirect comparisons with placebo are valid, as evidenced by independent research on the topic. There is, however, a very large body of information amenable to network meta-analysis. While unlikely to provide much in the way of new insights, it could prove an invaluable tool for testing network meta-analytical methods.

Reporting

The continued omission of details about methods, such as how the random sequence was generated and how its allocation was concealed, should be addressed.

ACKNOWLEDGEMENTS

Jodie Barden (JB) and Jayne Edwards (JE) were authors on the earliest review, and Philip Derry (PD) and Henry McQuay (HM) were authors on the immediately previous review.

This review received infrastructure support from the Oxford Pain Relief Trust.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service, or the Department of Health.

REFERENCES

References to studies included in this review

Ahlstrom 1993 {published data only}

Ahlstrom U, Bakshi R, Nilsson P, Wahlander L. The analgesic efficacy of diclofenac dispersible and ibuprofen in postoperative pain after dental extraction. *European Journal of Clinical Pharmacology* 1993;**44**(6):587-8.

Bakshi 1992 {published data only}

Bakshi R, Jacobs LD, Lehnert S, Picha B, Reuther J. A double-blind, placebo controlled trial comparing the analgesic efficacy of two formulations of diclofenac in postoperative dental pain. *Current Therapeutic Research* 1992;**52**(3):435-42.

Bakshi 1994 {published data only}

Bakshi R, Frenkel G, Dietlein G, Meurer Witt B, Schneider B, Sinterhauf U. A placebo-controlled comparative evaluation of diclofenac dispersible versus ibuprofen in postoperative pain after third molar surgery. *Journal of Clinical Pharmacology* 1994;**34**(3):225-30.

Chang 2002 {published data only}

Chang DJ, Desjardins PJ, Chen E, Polis AB, McAvoy M, Mockoviak SH, et al. Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: a randomized, placebo-controlled clinical trial. *Clinical Therapeutics* 2002;**24**(4):490-503.

Cooper 1996 {published data only}

Cooper SA, Cowan A, Tallarida RJ, Hargreaves K, Roszkowski M, Jamali F, et al. The analgesic interaction of misoprostol with nonsteroidal anti-inflammatory drugs. *American Journal of Therapeutics* 1996;**3**(4):261-7.

Desjardins 2004 {published data only}

Desjardins PJ, Black PM, Daniels S, Bird SR, Fitzgerald BJ, Petruschke RA, et al. A randomized controlled study comparing rofecoxib, diclofenac sodium, and placebo in post-bunionectomy pain. *Current Medical Research and Opinion* 2004;**20**(10):1523-37.

Herbertson 1995 {published data only}

Herbertson RM, Storey N. The comparative efficacy of diclofenac potassium, aspirin and placebo in the treatment of patients with pain following gynecologic surgery. *Today's Therapeutic Trends* 1995;**12**(Suppl 1):33-45.

Hersh 2004 {published data only}

Hersh EV, Levin LM, Adamson D, Christensen S, Kiersch TA, Noveck R, et al. Dose-ranging analgesic study of Prosorb diclofenac potassium in postsurgical dental pain. *Clinical Therapeutics* 2004;**26**(8):1215-27. [DOI: [10.1016/S0149-2918\(04\)80033-X](https://doi.org/10.1016/S0149-2918(04)80033-X)]

Hofele 2006 {published data only}

Hofele CM, Gyenes V, Daems LN, Stypula-Ciuba B, Wagener H, et al. Efficacy and tolerability of diclofenac potassium sachets in acute postoperative dental pain: a placebo-

controlled, randomised, comparative study vs. diclofenac potassium tablets. *International Journal of Clinical Practice* 2006;**60**(3):300-7. [DOI: [10.1111/j.1368-5031.2006.00828.x](https://doi.org/10.1111/j.1368-5031.2006.00828.x)]

Kubitzek 2003 {published data only}

Kubitzek F, Ziegler G, Gold MS, Liu JM, Ionescu E. Analgesic efficacy of low-dose diclofenac versus paracetamol and placebo in postoperative dental pain. *Journal of Orofacial Pain* 2003;**17**(3):237-44.

Manvelian 2012a {published data only}

Manvelian G, Daniels S, Gibofsky A. A phase 2 study evaluating the efficacy and safety of a novel, proprietary, nano-formulated, lower dose oral diclofenac. *Pain Medicine* 2012;**13**(11):1491-8. [DOI: [10.1111/j.1526-4637.2012.01479.x](https://doi.org/10.1111/j.1526-4637.2012.01479.x)]

Mehlisch 1995 {published data only}

Mehlisch DR, Brown P. Single-dose therapy with diclofenac potassium, aspirin or placebo following dental impaction surgery. *Today's Therapeutic Trends* 1995;**12**(Suppl 1):15-31.

Nelson 1994 {published data only}

Nelson S, Brahim J. An evaluation of the analgesic efficacy of diclofenac potassium, aspirin, and placebo in postoperative dental pain. *Today's Therapeutic Trends* 1994;**12**:3-14.

Olson 1997 {published data only}

Olson NZ, Sunshine A, Zigelboim I, DeCastro A. Onset and duration of analgesia of diclofenac potassium in the treatment of postepisiotomy pain. *American Journal of Therapeutics* 1997;**4**:239-46.

Riff 2009 {published data only}

Riff DS, Duckor S, Gottlieb I, Diamond E, Soulier S, Raymond G, et al. Diclofenac potassium liquid-filled soft gelatin capsules in the management of patients with postbunionectomy pain: a Phase III, multicenter, randomized, double-blind, placebo-controlled study conducted over 5 days. *Clinical Therapeutics* 2009;**31**(10):2072-85. [DOI: [10.1016/j.clinthera.2009.09.011](https://doi.org/10.1016/j.clinthera.2009.09.011)]

Torres 2004 {published data only}

Torres LM, Cabrera J, Martínez J, Calderón E, Fernández S, Chaves J. The specific cox-2 inhibitor valdecoxib provides effective analgesia after inguinal hernia surgery. *Revista Espanola Anestesiologia y Reanimacion* 2004;**51**(10):576-82.

Zuniga 2004 {published data only}

Zuniga JR, Phillips CL, Shugars D, Lyon JA, Peroutka SJ, Swarbrick J, et al. Analgesic safety and efficacy of diclofenac sodium softgels on postoperative third molar extraction pain. *Journal of Oral Maxillofacial Surgery* 2004;**62**(7):806-15. [DOI: [10.1016/j.joms.2003.12.019](https://doi.org/10.1016/j.joms.2003.12.019)]

Zuniga 2010 {published data only}

Zuniga JR, Malmström H, Noveck RJ, Campbell JH, Christensen S, Glickman RS, et al. Controlled phase III clinical trial of diclofenac potassium liquid-filled soft gelatin capsule for treatment of postoperative dental pain. *Journal of Oral*

and Maxillofacial Surgery 2010;**68**(11):2735-42. [DOI: [10.1016/j.joms.2010.05.075](https://doi.org/10.1016/j.joms.2010.05.075)]

References to studies excluded from this review

Daniels 2012 {published data only}

Daniels SE, Riff D, Diamond E, Clark F, Boesing SE. An assessment of the efficacy and safety of diclofenac potassium liquid-filled capsules inpatients with various levels of baseline pain intensity. *Current Medical Research & Opinion* 2012;**28**(6):953-61. [DOI: [10.1185/03007995.2012.694363](https://doi.org/10.1185/03007995.2012.694363)]

Zuniga 2011 {published data only}

Zuniga JR, Noveck RJ, Schmidt WK, Boesing SE, Hersh EV. Onset of action of diclofenac potassium liquid-filled capsules in dental surgery patients. *Current Medical Research and Opinion* 2011;**27**(9):1733-9. [DOI: [10.1185/03007995.2011.600300](https://doi.org/10.1185/03007995.2011.600300)]

References to ongoing studies

NCT01462435 {published data only}

NCT01462435. Study of diclofenac capsules to treat pain following bunionectomy. www.clinicaltrials.gov/ct2/results?term=NCT01462435&Search=Search (accessed 9 March 2015). [Clinicaltrials.gov: NCT01462435]

Additional references

Chen 2015

Chen C, Bujanover S, Kareht S, Rapoport AM. Differential pharmacokinetics of diclofenac potassium for oral solution vs immediate-release tablets from a randomized trial: effect of fed and fasting conditions. *Headache* 2015;**55**(2):265-75. [DOI: [10.1111/head.12483](https://doi.org/10.1111/head.12483)]

Clarke 2012

Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: [10.1002/14651858.CD004309.pub3](https://doi.org/10.1002/14651858.CD004309.pub3)]

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. [DOI: [10.1016/S0304-3959\(97\)00005-5](https://doi.org/10.1016/S0304-3959(97)00005-5)]

Collins 1998

Collins SL, Moore RA, McQuay HJ, Wiffen PJ. Oral ibuprofen and diclofenac in postoperative pain: a quantitative systematic review. *European Journal of Pain* 1998;**2**(4):285-91. [DOI: [10.1016/S1090-3801\(98\)90027-1](https://doi.org/10.1016/S1090-3801(98)90027-1)]

Collins 2001

Collins SL, Edwards JE, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough?. *Pain* 2001;**91**(1-2):189-94. [DOI: [10.1016/S0304-3959\(00\)00435-8](https://doi.org/10.1016/S0304-3959(00)00435-8)]

Cook 1995

Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**:452-4. [DOI: [10.1136/bmj.310.6977.452](https://doi.org/10.1136/bmj.310.6977.452)]

Cooper 1991

Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max MB, Portenoy RK, Laska EM editor(s). *The design of analgesic clinical trials. Advances in Pain Research and Therapy*. Vol. **18**, New York: Raven Press, 1991:117-24.

Dechartres 2013

Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304. [DOI: [10.1136/bmj.f2304](https://doi.org/10.1136/bmj.f2304)]

Derry 2009b

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](https://doi.org/10.1002/14651858.CD004234.pub3)]

Derry 2010

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](https://doi.org/10.1002/14651858.CD008099.pub2)]

Derry 2013a

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

Derry 2013b

Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: [10.1002/14651858.CD010107.pub2](https://doi.org/10.1002/14651858.CD010107.pub2)]

Derry 2013c

Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: [10.1002/14651858.CD010289.pub2](https://doi.org/10.1002/14651858.CD010289.pub2)]

Fineschi 1997

Fineschi G, Tamburrelli FC, Francucci BM, Pisati R. Oral diclofenac dispersible provides a faster onset of analgesia than intramuscular ketorolac in the treatment of postoperative pain. *Clinical Drug Investigation* 1997;**13**:1-7.

FitzGerald 2001

FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *The New England Journal of Medicine* 2001;**345**(6):433-42. [DOI: [10.1056/NEJM200108093450607](https://doi.org/10.1056/NEJM200108093450607)]

Forrest 2002

Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. *British Journal of Anaesthesia* 2002;**88**(2):227-33. [DOI: [10.1093/bja/88.2.227](https://doi.org/10.1093/bja/88.2.227)]

Grahame-Smith 2002

Grahame-Smith DG, Aronson JK. Oxford Textbook of Clinical Pharmacology and Drug Therapy. 3rd Edition. Oxford: Oxford University Press, 2002. [ISBN: 13: 978-0-19-263234-0]

Hawkey 1999

Hawkey CJ. Cox-2 inhibitors. *The Lancet* 1999;**353**(9149):307-14. [DOI: [10.1016/S0140-6736\(98\)12154-2](https://doi.org/10.1016/S0140-6736(98)12154-2)]

Hernández-Díaz 2001

Hernández-Díaz S, García-Rodríguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *American Journal of Medicine* 2001;**110**(Suppl 3A):20S-7S. [DOI: [10.1016/S0002-9343\(00\)00682-3](https://doi.org/10.1016/S0002-9343(00)00682-3)]

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jadad 1996a

Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;**66**:239-46. [DOI: [10.1016/0304-3959\(96\)03033-3](https://doi.org/10.1016/0304-3959(96)03033-3)]

Jadad 1996b

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12. [DOI: [10.1016/0197-2456\(95\)00134-4](https://doi.org/10.1016/0197-2456(95)00134-4)]

L'Abbé 1987

L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**:224-33. [DOI: [10.7326/0003-4819-107-2-224](https://doi.org/10.7326/0003-4819-107-2-224)]

Manvelian 2012b

Manvelian G, Daniels S, Gibofsky A. The pharmacokinetic parameters of a single dose of a novel nano-formulated, lower-dose oral diclofenac. *Postgraduate Medicine* 2012;**124**(1):117-23. [DOI: [10.3810/pgm.2012.01.2524](https://doi.org/10.3810/pgm.2012.01.2524)]

Martindale 2015

Diclofenac. Martindale: The Complete Drug Reference (available at: medicinescomplete.com/mc/martindale/current/ms-13409-w.htm?q=diclofenac&t=search&ss=text&p=1#_hit) (accessed 9 March 2015). The Pharmaceutical Press, 2015.

McQuay 2005

McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005;**81**:155-60. [DOI: [10.1136/pgmj.2004.024737](https://doi.org/10.1136/pgmj.2004.024737)]

McQuay 2012

McQuay HJ, Derry S, Eccleston C, Wiffen PJ, Moore RA. Evidence for analgesic effect in acute pain - 50 years on. *Pain* 2012;**153**(7):1364-7. [DOI: [10.1016/j.pain.2012.01.024](https://doi.org/10.1016/j.pain.2012.01.024)]

Moore 1997a

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**(93):311-5. [DOI: [10.1016/S0304-3959\(96\)03306-4](https://doi.org/10.1016/S0304-3959(96)03306-4)]

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**(1-2):127-30. [DOI: [10.1016/S0304-3959\(96\)03251-4](https://doi.org/10.1016/S0304-3959(96)03251-4)]

Moore 1998

Moore RA, Gavaghan D, Tramèr 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**(3):209-16. [DOI: [10.1016/S0304-3959\(98\)00140-7](https://doi.org/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. [ISBN: 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](https://doi.org/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, 2008:15-24. [ISBN: 978-0-931092-69-5]

Moore 2011a

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

Moore 2011b

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. [DOI: [10.1016/j.pain.2010.11.030](https://doi.org/10.1016/j.pain.2010.11.030)]

Moore 2013

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400-12. [DOI: [10.1111/anae.12148](https://doi.org/10.1111/anae.12148)]

Moore 2014

Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. *Pain* 2014;**155**(1):14-21. [DOI: [10.1016/j.pain.2013.08.013](https://doi.org/10.1016/j.pain.2013.08.013)]

Moore 2015a

Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Validating speed of onset as a key component of good analgesic response in acute pain. *European Journal of Pain* 2015;**19**(2):187-92. [DOI: [10.1002/ejp.536](https://doi.org/10.1002/ejp.536)]

Moore 2015b

Moore RA, Derry S, Wiffen PJ, Staube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyron, paracetamol, and NSAIDs – systematic review. *British Journal of Clinical Pharmacology* 2015 Epub. [DOI: [10.1111/bcp.12628](https://doi.org/10.1111/bcp.12628)]

Morris 1995

Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratio and standardised ratios and rates. In: Gardner MJ, Altman DG editor(s). *Statistics With Confidence - Confidence Intervals and Statistical Guidelines*. London: British Medical Journal, 1995:50-63. [ISBN: 0-7279-0222-9]

Nüesch 2010

Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515. [DOI: [10.1136/bmj.c3515](https://doi.org/10.1136/bmj.c3515)]

PCA 2014

Prescribing and Primary Care team, Health and Social Care Information Centre. Prescription Cost Analysis, England 2013. hscic.gov.uk/catalogue/PUB13887/pres-cost-anal-eng-2013-rep.pdf (accessed 9 March 2015). [ISBN: 978-1-78386-089-0]

Rapoport 1999

Rapoport RJ. The safety of NSAIDs and related drugs for the management of acute pain: maximizing benefits and

minimizing risks. *Cancer Control* 1999;**6**(2 Suppl 1):18-21. [PUBMED: 12118235]

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Scallion 2009

Scallion R, Moore KA. Effects of food intake on the pharmacokinetics of diclofenac potassium soft gelatin capsules: a single-dose, randomized, two-way crossover study. *Clinical Therapeutics* 2009;**31**(10):2233-41. [DOI: [10.1016/j.clinthera.2009.10.001](https://doi.org/10.1016/j.clinthera.2009.10.001)]

Toms 2008

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

Tramèr 1997

Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate results on meta-analysis: a case study. *BMJ* 1997;**315**:635-9. [DOI: [10.1136/bmj.315.7109.635](https://doi.org/10.1136/bmj.315.7109.635)]

Willis 1979

Willis JV, Kendall MJ, Flinn RM, Thornhill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. *European Journal of Clinical Pharmacology* 1979;**16**(6):405-10. [PUBMED: 527637]

References to other published versions of this review

Barden 2004

Barden J, Edwards J, Moore RA, McQuay HJ. Single dose oral diclofenac for postoperative pain. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: [10.1002/14651858.CD004768](https://doi.org/10.1002/14651858.CD004768)]

Collins 1999

Collins SL, Moore RA, McQuay HJ, Wiffen PJ, Edwards JE. Single dose oral ibuprofen and diclofenac for postoperative pain. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: [10.1002/14651858.CD001548](https://doi.org/10.1002/14651858.CD001548)]

Derry 2009a

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](https://doi.org/10.1002/14651858.CD004768.pub2)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahlstrom 1993

Methods

RCT, DB, double-dummy, single oral dose, 3 parallel groups

Medication administered when baseline pain was of moderate to severe intensity

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

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ahlstrom 1993 (Continued)

Pain assessed at 0, 20, 40, 60 mins then hourly up to 6 hours

Participants	Third molar extraction N = 97 M = 46, F = 51 Mean age 25 years
Interventions	Diclofenac dispersible 50 mg, n = 35 Ibuprofen (tablets) 400 mg, n = 32 Placebo, n = 30
Outcomes	PI: std 100 mm VAS PR: std 100 mm VAS PGE: std 5 point scale
Notes	Oxford Quality Score: R1, DB2, W1 No details about rescue medication used or any restrictions on time before use was permitted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Size	High risk	< 50 participants in treatment arms

Bakshi 1992

Methods	RCT, DB, single dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, and 60 mins then hourly up to 6 hours
Participants	Third molar extraction N = 151 M = 70, F = 81 Mean age 26 years

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

Bakshi 1992 (Continued)

Interventions	Diclofenac K 50 mg, n = 51 Diclofenac Na (enteric coated) 50 mg, n = 54 Placebo, n = 46
Outcomes	PI: std 4 point scale PR: 4 point scale (non std) PGE: 4 point scale (non std)
Notes	Oxford Quality Score: R1, DB1, W1 Rescue medication permitted after 1 hour. No details about drug used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Size	High risk	< 50 participants in one treatment arm

Bakshi 1994

Methods	RCT, DB, double-dummy, single oral dose, 3 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 20, 40, 60, 90, 120, and 150 mins then hourly up to 6 hours
Participants	Third molar extraction N = 257 M = 151, F = 94 Mean age 27 years
Interventions	Diclofenac free acid in dispersible preparation 50 mg, n = 83 Ibuprofen 400 mg, n = 80 Placebo, n = 82
Outcomes	PI: std 100 mm VAS PR: std 5 point scale

Bakshi 1994 (Continued)

PGE: 4 point (non std)

Notes	Oxford Quality Score: R1 DB2, W1
	Rescue medication permitted after 1 hour. No details of drug used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Chang 2002

Methods	RCT, DB, double-dummy, 3 parallel groups, single and multiple oral dose phases Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30, 60, 90, 120 mins, then hourly to 12 hours, then at 16, 20, 24 hours
Participants	Third molar extraction N = 305 M = 143, F = 162 Mean age 23 years
Interventions	Diclofenac Na (enteric coated) 50 mg, n = 121 Rofecoxib 50 mg, n = 121 Placebo, n = 63
Outcomes	PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1

Chang 2002 (Continued)

Rescue medication permitted at any time (hydrocodone/paracetamol 5/500 mg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated allocation schedule"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy technique with matching placebos"
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Cooper 1996

Methods	RCT, DB, 4 parallel groups, single oral dose Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 60 mins then hourly to 6 hours
Participants	Third molar extraction N = 70 M = 27, F = 43 Mean age 24 years
Interventions	Diclofenac Na 50 mg, n = 18 Misoprostol 200 µg, n = 21 Diclofenac Na + misoprostol 50 mg/200 µg, n = 20 Placebo, n = 11
Outcomes	PI: std 4 point scale PR: std 5 point scale Time to use of rescue medication Numbers with serious adverse events
Notes	Oxford Quality Score: R1, DB2, W0 Rescue medication permitted after 2 hours. No details of drug used

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Cooper 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not stated specifically for a second pilot study, but randomised specifically stated for first pilot study (on ibuprofen). In our judgement, it is likely that this was randomised
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated specifically for a second pilot study, but randomised specifically stated for first pilot study (on ibuprofen). In our judgement, it is likely that this was double-blind
Size	High risk	< 50 participants in relevant treatment arms

Desjardins 2004

Methods	<p>RCT, DB, 3 parallel groups, single and multiple oral dose phases</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly to 6 hours, and at 8, 10, 12, 14, and 24 hours</p>	
Participants	<p>First metatarsal bunionectomy</p> <p>N = 252</p> <p>M = 34, F = 218</p> <p>Mean age 41 years</p>	
Interventions	<p>Diclofenac Na (enteric coated) 100 mg, n = 85</p> <p>Rofecoxib 50 mg, n = 85</p> <p>Placebo, n = 82</p>	
Outcomes	<p>PI: std 4 point scale and VAS</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event and serious adverse events</p> <p>Withdrawals</p>	
Notes	<p>Oxford Quality Score: R2, DB2, W1</p> <p>Rescue medication permitted after 90 mins (hydrocodone/paracetamol 7.5/500 mg)</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Desjardins 2004 (Continued)

Random sequence generation (selection bias)	Low risk	"computer generated allocation schedule"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy technique with matching placebos"
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Herbertson 1995

Methods	<p>RCT, DB, 4 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 30, and 60 mins then hourly to 8 hours</p>	
Participants	<p>Gynaecological surgery</p> <p>N = 217</p> <p>All F</p> <p>Mean age 43 years</p>	
Interventions	<p>Diclofenac K 50 mg, n = 52</p> <p>Diclofenac K 100 mg, n = 52</p> <p>Aspirin 650 mg, n = 53</p> <p>Placebo, n = 52</p>	
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p>	
Notes	<p>Oxford Quality Score: R1, DB1, W1</p> <p>Rescue medication permitted after 1 hour, but 2 hours recommended. No details of drug used</p>	

Risk of bias

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

Herbertson 1995 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Hersh 2004

Methods	RCT, DB, double-dummy, 4 parallel groups, single oral dose Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins then hourly to 6 hours
Participants	Third molar extraction N = 265 M = 111, F = 154 Mean age 21 years
Interventions	Diclofenac K 25 mg, n = 63 Diclofenac K 50 mg, n = 68 Diclofenac K 100 mg, n = 66 Placebo, n = 68
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 1 hour (hydrocodone/paracetamol 5/500 mg or oxycodone/paracetamol 5/325 mg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random number table"
Allocation concealment (selection bias)	Unclear risk	Not reported

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

Hersh 2004 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, double-dummy", "identical appearance"
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Hofele 2006

Methods	<p>RCT, DB, double-dummy, 3 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly to 6 hours, and at 8 and 24 hours</p>	
Participants	<p>Third molar extraction</p> <p>N = 184</p> <p>M = 85, F = 99</p> <p>Mean age 27 years</p>	
Interventions	<p>Diclofenac K sachet 50 mg (fast-acting), n = 74</p> <p>Diclofenac K tablet 50 mg, n = 71</p> <p>Placebo, n = 39</p>	
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event</p> <p>Withdrawals</p>	
Notes	<p>Oxford Quality Score: R2, DB2, W1</p> <p>Rescue medication permitted after 2 hours (paracetamol 1000 mg)</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation scheme prepared by Novartis Pharma AG
Allocation concealment (selection bias)	Unclear risk	Not reported

Hofele 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind, double-dummy"
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Kubitzek 2003

Methods	<p>RCT, DB, 3 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 30, 60 mins then hourly to 6 hours</p>	
Participants	<p>Third molar extraction</p> <p>N = 245</p> <p>M = ~40%, F = ~60%</p> <p>Age not given</p>	
Interventions	<p>Diclofenac K 25 mg, n = 83</p> <p>Paracetamol 1000 mg, n = 78</p> <p>Placebo, n = 84</p>	
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event and serious adverse events</p> <p>Withdrawals</p>	
Notes	<p>Oxford Quality Score: R1, DB2, W1</p> <p>Rescue medication permitted after 1 hour (ibuprofen 200 mg)</p>	

Risk of bias

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

Kubitzek 2003 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind, double-dummy"
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Manvelian 2012a

Methods	<p>RCT, DB, 4 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 15, 30, 45, 60, 90, and 120 mins, then hourly to 8 hours, then 10 and 12 hours</p>	
Participants	<p>Third molar extraction</p> <p>N = 202</p> <p>M = 43%, F = 57%</p> <p>Mean age 22 years</p>	
Interventions	<p>Diclofenac K nanoparticle 18 mg, n = 49</p> <p>Diclofenac K nanoparticle 36 mg, n = 51</p> <p>Celecoxib 400 mg, n = 51</p> <p>Placebo, n = 51</p>	
Outcomes	<p>VAS PI and PR</p> <p>Adverse events</p>	
Notes	<p>Oxford Quality Score: R1, DB1, W1</p> <p>Rescue medication permitted after 1 hour (ibuprofen 200 mg)</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Mehlisch 1995

Methods	<p>RCT, DB, double-dummy, 4 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 30, 60 mins then hourly to 8 hours</p>
Participants	<p>Third molar extraction</p> <p>N = 208</p> <p>M = 91, F = 117</p> <p>Mean age 26 years</p>
Interventions	<p>Diclofenac K 50 mg, n = 53</p> <p>Diclofenac K 100 mg, n = 52</p> <p>Aspirin 650 mg, n = 51</p> <p>Placebo, n = 52</p>
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event and serious adverse events</p> <p>Withdrawals</p>
Notes	<p>Oxford Quality Score: R1, DB2, W1</p> <p>Rescue medication permitted after 2 hours. No details of drug used</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Nelson 1994

Methods	<p>RCT, DB, 5 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins then hourly to 6 hours</p>
Participants	<p>Third molar extraction</p> <p>N = 183</p> <p>M = 126, F = 129</p> <p>Mean age 25 years</p>
Interventions	<p>Diclofenac K 25 mg, n = 50</p> <p>Diclofenac K 50 mg, n = 50</p> <p>Diclofenac K 100 mg, n = 50</p> <p>Aspirin 650 mg, n = 50</p> <p>Placebo, n = 50</p>
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: std 5 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event</p> <p>Withdrawals due to adverse events</p>
Notes	<p>Oxford Quality Score: R1, DB2, W1</p> <p>Rescue medication permitted after 1 hour. No details of drug used</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"matching placebo identical in appearance"
Size	High risk	50 participants in treatment groups

Olson 1997

Methods	<p>RCT, DB, 5 parallel groups, single oral dose</p> <p>Medication administered when baseline pain was of moderate to severe intensity</p> <p>Pain assessed at 0, 30, 60 mins then hourly to 8 hours</p>
Participants	<p>Post-episiotomy</p> <p>N = 255</p> <p>All F</p> <p>Mean age 24 years</p>
Interventions	<p>Diclofenac K 25 mg, n = 52</p> <p>Diclofenac K 50 mg, n = 50</p> <p>Diclofenac K 100 mg, n = 51</p> <p>Aspirin 650 mg, n = 50</p> <p>Placebo, n = 52</p>
Outcomes	<p>PI: std 4 point scale</p> <p>PR: std 5 point scale</p> <p>PGE: non std 4 point scale</p> <p>Numbers using rescue medication</p> <p>Time to use of rescue medication</p> <p>Numbers with any adverse event and serious adverse events</p> <p>Withdrawals</p>
Notes	<p>Oxford Quality Score: R1, DB2, W1</p> <p>Rescue medication permitted after 1 hour (non-study analgesic)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer program generated a random number permutation"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebo"
Size	Unclear risk	50 or more participants in relevant treatment groups

Riff 2009

Methods	R, DB, 4 parallel groups, single oral dose Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 10, 15, 20, 30, 45, 60, 90, 120 mins then hourly to 8 hours
Participants	Day after bunionectomy (fasted until 1.5 hours after dose) N = 201 M = 27, F = 174 Mean age 45 years
Interventions	Diclofenac K softgel 25 mg, n = 102 Placebo, n = 99 Note: second dose permitted if pain relief insufficient after 1 hour
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers using rescue medication Time to use of rescue medication Numbers with any adverse event and serious adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1 Rescue medication permitted after 1 hour

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pre-randomised by sponsor
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Torres 2004

Methods	RCT, DB, 4 parallel groups, single and multiple dose phases
---------	---

Torres 2004 (Continued)

Medication administered when baseline pain was of moderate to severe intensity

Pain assessed at 0, 30, 45, 60 mins, then hourly to 6 hours, then at 10, 12, 18, 24, 36 hours

Participants	Inguinal hernia surgery N = 269 All M Mean age 53 years
Interventions	Diclofenac SR 75 mg, n = 68 Valdecoxib 20 mg, n = 68 Valdecoxib 40 mg, n = 69 Placebo, n = 67
Outcomes	PI: std 4 point scale and VAS PGE: non std 4 point scale Numbers using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 Rescue medication permitted at any time (usual analgesic for hospital)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	> 50 but < 200 participants in treatment groups

Zuniga 2004

Methods	R, DB, 3 parallel groups, single oral dose Medication administered when baseline pain was of moderate to severe intensity
---------	--

Zuniga 2004 (Continued)

Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins, then hourly to 6 hours, then at 8 and 24 hours

Participants	Third molar extraction N = 75 M = 25, F = 50 Mean age 23 years
Interventions	Diclofenac K 100 mg, n = 31 Diclofenac Na softgel 100 mg (fast-acting), n = 29 Placebo, n = 15
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers using rescue medication Time to use of rescue medication Numbers with any adverse event and serious adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted at any time. No details of drug used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment using computer program
Allocation concealment (selection bias)	High risk	"surgeon who dispensed medication not masked to allocation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"placebo constituted using same packaging as softgel"
Size	High risk	< 50 participants in treatment groups

Zuniga 2010

Methods	R, DB, 4 parallel groups, single oral dose Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90, 120 mins then hourly to 6 hours
Participants	Third molar extraction

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

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Zuniga 2010 (Continued)

N = 249

M = 115, F = 134

Mean age 24 years

Interventions	Diclofenac K softgel 25 mg, n = 63 Diclofenac K softgel 50 mg, n = 62 Diclofenac K softgel 100 mg, n = 63 Placebo, n = 61
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers using rescue medication Time to use of rescue medication Numbers with any adverse event and serious adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1 Rescue medication permitted after 1 hour

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	> 50 but < 200 participants in treatment groups

DB: double blind; F: female; M: male; N: total number in trial; n: number in treatment arm; PI: pain intensity; PR: pain relief; PGE: patient global evaluation; SR: slow release; std: standard; R: randomised; W: withdrawals

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Daniels 2012	Pooled analysis of two previous studies looking at effect of initial pain intensity
Zuniga 2011	Pooled analysis of two previous studies looking at stop-watch time to onset results only

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

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Characteristics of ongoing studies [ordered by study ID]

NCT01462435

Trial name or title	NCT01462435
Methods	Randomised, double-blind, multiple-dose, parallel-group, active- and placebo-controlled study
Participants	Bunionectomy surgery
Interventions	Diclofenac, celecoxib, placebo
Outcomes	Various pain intensity and relief measures
Starting date	October 2011
Contact information	Iroko Pharmaceuticals, LLC
Notes	

DATA AND ANALYSES

Comparison 1. Diclofenac fast-acting versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 50% of maximum pain relief over 6 hours	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 25 mg	2	325	Risk Ratio (M-H, Fixed, 95% CI)	8.73 [3.18, 23.97]
1.2 50 mg	4	486	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [2.23, 3.76]
1.3 100 mg	2	168	Risk Ratio (M-H, Fixed, 95% CI)	18.09 [3.60, 90.75]
2 Remedication within 6 or 8 hours	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 50 mg	4	486	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.38, 0.56]
2.2 100 mg	2	168	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.48, 0.77]

Analysis 1.1. Comparison 1 Diclofenac fast-acting versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours.

Analysis 1.2. Comparison 1 Diclofenac fast-acting versus placebo, Outcome 2 Remedication within 6 or 8 hours.

Comparison 2. Diclofenac potassium versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 50% of maximum pain relief over 6 hours	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 25 mg	4	502	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [2.84, 5.32]
1.2 50 mg	7	757	Risk Ratio (M-H, Fixed, 95% CI)	3.68 [2.90, 4.68]
1.3 100 mg	6	589	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [3.74, 6.82]
2 Remedication within 6 or 8 hours	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 25 mg	4	502	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
2.2 50 mg	7	757	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.45, 0.60]
2.3 100 mg	6	589	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.38, 0.54]

Analysis 2.1. Comparison 2 Diclofenac potassium versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours.

Analysis 2.2. Comparison 2 Diclofenac potassium versus placebo, Outcome 2 Remedication within 6 or 8 hours.

Comparison 3. Diclofenac sodium versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 50% of maximum pain relief over 6 hours	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 50 mg	3	313	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.26, 3.31]
1.2 100 mg	1	167	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [1.07, 9.22]
2 Remedication within 6 or 8 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 50 mg	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]

Analysis 3.1. Comparison 3 Diclofenac sodium versus placebo, Outcome 1 At least 50% of maximum pain relief over 6 hours.

Analysis 3.2. Comparison 3 Diclofenac sodium versus placebo, Outcome 2 Remedication within 6 or 8 hours.

Comparison 4. Adverse events - diclofenac versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events within 24 hours	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Fast-acting formulations (all doses)	5	636	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.60, 1.83]
1.2 Diclofenac potassium (all doses)	7	1090	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.66, 1.62]

Analysis 4.1. Comparison 4 Adverse events - diclofenac versus placebo, Outcome 1 Adverse events within 24 hours.

APPENDICES

Appendix 1. Search strategy for CENTRAL (via CRSO)

- MESH DESCRIPTOR diclofenac EXPLODE ALL TREES (1342)
- diclofenac:TI,AB,KY (3052)
- 1 or 2
- MESH DESCRIPTOR Pain, Postoperative EXPLODE ALL TREES (9177)
- ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*"):TI,AB,KY (15252)
- ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)):TI,AB,KY (99)
- ("pain-relief after surg*" or "pain following surg*" or "pain control after"):TI,AB,KY (309)
- ("post surg*" or post-surg*) AND (pain* or discomfort):TI,AB,KY (329)
- ((pain* adj4 "after surg*" or pain* adj4 "after operat*" or (pain* adj4 "follow* operat*" or (pain* adj4 "follow* surg*"))):TI,AB,KY (713)
- ((analgesi* adj4 "after surg*" or analgesi* adj4 "after operat*" or (analgesi* adj4 "follow* operat*" or (analgesi* adj4 "follow* surg*"))):TI,AB,KY (285)
- 4 or 5 or 6 or 7 or 8 or 9 or 10 (18203)
- 3 and 11 (895)
- 2008 TO 2015:YR (246363)
- 12 and 13 (354)

Appendix 2. Search strategy for MEDLINE via Ovid

- Diclofenac/ (6116)
- diclofenac.mp. (8832)
- 1 or 2 (8835)
- Pain, postoperative/ (28041)
- exp Surgical Procedures, Operative/ (2440682)
- ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (45590)
- ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (311)
- ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (564)
- ((("post surg*" or post-surg*) and (pain* or discomfort)).mp. (1164)

- 10.((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (2617)
- 11.((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (555)
- 12.4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (2456902)
- 13.randomized controlled trial.pt. (386549)
- 14.controlled clinical trial.pt. (88799)
- 15.randomized.ab. (284481)
- 16.placebo.ab. (149366)
- 17.drug therapy.fs. (1745898)
- 18.randomly.ab. (201462)
- 19.trial.ab. (293536)
- 20.groups.ab. (1288153)
- 21.13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (3290048)
- 22.3 and 12 and 21 (1115)
- 23.limit 22 to yr="2008 -Current" (324)

For the earlier review the following brand names were also searched:

allvoran; dolotren; nu-diclo; anfenax; ecofenac; oflen; apo-diclo; effekton; panamor; arcanafenac; fenac; pharmaflam; arthrotec; fenaren; polyflam; benfofen; flamarase; primofenac; brovaflamp; flector; rewodina; cataflam; flexagen; rheufenac; clinifam; flogofenac; rheumasan; dedolor; forgenac; rhumalgan; deflamat; fortfen; ribex; delphimix; grofenac; sigafenac; delphinac; inflamac; silino; diclac; isclofen; sodiclo; diclo; jenafenac; toryxil; diclobene; lexobene; tratul; dicloberl; liberalgium; valenac; diclofex; luase; veltex; diclomax; magluphen; voldal; diclomelan; monoflam; vologen; dicloreum; motifene; volraman; diclosyl; myogit; voltaren; diclozip; naclof; voltarene; dignofenac; novapirina; voltarol; dolobasan; novo-difenac; xenid.

Appendix 3. Search strategy for EMBASE (via Ovid)

1. Diclofenac/ (30696)
2. diclofenac.mp. (31948)
3. 1 or 2 (31948)
4. Pain, postoperative/ (44185)
5. exp Surgical Procedures, Operative/ (3553121)
6. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (90276)
7. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (796)
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (869)
9. (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (2995)
- 10.((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (4013)
- 11.((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (799)
- 12.4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (3578345)
- 13.RANDOMIZED CONTROLLED TRIAL/ (363913)
- 14.DOUBLE-BLIND PROCEDURE/ (120687)
- 15.CROSSOVER PROCEDURE/ (41726)
- 16.random*.ti.ab. (954095)
- 17.factorial*.ti.ab. (24784)
- 18.(crossover* or cross over* or cross-over*).ti.ab. (74478)
- 19.placebo*.ti.ab. (214812)
- 20.(doubl* adj blind*).ti.ab. (154353)
- 21.assign*.ti.ab. (256178)
- 22.allocat*.ti.ab. (90878)
- 23.13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (1367881)
- 24.3 and 12 and 23 (2021)
- 25.limit 24 to yr="2008 -Current" (943)

For the earlier review the following brand names were also searched:

allvoran; dolotren; nu-diclo; anfenax; ecofenac; olfen; apo-diclo; efekton; panamor; arcanafenac; fenac; pharmaflam; arthrotec; fenaren; polyflam; benfofen; flarnase; primofenac; brovaflamp; flector; rewodina; cataflam; flexagen; rheufenac; clinifam; flogofenac; rheumasan; dedolor; forgenac; rhumalgan; deflamat; fortfen; ribex; delphimix; grofenac; sigafenac; delphinac; inflamac; silino; diclac; isclofen; sodiclo; diclo; jenafenac; toryxil; diclobene; lexobene; tratul; dicloberl; liberalgium; valenac; diclofex; luase; veltex; diclomax; magluphen; voldal; diclomelan; monoflam; vologen; dicloreum; motifene; volraman; diclosyl; myogit; voltaren; diclozip; naclof; voltarene; dignofenac; novapirina; voltarol; dolobasan; novo-difenac; xenid.

Appendix 4. Glossary

Categorical rating scale:

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

Visual analogue scale (VAS):

Lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain" seem to overcome this limitation imposed by discrete categories. Participants mark the line at the point that corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the participant's mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms, and provide many points from which to choose. More concentration and co-ordination are needed, which can be difficult postoperatively or with neurological disorders.

Total pain relief (TOTPAR):

TOTPAR is calculated as the sum of pain relief scores over a period of time. If a participant had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for 6 hours, they would have a 6-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the composite trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

Summed pain intensity difference (SPID):

SPID is calculated as the sum of the differences between the pain scores over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the trapezoidal rule.

VAS TOTPAR and VAS SPID are visual analogue versions of TOTPAR and SPID.

See "Measuring pain" in Bandolier's Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13 ([Moore 2003](#)).

Appendix 5. Results for individual studies: efficacy

Study ID	Treatment	Analgesia		Rescue medication		
		PI or PR	Number with 50% PR	PGR: v good or excellent	Median time to use (hr)	% using
Ahlstrom 1993	(1) Diclofenac (soluble) 50 mg, n = 35	TOTPAR 6:	(1) 21/35	at 6 hours:	no data	at 6 hours:
	(2) Ibuprofen (tablets) 400 mg, n = 32	(1) 153 mm	(3) 3/50	(1) 23/35		(1) 40
	(3) Placebo, n = 30	(3) 292 mm		(3) 5/30		(3) 77
Bakshi 1992	(1) Diclofenac K 50 mg, n = 51	TOTPAR 6:	(1) 35/51	no usable data	no usable data	at 6 hours:
		(1) 10	(2) 16/54			(1) 33

(Continued)

	(2) Diclofenac Na (enteric coated) 50 mg, n = 54	(2) 7.3	(3) 10/46			(2) 41
	(3) Placebo, n = 46	(3) 5.2				(3) 59
Bakshi 1994	(1) Diclofenac (soluble) 50 mg, n = 83	TOTPAR 6:	(1) 62/83	no usable data	Mean:	at 6 hours:
	(2) Ibuprofen 400 mg, n = 80	(1) 15.5	(3) 31/82		(1) 5.35	(1) 24
	(3) Placebo, n = 82	(3) 8.9			(3) 3.36	(3) 65
Chang 2002	(1) Diclofenac Na (enteric coated) 50 mg, n = 121	TOTPAR 6:	(1) 32/121	no usable data	(1) 1.62	at 8 hours:
	(2) Rofecoxib 50 mg, n = 121	(1) 5.8	(3) 8/63		(3) 1.62	(1) 67
	(3) Placebo, n = 63	(3) 4.3				(3) 76
Cooper 1996	(1) Diclofenac Na 50 mg, n = 18	TOTPAR 6:	(1) 10/18	no usable data	Mean:	no data
	(2) Misoprostol 200 µg, n = 21	(1) 12.5	(4) 0/11		(1) 4.68	
	(3) Diclofenac Na + misoprostol 50 mg/200 µg, n = 20	(4) 1.9			(4) 2.11	
	(4) Placebo, n = 11					
Desjardins 2004	(1) Diclofenac Na 100 mg, n = 85	TOTPAR 6:	(1) 13/85	at 8 hours:	(1) 2.03	no data
	(2) Rofecoxib 50 mg, n = 85	(1) 4.8	(3) 4/82	(1) 6/85	(3) 1.41	
	(3) Placebo, n = 82	(3) 2.9		(3) 3/82		
Herbertson 1995	(1) Diclofenac K 50 mg, n = 52	TOTPAR 6:	(1) 29/52	at 8 hours:	(1) 5.6	at 6 hours:
	(2) Diclofenac K 100 mg, n = 52	(1) 12.1	(2) 29/52	(1) 28/52	(2) 6.1	(1) 50
	(3) Aspirin 650 mg, n = 53	(2) 12.2	(4) 5/52	(2) 25/52	(4) 1.5	(2) 54
	(4) Placebo, n = 52	(4) 3.7		(4) 6/52		(4) 82
Hersh 2004	(1) Diclofenac K 25 mg, n = 63	TOTPAR 6:	(1) 43/63	no usable data	(1) 5.83	at 6 hours:
	(2) Diclofenac K 50 mg, n = 68	(1) 11.68	(2) 44/68		(2) > 6	(1) 51
	(3) Diclofenac K 100 mg, n = 66	(2) 13.86	(3) 52/66		(3) > 6	(2) 37
	(4) Placebo, n = 68	(3) 16.16	(4) 11/68		(4) 1.67	(3) 32
		(4) 4.99				(4) 79
Hofele 2006	(1) Diclofenac K sachet 50 mg, n = 74	TOTPAR 6:	(1) 55/74	no usable data	Ka-plan-Meier estimate	at 8 hours:
	(2) Diclofenac K tablet 50 mg, n = 71	(1) 15.5	(2) 47/71		Mean:	(1) 37
	(3) Placebo, n = 39	(2) 14.1	(3) 11/39		(1) 8.7	(2) 37
		(3) 7.2			(2) 8.9	(3) 72
					(3) 4.5	
Kubitzeck 2003	(1) Diclofenac K 25 mg, n = 83	TOTPAR 6: values not given	(1) 42/83	at 6 hours:	(1) 3.94	at 6 hours:

(Continued)

	(2) Paracetamol 1000 mg, n = 78		(3) 7/84	(1) 25/83	(3) 1.47	(1) 77
	(3) Placebo, n = 84			(3) 1/84		(3) 89
Manvelian 2012a	(1) Diclofenac K nanoparticle 18 mg, n = 49	TOTPAR 6 (estimated):	(1) 24/49 (2) 25/51	no data	no data	no data
	(2) Diclofenac K nanoparticle 36 mg, n = 51	(1) 11 (2) 11	(3) 18/51 (4) 3/51			
	(3) Celecoxib 400 mg, n = 51	(3) 8.5				
	(4) Placebo, n = 51	(4) 3				
Mehlich 1995	(1) Diclofenac K 50 mg, n = 53	TOTPAR 6:	(1) 28/53	no usable data	(1) 5.9	at 6 hours:
	(2) Diclofenac K 100 mg, n = 52	(1) 11.6	(2) 35/52		(2) 7.3	(1) 49
	(3) Aspirin 650 mg, n = 51	(2) 14.3	(4) 4/52		(4) 1.8	(2) 30
	(4) Placebo, n = 52	(4) 3.3				(4) 84
Nelson 1994	(1) Diclofenac K 25 mg, n = 50	TOTPAR 6:	(1) 23/50	no data	(1) 5.3	at 6 hours:
	(2) Diclofenac K 50 mg, n = 50	(1) 10.5	(2) 28/50		(2) > 8	(1) 57
	(3) Diclofenac K 100 mg, n = 50	(2) 12.2	(3) 35/50		(3) > 8	(2) 39
	(4) Aspirin 650 mg, n = 50	(3) 14.8	(5) 4/50		(5) 2.8	(3) 32
	(5) Placebo, n = 50	(5) 3.6				(5) 65
Olson 1997	(1) Diclofenac K 25 mg, n = 52	TOTPAR 4:	(1) 32/52	no usable data	(1) 5.4	at 6 hours:
	(2) Diclofenac K 50 mg, n = 50	(1) 8.9	(2) 34/50		(2) 3.0	(1) 4
	(3) Diclofenac K 100 mg, n = 51	(2) 9.5	(3) 37/51		(3) 5.4	(2) 2
	(4) Aspirin 650 mg, n = 50	(3) 10.1	(5) 15/52		(5) 2.3	(3) 0
	(5) Placebo, n = 52	(5) 4.9				(5) 37
Riff 2009	(1) Diclofenac K softgel 25 mg, n = 73	SPID 6:		No data	No data	(1) 19/73
	(2) Placebo, n = 59	(1) 21/102 (2) 3/99				(2) 52/59
Torres 2004	(1) Diclofenac SR 75 mg, n = 68	SPID 6 could not be calculated because baseline pain was not reported	no data	no usable data	no usable data	at 12 hours:
	(2) Valdecoxib 20 mg, n = 68					(1) 39
	(3) Valdecoxib 40 mg, n = 69					(4) 52
	(4) Placebo, n = 67					
Zuniga 2004	(1) Diclofenac K 100 mg, n = 31	TOTPAR 6:	(1) 13/31	at 6 hours:	Mean:	at 6 hours:
	(2) Diclofenac Na softgel 100 mg, n = 29	(1) 9.7	(2) 16/29	(1) 14/31	(1) 4.5	(1) 71
	(3) Placebo, n = 15	(2) 12.2 (3) 0.91	(3) 0/15	(2) 21/29 (3) 1/15	(2) 5 (3) 1.1	(2) 69 (3) 100

(Continued)

Zuniga 2010	(1) Diclofenac K softgel 25 mg, n = 63	TOTPAR 6:	(1) 15/63	No data	(1) 5.1	(1) 34/63
	(2) Diclofenac K softgel 50 mg, n = 62	(1) 6.3	(2) 18/62		(2) > 6	(2) 22/62
	(3) Diclofenac K softgel 100 mg, n = 63	(2) 7.2	(3) 19/63		(3) > 6	(3) 25/63
	(4) Placebo, n = 61	(3) 7.5	(4) 1/61		(4) 1.6	(4) 44/61
		(4) 2.3				

K: potassium; Na: sodium; SPID: summed pain intensity difference; SR: slow release; TOTPAR: total pain relief

Appendix 6. Results for individual studies: adverse events

Study ID	Treatment	Adverse events		Withdrawals	
		Any	Serious	Adverse event	Other
Ahlstrom 1993	(1) Diclofenac (soluble) 50 mg, n = 35	At 6 hours	None reported	None	30 exclusions: various protocol violations
	(2) Ibuprofen (tablets) 400 mg, n = 32	(1) 6/35			
	(3) Placebo, n = 30	(3) 2/30			
		considered treatment-related in 1 diclofenac and 1 ibuprofen participant			
Bakshi 1992	(1) Diclofenac K 50 mg, n = 51	Possibly or probably treatment-related at 6 hours	None	None	29 exclusions: 26 did not need medication, 3 lost to follow-up
	(2) Diclofenac Na (enteric coated) 50 mg, n = 54	(1) 3/51			
	(3) Placebo, n = 46	(2) 1/54			
		(3) 3/46			
Bakshi 1994	(1) Diclofenac (soluble) 50 mg, n = 83	At 6 hours	None reported	None	12 exclusions: various protocol violations
	(2) Ibuprofen 400 mg, n = 80	(1) 4/83			
	(3) Placebo, n = 82	(3) 5/82			
Chang 2002	(1) Diclofenac Na (enteric coated) 50 mg, n = 121	No single dose data	No single dose data	at 36 hours: (3) 1/63 (asthma flare)	None
	(2) Rofecoxib 50 mg, n = 121				
	(3) Placebo, n = 63				
Cooper 1996	(1) Diclofenac Na 50 mg, n = 18	No usable data. All adverse events were transient and mild, and consid-	None		
	(2) Misoprostol 200 µg, n = 21				

(Continued)

	(3) Diclofenac Na + misoprostol 50 mg/200 µg, n = 20 (4) Placebo, n = 11	ered normal sequelae of surgical procedure and probably unrelated to study drug			
Desjardins 2004	(1) Diclofenac Na 100 mg, n = 85 (2) Rofecoxib 50 mg, n = 85 (3) Placebo, n = 82	at 24 hours: (1) 38/85 (3) 41/82	None	(1) 1/85 (3) 3/82	None reported
Herbertson 1995	(1) Diclofenac K 50 mg, n = 52 (2) Diclofenac K 100 mg, n = 52 (3) Aspirin 650 mg, n = 53 (4) Placebo, n = 52	At 8 hours (1) 6/54 (2) 6/55 (4) 2/54	None	8 in total	In total, 8 participants did not contribute to any efficacy analysis, 23 did not contribute to reported TOTPAR 8
Hersh 2004	(1) Diclofenac K 25 mg, n = 63 (2) Diclofenac K 50 mg, n = 68 (3) Diclofenac K 100 mg, n = 66 (4) Placebo, n = 68	At 6 hours (1) 8/63 (2) 8/68 (3) 7/66 (4) 9/68	None reported	None	1 placebo participant unwilling to continue
Hofele 2006	(1) Diclofenac K sachet 50 mg, n = 74 (2) Diclofenac K tablet 50 mg, n = 71 (3) Placebo, n = 39	at 8 hours: (1) 2/74 (2) 2/71 (3) 2/39	None	None	4 exclusions for protocol violations: 2 diclofenac sachet, 1 diclofenac tablet, 1 placebo
Kubitzeck 2003	(1) Diclofenac K 25 mg, n = 83 (2) Paracetamol 1000 mg, n = 78 (3) Placebo, n = 84	at 48 hrs: (1) 6/83 (3) 2/84	None	None	1 placebo participant excluded for protocol violation
Manvelian 2012a	(1) Diclofenac K nanoparticle 18 mg, n = 49 (2) Diclofenac K nanoparticle 36 mg, n = 51 (3) Celecoxib 400 mg, n = 51 (4) Placebo, n = 51	Any treatment-emergent adverse event at 12 hours: (1) 27/49 (2) 31/51 (3) 32/51 (4) 27/51	None reported	None	None reported
Mehlisch 1995	(1) Diclofenac K 50 mg, n = 53 (2) Diclofenac K 100 mg, n = 52	at 7 days: (1) 5/53	None	None	None reported

(Continued)

	(3) Aspirin 650 mg, n = 51	(2) 8/52			
	(4) Placebo, n = 52	(4) 4/52			
Nelson 1994	(1) Diclofenac K 25 mg, n = 50	at 8 hours:	None reported	None	1 participant excluded from safety analysis, 3 excluded from any efficacy analysis, 7 excluded from 8-hour efficacy analysis
	(2) Diclofenac K 50 mg, n = 50	(1) 5/51			
	(3) Diclofenac K 100 mg, n = 50	(2) 4/51			
	(4) Aspirin 650 mg, n = 50	(3) 4/51			
	(5) Placebo, n = 50	(5) 6/51			
Olson 1997	(1) Diclofenac K 25 mg, n = 52	at 8 hours:	None	None	None
	(2) Diclofenac K 50 mg, n = 50	(1) 1/52			
	(3) Diclofenac K 100 mg, n = 51	(2) 0/50			
	(4) Aspirin 650 mg, n = 50	(3) 1/51			
	(5) Placebo, n = 52	(5) 1/52			
Riff 2009	(1) Diclofenac K softgel 25 mg, n = 102	No single dose data			
	(2) Placebo, n = 99				
Torres 2004	(1) Diclofenac SR 75 mg, n = 68	at 12 hours:	None reported	No usable data	No usable data
	(2) Valdecoxib 20 mg, n = 68	(1) 14/65			
	(3) Valdecoxib 40 mg, n = 69	(4) 17/67			
	(4) Placebo, n = 67				
Zuniga 2004	(1) Diclofenac K 100 mg, n = 31	at 24 hours:	None	None	1 participant excluded due to protocol violation
	(2) Diclofenac Na softgel 100 mg, n = 29	(1) 5/31			
		(2) 5/29			
	(3) Placebo, n = 15	(3) 1/15			
		most occurred after rescue medication			
Zuniga 2010	(1) Diclofenac K softgel 25 mg, n = 63	at 6 hours:	None	None	None reported
	(2) Diclofenac K softgel 50 mg, n = 62	(1) 7/63			
	(3) Diclofenac K softgel 100 mg, n = 63	(2) 5/62			
	(4) Placebo, n = 61	(3) 5/63			
		(4) 7/61			

K: potassium; Na: sodium; SR: slow release

WHAT'S NEW

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

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 2, 2004

Date	Event	Description
8 July 2015	Review declared as stable	This review will be assessed for updating in 2018.
10 March 2015	New citation required and conclusions have changed	Change in emphasis to take into account new insights into drug formulation. Results have changed, with significantly improved efficacy found for diclofenac potassium over previous versions of this review
9 March 2015	New search has been performed	New searches. Three new studies (652 participants) added, with 26% increase in number of participants in diclofenac versus placebo comparisons. 'Risk of bias' and 'Summary of findings' tables added
15 September 2011	Review declared as stable	The authors of this review scanned the literature in August 2011 and are confident that there should be no need to update this review until 2015.
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.
23 December 2008	New citation required and conclusions have changed	Eight new studies (1206 participants in comparisons of diclofenac and placebo) were added in December 2008 (Chang 2002a; Cooper 1996 ; Desjardins 2004a; Hersh 2004 ; Hofele 2006 ; Kubitzek 2003 ; Torres 2004 ; Zuniga 2004). Overall the NNT for at least 50% pain relief over 4 to 6 hours was not changed, but the potassium salt was significantly better than the sodium salt.
26 September 2008	New search has been performed	New studies added, analyses updated, additional data on use of rescue medication, and new authors.
22 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For the earliest review: JB and JE were involved with searching, quality scoring, data extraction, analysis, and writing. RAM and HM were involved with planning, quality scoring, analysis, and writing.

For the previous update: PD and SD were involved with searching, data extraction, quality scoring, analysis and writing. RAM was involved in analysis and writing. HM acted as arbitrator and was involved in writing.

For this version of the review, RAM and SD were involved with searching, data extraction, quality scoring, analysis and writing. PW acted as arbitrator and was involved in writing.

SD will be responsible for updating.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

For transparency, SD, PW, and RAM have received research support from charities, government, and industry sources at various times, but none relate to this review. SD, PW, and RAM are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was no protocol for this review. The major difference between this review and previous versions was the addition of 'Risk of bias' and 'Summary of findings' tables, and a concentration on formulation of diclofenac in the analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects] [chemistry]; Chemistry, Pharmaceutical; Cyclooxygenase Inhibitors [administration & dosage] [adverse effects] [chemistry]; Diclofenac [*administration & dosage] [adverse effects] [chemistry]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans