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Single fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults (Review)

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[Intervention Review]

Single fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults

Sheena Derry[1], Tess E Cooper[2], Tudor Phillips[3]

[1]Oxford, UK. [2]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [3]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK

Contact: Sheena Derry, Oxford, Oxfordshire, UK. sheena.derry@retired.ox.ac.uk.

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ABSTRACT

Background

Combining two different analgesics in fixed doses in a single tablet can provide better pain relief than either drug alone in acute pain. This appears to be broadly true across a range of different drug combinations, in postoperative pain and migraine headache. A new combination of dexketoprofen (a nonsteroidal anti-inflammatory drug) plus tramadol (an opioid) has been tested in acute postoperative pain conditions. It is not yet licensed for use. This review is one of a series on oral analgesics for acute postoperative pain. Individual reviews have been brought together in two overviews to provide information about the relative efficacy and harm of the different interventions.

Objectives

To assess the analgesic efficacy and adverse effects of a single fixed-dose of oral dexketoprofen plus tramadol, compared with placebo, for moderate to severe postoperative pain in adults, using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes. A secondary objective was to compare the combination with the individual analgesics alone.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via CRSO, MEDLINE via Ovid, and Embase via Ovid from inception to 31 May 2016. We also searched the reference lists of retrieved studies and reviews, and two online clinical trial registries.

Selection criteria

Randomised, double-blind trials of oral dexketoprofen plus tramadol administered as a single oral dose, for the relief of acute postoperative pain in adults, and compared to placebo.

Data collection and analysis

Two review authors independently considered trials for inclusion in the review, examined issues of study quality and potential bias, and extracted data. For dichotomous outcomes, we calculated risk ratio (RR) and number needed to treat for an additional beneficial outcome (NNT) for dexketoprofen plus tramadol, compared with placebo with 95% confidence intervals (CI). We collected information on the number of participants with at least 50% of the maximum possible pain relief over six hours, the median time to use of rescue medication, and the proportion of participants requiring rescue medication. We also collected information on adverse events and withdrawals. We assessed the quality of the evidence using GRADE and created a 'Summary of findings' table.

We also collected information on the number of participants with at least 50% of the maximum possible pain relief over six hours for dexketoprofen alone and tramadol alone.

Main results

We included three studies with 1853 participants who had undergone surgical removal of impacted wisdom teeth, hip replacement, or hysterectomy. The overall risk of bias across the three included studies was low, with unclear risk of bias in relation to the size of the three studies. Two studies did not report all our prespecified outcomes, which limited the analyses we could do.

The proportion of participants achieving at least 50% pain relief over six hours with dexketoprofen 25 mg plus tramadol 75 mg was 66%, compared to 32% with placebo, giving an NNT of 3.0 (95% CI 2.5 to 3.7) (RR 2.1 (95% CI 1.7 to 2.4); 748 participants; 3 studies) (moderate quality evidence). The response rate with dexketoprofen 25 mg alone was 53% (RR 1.3 (95% CI 1.1 to 1.4); 744 participants; 3 studies) and with tramadol alone was 45% (RR 1.5 (95% CI 1.3 to 1.7); 741 participants; 3 studies) (moderate quality evidence). We downgraded the evidence because of some inconsistency in the results.

The median time to use of rescue medication could not be estimated exactly, but was probably eight hours or more, indicating a long duration of effect (moderate quality evidence). We downgraded the evidence because it was not possible to estimate the effect exactly in the two multiple dose studies, resulting in imprecision. Fewer participants used rescue medication with higher doses of active treatment (summary statistic not calculated; 123 participants; 1 study) (very low quality evidence). We downgraded the evidence because the data came from a single study with few participants and events.

Adverse events and serious adverse events were not reported consistently for the single dose phase of the studies. In the single dose study, 11% of participants experienced adverse events with dexketoprofen 25 mg plus tramadol 75 mg, which were mostly mild or moderate nausea, vomiting, or dizziness, and typical with these medicines. Rates were lower with placebo and lower doses (very low quality evidence). We downgraded the evidence because the data came from a single study with few participants and events. Information on multiple dosing over three and five days supported a low event rate with the combination. Overall, rates were generally low in all treatment arms, as they were for withdrawals for adverse events or other reasons.

Authors' conclusions

A single oral dose of dexketoprofen 25 mg plus tramadol 75 mg provided good levels of pain relief with long duration of action to more people than placebo or the same dose of dexketoprofen or tramadol alone. The magnitude of the effect was similar to other good analgesics. Adverse event rates were low.

There is modest uncertainty about the precision of the point estimate for efficacy, but the NNT of 3 is consistent with other analgesics considered effective and commonly used.

PLAIN LANGUAGE SUMMARY

Fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults

Bottom line

This review found that most people with moderate or severe pain after an operation get good pain relief from taking dexketoprofen 25 mg plus tramadol 75 mg.

Background

Acute pain is short-lived pain often felt soon after injury, including after operations. Most people who have an operation have moderate or severe pain afterwards. Painkillers are tested in people with acute pain, often following 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.

The use of two different painkillers in a single tablet at fixed doses has been found to provide good pain relief to a high proportion of people with moderate or severe pain after an operation. This review examined a new fixed-dose combination of two painkillers, a nonsteroidal anti-inflammatory medicine (dexketoprofen) with an opioid medicine (tramadol).

Study characteristics

In May 2016, we found three studies involving 1853 people. The main comparison was between the fixed-dose of dexketoprofen 25 mg plus tramadol 75 mg and placebo (a dummy treatment). The studies tested single doses after wisdom tooth extraction, hip replacement operations, and gynaecological (female reproductive system) operations. Studies included adults over a range of ages, and 7 out of 10 participants were women. The main outcome was the number of participants having at least half of the maximum possible pain relief over the first six hours after taking the tablets.

Key results

All three studies reported the main outcome for dexketoprofen 25 mg plus tramadol 75 mg. There were 748 participants in the comparison with placebo. About 7 in 10 people achieved this outcome with dexketoprofen 25 mg plus tramadol 75 mg, compared with 3 in 10 with placebo. The combination was significantly better than placebo, and better than either dexketoprofen or tramadol alone. The pain relief

lasted a long time, probably eight hours or more, but the exact duration could not be determined. Fewer people needed to take additional painkillers with the combination treatment than with placebo.

About 1 in 10 people had side effects with dexketoprofen 25 mg plus tramadol 75 mg. These were mostly mild or moderate nausea (feeling sick), vomiting (being sick), and dizziness, which are typical with these medicines. Serious side effects were uncommon. Few people dropped out of the studies.

Quality of the evidence

We judged the quality of the evidence as moderate for the painkilling effect of dexketoprofen 25 mg plus tramadol 75 mg. For side effects we judged the quality of the evidence about a single dose as very low because there were so few participants and events, but we judged it as moderate when we included evidence from the three- and five-day studies. Moderate quality evidence means that more information might change our estimate of the effect. Very low quality evidence means that we are very uncertain about the results.

Summary of findings for the main comparison. Dexketoprofen 25 mg plus tramadol 75 mg compared with placebo for acute postoperative pain

Dexketoprofen 25 mg plus tramadol 75 mg compared with placebo for acute postoperative pain

Patient or population: adults with moderate or severe acute postoperative pain

Settings: clinic or hospital

Intervention: dexketoprofen 25 mg plus tramadol 75 mg

Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR, NNT (95% CI)	Number of studies, participants, events	Quality of the evidence (GRADE)	Comments
Participants with ≥ 50% pain relief over 6 hours	660 in 1000	320 in 1000	RR 2.1 (1.7 to 2.4) NNT 3.0 (2.5 to 3.7)	3 studies, 748 participants, 367 events	Moderate	Downgraded 1 level due to a degree of inconsistency in the results
Median time to use of rescue medication	1.4 hours	> 8 hours	Not applicable	1 study, 62 participants for placebo; 3 studies, 372 participants for combination	Moderate	Downgraded 1 level due to a degree of imprecision[1]
Participants using rescue medication over 6 hours	23/61 events	45/62 events	Not calculated	1 study, 123 participants, 68 events	Very low	Data from a single study with few participants and events means we are very uncertain about the estimate[2]
Participants with ≥ 1 adverse event following a single dose, and after 3 to 5 days	Following a single dose: 7/61 events After 3 to 5 days: 15/406	Following a single dose: 0/62 events	Not calculated	Single dose: 1 study, 123 participants, 7 events 3 to 5 days: 2 studies, 406 participants in combination arm (no placebo arm)	Very low	Data from a single study with few participants and events means we are very uncertain about the estimate[2] Data from the multiple dose studies support a low event rate
Participants with a serious adverse event following a single dose, and after 3 to 5 days	No events following a single dose	No events following a single dose or after 3 to 5 days of treatment	Not calculated	Single dose: 1 study, 123 participants 3 to 5 days: 2 studies, 406 participants in combination	Very low	Data from a single study with few participants and no events means we are very uncertain about the estimate[2] Data from the multiple dose studies support a low event rate

				arm (no placebo arm), no events

CI: confidence interval; **NNT:** number needed to treat for one additional beneficial outcome; **RR:** risk ratio

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

[1] The multiple dose studies were censored at 8 hours (second dose given) and there were few participants providing information with placebo.
[2] It is not possible to make any estimation of effects in the face of very low numbers of events. This means that we are very uncertain about the estimate, and have consequently graded the level of evidence as very low.

BACKGROUND

This review is partly based on suggested wording from the Pain, Palliative and Supportive Care Cochrane Review Group (PaPaS CRG) that has been used in other reviews from this series on oral analgesics for acute postoperative pain. Individual reviews have been brought together in two overviews to provide information about the relative efficacy and harm of the different interventions (Moore 2015a; Moore 2015b).

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.

This is one of a series of reviews whose aim is to increase awareness of the range of analgesics that are potentially available, and 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 person, but guides policy-making at the local level. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in overviews of efficacy and harm (Moore 2015a; Moore 2015b), and related individual reviews include ibuprofen (Derry 2009); paracetamol (acetaminophen) (Toms 2008); ketoprofen and dexketoprofen (Barden 2009); codeine (Derry 2010); and combinations such as ibuprofen plus paracetamol (Derry 2013), ibuprofen plus codeine (Derry 2015), and paracetamol plus codeine (Toms 2009). Single dose tramadol was the subject of a review of otherwise unpublished clinical trial data (Moore 1997a).

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 a 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 one 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. Hence, the use of additional or rescue analgesia is 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 four to six hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome (Moore 2011). 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.

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful (Moore 2015a).

Dexketoprofen

Dexketoprofen is the optically pure S(+)-enantiomer of ketoprofen, (RS)2-(3-benzoylphenyl)-propionic acid. It is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs) and has analgesic and antipyretic effects (Moore 2008a). The trometamol salt of dexketoprofen is thought to be particularly rapidly absorbed from the gastrointestinal tract, giving a rapid onset of effects. The duration of effect is only about four to five hours (Barden 2009).

Dexketoprofen is available as 12.5 mg and 25 mg tablets for oral administration, and injectable and topical forms are also available. It is normally used for the treatment of mild to moderate pain over short periods of time. In postoperative pain, it's license typically limits its use to about one week, but licensed indications vary between countries. In some countries, it is available without prescription.

Tramadol

Tramadol is a synthetic analogue of codeine. Immediate-release formulations are usually as 50 mg tablets or capsules, and oral drops (100 mg/mL) and injectable forms are also available. The analgesic effect of tramadol begins after about one hour, and it lasts for about six hours with the immediate-release formulation (Grond 2004). Sustained-release formulations (12-hour and 24-hour) are available as tablets with doses ranging from 50 mg to 400 mg. It is normally used for treatment of moderate to severe pain.

The fixed-dose combination is currently at the pre-registration phase and not yet available, but marketing approval is likely to be sought in the near future (Menarini 2016).

How the intervention might work

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. Dexketoprofen, like most NSAIDs, causes reversible inhibition of the cyclooxygenases, which interferes with thromboxane and prostaglandin synthesis, and increases production of anti-inflammatory lipoxins.

Dexketoprofen is the S(+)-enantiomer of ketoprofen. This S(+)-enantiomer is responsible for the analgesic effect seen with racemic ketoprofen, while the R(-)-enantiomer is devoid of analgesic activity (Barbanoj 2001). Ketoprofen is one of the most potent in vitro inhibitors of prostaglandin synthesis, but is also implicated as having an association with higher risk of serious gastrointestinal bleeding events than other NSAIDs (Hernández-Díaz 2000; Laporte 2004). Because the R(-)-enantiomer does appear to have ulcerogenic activity, at least in rats (Barbanoj 2001; Herrero 2003), the implication is that use of dexketoprofen alone should produce the same analgesic effect as ketoprofen, but at half the dose, potentially lowering the risk of harm.

Tramadol is a centrally acting analgesic. It has dual action, binding to μ-opioid receptors and also inhibiting serotonin and noradrenaline (norepinephrine) re-uptake, with effects on spinal pain transmission. The (+)-enantiomer of tramadol and its metabolite (+)-O-desmethyl-tramadol are agonists of the μ-opioid receptor, and (+)-tramadol is also an inhibitor of serotonin re-uptake while (-)-tramadol is an inhibitor of noradrenaline re-uptake (Grond 2004). The actions of tramadol are affected by genetic factors, with the principal focus on CYP2D6 polymorphisms, which may be influenced by ethnicity (Lassen 2015).

Combination analgesics

We now have convincing evidence that combining two analgesics can provide additional levels of analgesia in acute pain and headache (Moore 2012; Moore 2015a), and that the drug-specific effects are essentially additive. Results confirm that the assumption that the efficacy of combination analgesics is the sum of the efficacies of the individual analgesic components is broadly true across a range of different drug combinations, in postoperative pain and migraine headache, and when tested in the same and different trials (Moore 2012). There is no convincing evidence for combination analgesics in chronic pain, however (Chaparro 2012).

Why it is important to do this review

No single analgesic provides good levels of pain relief in everyone, and increasing the dose of an analgesic is likely to increase the problems of adverse events. One approach is to combine two analgesics with different modes of action, with the aim of delivering better analgesia using lower doses of each drug, and therefore potentially reducing adverse events. In similar reviews in acute pain, combination analgesics have provided some of the best results (Moore 2015a).

The pharmaceutical company, Menarini, has developed a fixed combination of oral dexketoprofen trometamol and tramadol hydrochloride to treat acute pain of moderate to severe intensity. Their rationale was based on the two drugs having different mechanisms of action (peripheral and central) and different pharmacokinetic profiles (rapid onset and long duration). This combination has been tested in clinical trials, is currently at a pre-registration phase, and marketing approval is likely to be sought in the near future (Menarini 2016).

OBJECTIVES

To assess the analgesic efficacy and adverse effects of a single fixed-dose of oral dexketoprofen plus tramadol, compared with placebo, for moderate to severe postoperative pain in adults, using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes. A secondary objective was to compare the combination with the individual analgesics alone.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), with at least 10 participants randomly allocated to each treatment group, and double-blind assessment of participant outcomes. 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 or could be obtained.

We excluded:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies of less than four hours' duration or studies that did not present data over four to six hours post dose.

For postpartum pain, we planned to include studies if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps, but to exclude studies investigating pain due to uterine cramps alone. In the event, there were no studies of postpartum pain.

We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis.

Types of participants

We included studies of adults (aged over 15 years) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analogue scale (VAS) (see 'Glossary'; Appendix 1), we considered that pain intensity of greater than 30 mm equated to pain of at least moderate intensity (Collins 1997).

Types of interventions

Dexketoprofen plus tramadol, administered as a single oral dose, for the relief of acute postoperative pain, and compared to placebo.

Types of outcome measures

Primary outcomes

- Participants achieving at least 50% pain relief over a four- to six-hour period.

Secondary outcomes

- Median (or mean) time to use of rescue medication.

- Number of participants using rescue medication over a four- to six-hour period.
- Number of participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event, at the end of the (single dose) study period.
- Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication) at the end of the (single dose) study period.

Quality of the evidence

Two review authors (TC, SD) independently rated the quality of each outcome. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro GDT 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (Appendix 2).

'Summary of findings' table

We have included a 'Summary of findings' table as set out in the PaPaS author guide (PaPaS 2012) and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 4.6.6 (Higgins 2011), to present the main findings for the comparison of dexketoprofen plus tramadol with placebo in a transparent and simple tabular format. In particular, we have included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of at least 50% pain relief over four to six hours, participants using rescue medication within four to six hours, participants with at least one adverse event, and participants with a serious adverse event. We chose not to include additional summary tables for the comparisons of dexketoprofen plus tramadol with the individual drugs because the studies were not powered to show these differences, and they would include only one outcome each.

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) on 31 May 2016.
- MEDLINE (via Ovid) from 1946 to 31 May 2016.
- EMBASE (via Ovid) from 1974 to 31 May 2016.

We tailored searches to individual databases using controlled vocabulary appropriate for each search platform and text word terms. The search strategy for CENTRAL, MEDLINE, and EMBASE are in Appendix 3, Appendix 4, and Appendix 5, respectively.

Searching other resources

We searched clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we checked reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials. We also contacted study authors where necessary for additional information.

Data collection and analysis

Selection of studies

Two review authors (TC, SD) independently determined eligibility by reading the abstract of each study identified by the search. Review authors independently eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. They read these studies independently to select relevant studies; a third review author (TP) would have adjudicated in the event of disagreement, but was not required. We did not anonymise the studies before assessment. We have included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart, to show the status of identified studies (Moher 2009), as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011). We included studies in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Data extraction and management

Two review authors (TC, SD) independently extracted data using a standard form and the third author (TP) checked for agreement before entry into Review Manager 5 (RevMan 2014). We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We collected information about the included studies (e.g. study methods, study population, baseline pain intensity) in sufficient detail to complete a 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors (TC, SD) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We have completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager 5 (RevMan 2014).

We assessed the following for each study.

- 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, e.g. 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 (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether 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 (e.g. 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 (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical

tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.

- Blinding of outcome assessment (checking for possible detection bias). In this review, outcomes were self assessed, so that the same considerations apply to detection bias as performance bias.
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We used risk ratio (RR) to establish statistical difference, and number needed to treat for an additional beneficial outcome (NNT) and pooled percentages as absolute measures of effect with 95% confidence intervals (CI).

We planned to use 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 additional harmful event (NNTp).
- When significantly more adverse outcomes occurred with treatment compared with control (placebo or active), we used the term the number needed for one additional harmful event (NNH).

Unit of analysis issues

We accepted only randomisation of the individual participant. For multiple dose studies, we used data for the first dose only. There were no cross-over studies.

Dealing with missing data

The only likely issue with missing data in these studies was from imputation using last observation carried forward when a participant 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, and using the I^2 statistic.

Assessment of reporting biases

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 8 or higher in this condition; Moore 2008b).

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.

For each study, we planned to convert the mean total pain relief (TOTPAR), or summed pain intensity difference (SPID), VAS TOTPAR, or VAS SPID (see 'Glossary'; Appendix 1) values for the active and placebo groups to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). We would then calculate the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b), convert 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 would have accepted the following pain measures for the calculation of TOTPAR or SPID (in order of priority: see Appendix 1).

- 5-point categorical pain relief (PR) scales with comparable wording to 'none', 'slight', 'moderate', 'good', and 'complete'.
- 4-point categorical pain intensity (PI) scales with comparable wording to 'none', 'mild', 'moderate', and 'severe'.
- VAS for pain relief.
- VAS for pain intensity.

In the event, all the included studies provided dichotomous information on the number of participants with this outcome at six hours ('TOTPAR responders at six hours'), derived from individual participant data. We used this information for active and placebo groups to calculate RR and NNT.

We also calculated 'response' using the number of participants reporting 'very good or excellent' on a 5-point categorical global scale with the wording 'poor', 'fair', 'good', 'very good', and 'excellent' for the number of participants achieving at least 50% pain relief (Collins 2001).

For each treatment group, we extracted the number of participants using rescue medication and the number reporting treatment-emergent adverse events.

We calculated RR estimates with 95% CIs using the Mantel-Haenszel method and a fixed-effect model in Review Manager 5 (RevMan 2014). We calculated NNT and NNH with 95% CIs using the pooled number of events and the method of Cook and Sackett (Cook 1995). We have assumed a statistically significant difference from control when the 95% CI of the RR did not include the number one. We required a minimum of two studies and 200 participants (in the comparison) for any pooled analysis.

We did not plan to pool data from individual studies for time to use of rescue medication.

Subgroup analysis and investigation of heterogeneity

We planned to analyse different doses separately, where there were sufficient data, and determine significant differences between different doses using the z test (Tramèr 1997). In the event, there were sufficient data for pooled analysis of only one dose.

Sensitivity analysis

We did not plan any sensitivity analyses, but have explored apparent heterogeneity in the analysis of the primary outcome by

using random-effects analysis, and by testing the effect of removing one study.

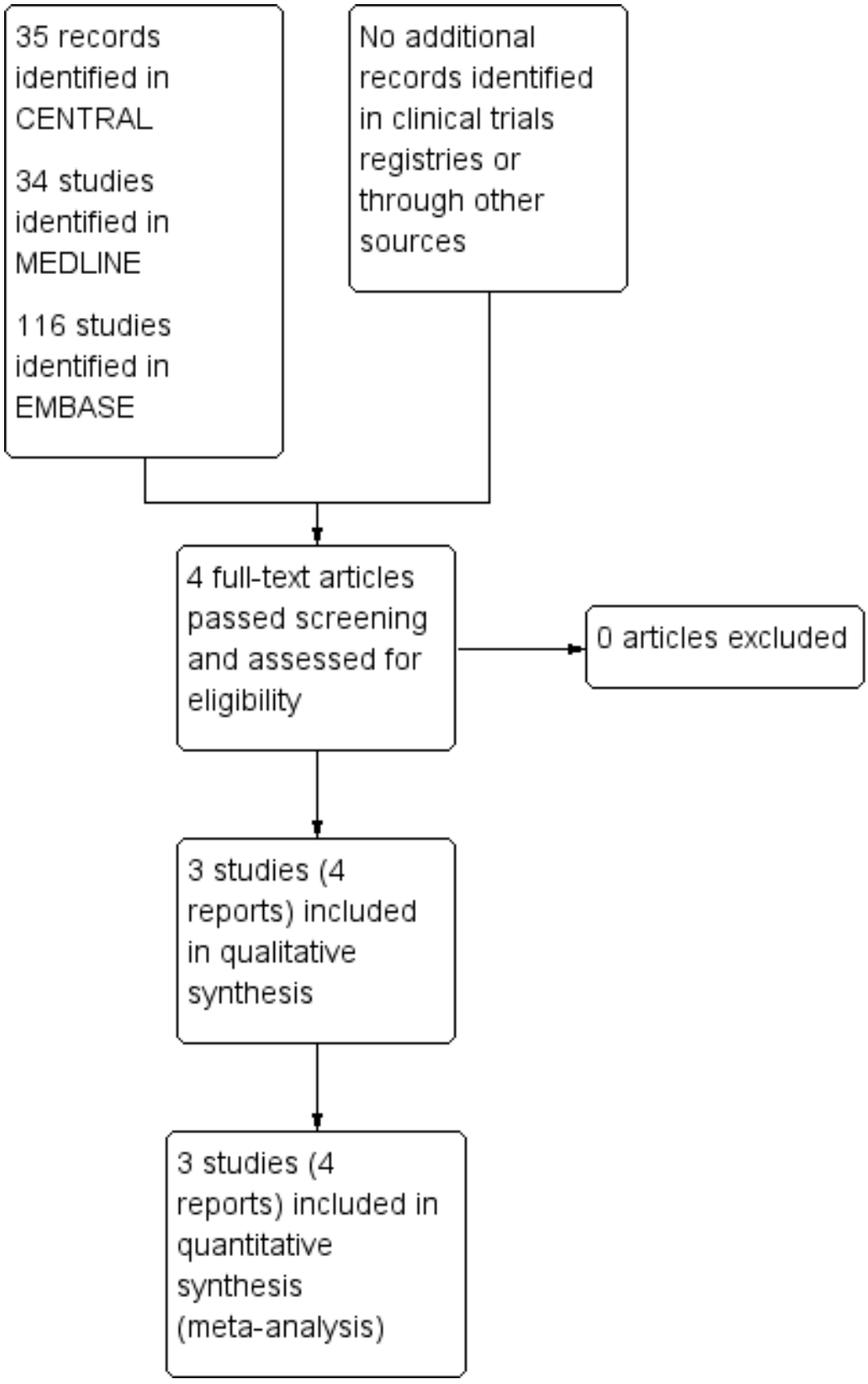
RESULTS

Description of studies

Results of the search

Searches identified four reports of three studies in bibliographic databases. We identified no additional studies in clinical trial registries or through contact with experts in the field (see Figure 1).

Figure 1. Study flow diagram.



Included studies

We identified three studies that satisfied our inclusion criteria (McQuay 2016; Moore 2015; Moore 2016). One study had been published in both an English language journal and a Spanish journal (McQuay 2016).

All the studies were randomised, double-blind, parallel group studies, using one or more fixed-dose combinations of dexketoprofen plus tramadol compared with placebo, dexketoprofen alone, and tramadol alone. All three studies were multicentre studies conducted at more than 50 sites ranging across Russian Federation, Taiwan, and 14 European countries.

Studies recruited participants aged 18 years or older (mean ages ranged from 27 to 62 years); 71% (1311) were women. Moore 2015 enrolled participants who had undergone surgical removal under local anaesthetic of one or more impacted third molar teeth, and who experienced moderate to severe pain within four hours of surgery. Participants received a single dose of study medication. McQuay 2016 included men and women who had undergone standard unilateral hip arthroplasty due to osteoarthritis and experienced moderate or severe pain at rest on the day after surgery. Participants received study medication every eight hours for five days, but data were presented separately for the first dose. Moore 2016 enrolled women who had undergone abdominal hysterectomy for benign conditions and experienced moderate to severe pain after the cessation of postoperative analgesia. Participants received study medication every eight hours for three days, but data were presented separately for the first dose.

The three studies involved 1853 participants treated with various combinations of dexketoprofen plus tramadol, dexketoprofen alone, tramadol alone, and placebo. Moore 2015 also included ibuprofen as an active comparator. The studies used the following treatments.

- Dexketoprofen 12.5 mg plus tramadol 37.5 mg (Moore 2015), n = 60.
- Dexketoprofen 12.5 mg plus tramadol 75 mg (Moore 2015), n = 62.
- Dexketoprofen 25 mg plus tramadol 37.5 mg (Moore 2015), n = 63.
- Dexketoprofen 25 mg plus tramadol 75 mg (McQuay 2016; Moore 2015; Moore 2016), n = 372.
- Dexketoprofen 12.5 mg (Moore 2015), n = 60.
- Dexketoprofen 25 mg (McQuay 2016; Moore 2015; Moore 2016), n = 372.
- Tramadol 37.5 mg (Moore 2015), n = 59.
- Tramadol 75 mg (Moore 2015), n = 59.
- Tramadol 100 mg (McQuay 2016; Moore 2016), n = 311.
- Ibuprofen 400 mg (Moore 2015), n = 60.
- Placebo (McQuay 2016; Moore 2015; Moore 2016), n = 376.

The main exclusion criteria for the studies were a contraindication to any of the study medications, significant medical condition that might interfere with the study, including moderate or severe renal dysfunction, severe hepatic or cardiac dysfunction, chronic opioid use, and a history of gastrointestinal disorder or drug or alcohol abuse.

Full details are in the Characteristics of included studies table.

Excluded studies

We did not exclude any studies after reading the full reports.

There are no studies awaiting classification or ongoing trials related to this topic.

Risk of bias in included studies

The overall risk of bias across the three included studies was low, with some unclear risk of bias in relation to the size of the three studies (see Figure 2; Figure 3).

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

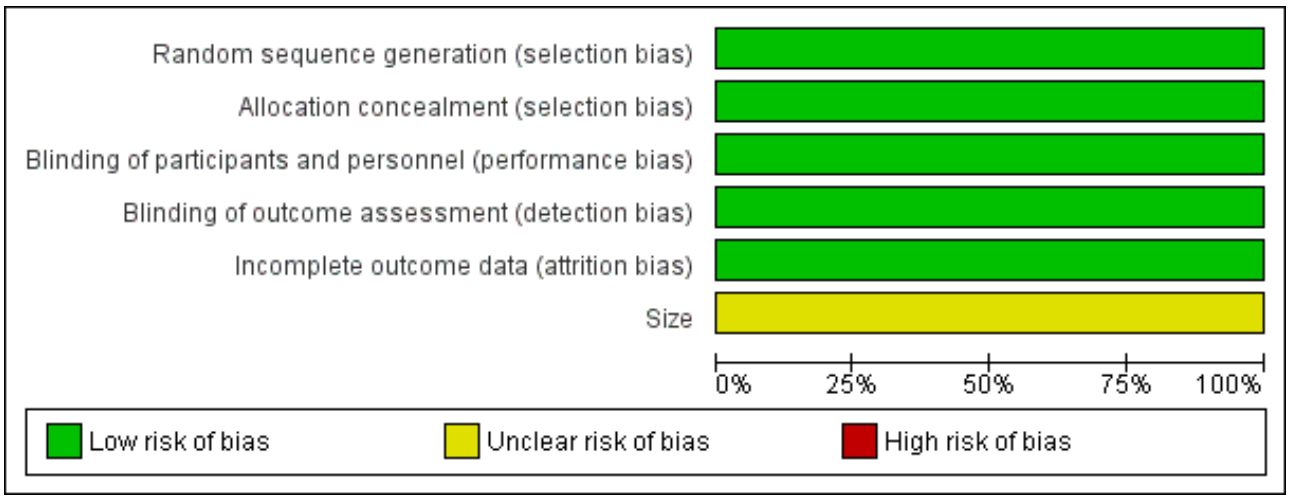
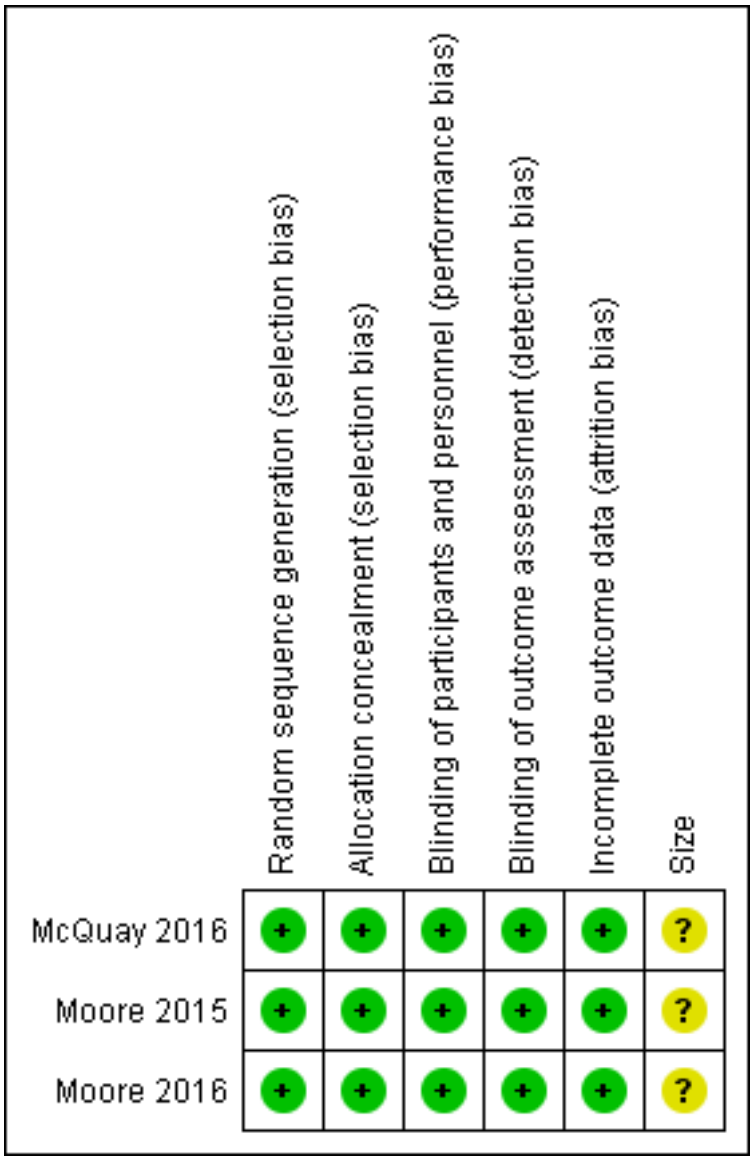


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All three studies used computer-generated randomisation methods, with block size of 10 or 12 to randomise participants, and used interactive voice/web response systems to allocate participants to their respective treatment groups. We judged the risk of bias for randomisation and allocation to be low.

Blinding

All three studies used a double-dummy method to maintain blinding of both participants and personnel. We judged them to be at low risk of bias for performance and detection bias.

Other potential sources of bias

The studies included between 50 and 199 participants per treatment arm, which we judged to present an unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Dexketoprofen 25 mg plus tramadol 75 mg compared with placebo for acute postoperative pain

Details of outcomes in individual studies are in Appendix 6 (efficacy) and Appendix 7 (adverse events and withdrawals).

Number of participants achieving at least 50% pain relief over a six-hour period

All studies reported the number of participants achieving at least 50% pain relief over a period of six hours. There were sufficient data for analysis of only the dexketoprofen 25 mg plus tramadol 75 mg dose. Results for all other dose combinations compared with placebo are tabulated in 'Summary of results A'.

Dexketoprofen 25 mg plus tramadol 75 mg versus placebo

All three studies provided data comparing dexketoprofen 25 mg plus tramadol 75 mg with placebo over six hours ('TOTPAR responders at six hours') (748 participants, McQuay 2016; Moore 2015; Moore 2016).

- The proportion of participants experiencing at least 50% pain relief over six hours with dexketoprofen 25 mg plus tramadol 75 mg was 66% (246/372; range 61% to 72%).
- The proportion of participants experiencing at least 50% pain relief over six hours with placebo was 32% (121/376; range 10% to 41%).
- The RR was 2.1 (95% CI 1.7 to 2.4); the NNT for at least 50% pain relief over six hours was 3.0 (95% CI 2.5 to 3.7) (Figure 4; Figure 5).

Figure 4. Forest plot of comparison: 1 Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus placebo, outcome: 1.1 Participants with ≥ 50% pain relief over 6 hours.

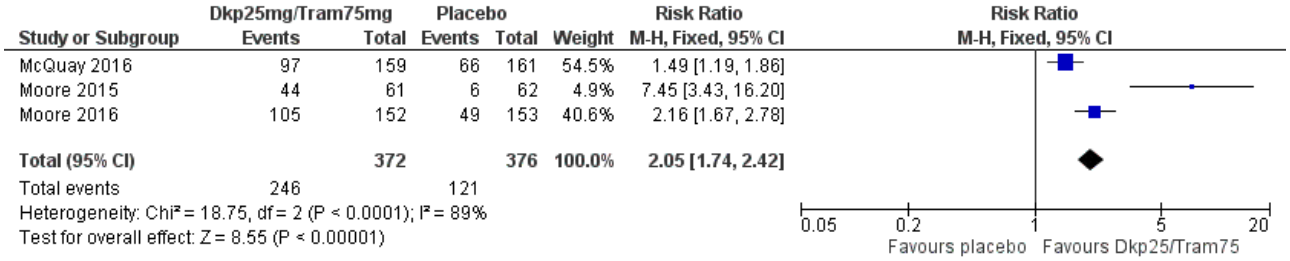


Figure 5. Studies comparing dexketoprofen 25 mg plus tramadol 75 mg with placebo, with the outcome of at least 50% maximum pain relief (PR) over 6 hours. The size of the circle is proportional to the size of the comparison. Yellow: Moore 2015; pink: Moore 2016; blue: McQuay 2016.

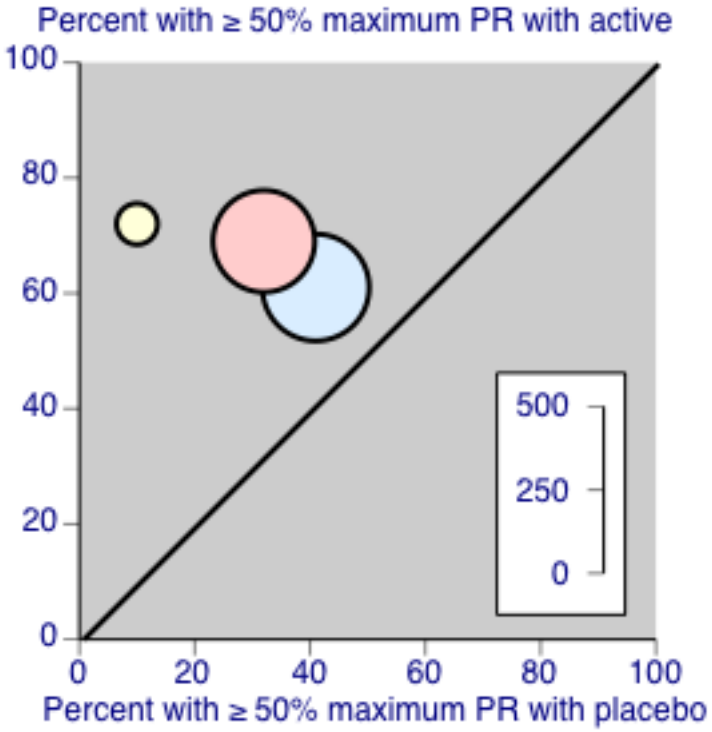


Figure 4 (I^2 = 89%) and Figure 5 indicated possible heterogeneity. Although we might expect apparent heterogeneity with a small number of studies, we carried out the analysis using a random-effects model; the RR was then 2.5 (95% CI 1.4 to 4.5), which is not significantly different. We also carried out a sensitivity analysis to investigate the effect of removing the single dose dental study; the RR was then 1.8 (95% CI 1.5 to 2.1) (fixed-effect) and 1.8 (95% CI 1.2 to 2.1) (random-effects); the I^2 statistic remained high at 79%. The NNT increased when Moore 2015 was removed, but not significantly so.

We judged the quality of the evidence as moderate because, while there was some uncertainty about the precision of the estimate, there was a consistent direction of response and size of response

with active treatment. Variability arose from the placebo response rates in these studies (see Summary of findings for the main comparison).

Summary of results A: number of participants with ≥ 50% pain relief over 6 hours in comparison with placebo

Dose: Dkp/Tram (mg)	Studies	Participants	Dkp + Tram (%)	Placebo (%)	NNT (95% CI)
12.5/37.5*	1	122	37	10	Not calculated
12.5/75*	1	124	60	10	Not calculated
25/37.5*	1	125	56	19	Not calculated
25/75	3	748	66	32	3.0 (2.5 to 3.7)

CI: confidence interval; Dkp: dexketoprofen; NNT: number needed to treat for one additional beneficial outcome; Tram: tramadol

* Data derived from one small comparison in the dental pain model and should be interpreted with caution.

Dexketoprofen 25 mg plus tramadol 75 mg versus dexketoprofen 25 mg

All three studies provided data comparing dexketoprofen 25 mg plus tramadol 75 mg with dexketoprofen 25 mg alone over six hours ('TOTPAR responders at six hours') (744 participants, McQuay 2016; Moore 2015; Moore 2016).

- The proportion of participants experiencing at least 50% pain relief over six hours with dexketoprofen 25 mg plus tramadol 75 mg was 66% (246/372; range 61% to 72%).
- The proportion of participants experiencing at least 50% pain relief over six hours with dexketoprofen 25 mg was 53% (197/372; range 48% to 57%).
- The RR (fixed-effect) was 1.3 (95% CI 1.1 to 1.4); the NNT for at least 50% pain relief over six hours was 7.6 (95% CI 5.0 to 16) (Analysis 2.1).

The I^2 statistic was 61%, indicating possible heterogeneity. The RR using the random-effects model was 1.3 (95% CI 1.03 to 1.5). The combination was significantly better than dexketoprofen alone. We judged the quality of the evidence as moderate because, while there was some uncertainty about the precision of the estimate, there was a consistent direction of response and size of response with active treatment.

Dexketoprofen 25 mg plus tramadol 75 mg versus tramadol 75 mg or 100 mg

Two studies compared dexketoprofen 25 mg plus tramadol 75 mg with tramadol 100 mg (McQuay 2016; Moore 2016), and one with tramadol 75 mg (Moore 2015). We chose to combine the two doses of tramadol in an exploratory analysis (741 participants).

- The proportion of participants experiencing at least 50% pain relief over six hours with dexketoprofen 25 mg plus tramadol 75 mg was 66% (246/372; range 61% to 72%).
- The proportion of participants experiencing at least 50% pain relief over six hours with tramadol 75 mg or 100 mg was 45% (165/369; range 25% to 54%).
- The RR (fixed-effect) was 1.5 (95% CI 1.3 to 1.7); the NNT for at least 50% pain relief over six hours was 4.7 (95% CI 3.5 to 6.9) (Analysis 3.1).

The I^2 statistic was 87%, indicating possible heterogeneity. The RR using the random-effects model was 1.7 (95% CI 1.1 to 2.5). The combination was significantly better than tramadol alone. We judged the quality of the evidence as moderate because while there was some uncertainty about the precision of the estimate, there was a consistent direction of response and size of response with active treatment.

Median time to use of rescue medication

The multiple dose studies gave a second dose of medication after eight hours (McQuay 2016; Moore 2016), and at that time point fewer than 50% of participants had requested rescue medication, so the median time to use was in excess of eight hours and could not be calculated.

Moore 2015 did report median time to use of rescue medication, which ranged from 4.9 to 8.5 hours with combination therapies, 3.6 to 5.6 hours with dexketoprofen alone, and 2.2 to 2.5 hours with tramadol alone, compared with 7.1 hours with ibuprofen 400 mg and 1.4 hours with placebo. Full details are in Appendix 6.

We judged the quality of the evidence for time to use of rescue medication as moderate because, while there remained uncertainty about the precision of the estimate, all three studies indicated a long duration of treatment, of eight hours or more for the dexketoprofen 25 mg plus tramadol 75 mg combination.

Number of participants using rescue medication over six hours

The multiple dose studies did not report participants using rescue medication (McQuay 2016; Moore 2016).

Moore 2015 did report the outcome, but no analysis was carried out because there were so few data. Fewer participants used rescue medication with the combination therapy and ibuprofen 400 mg

than with dexketoprofen or tramadol alone, or with placebo. Full details are in Appendix 6.

We judged the quality of the evidence for participants using rescue medication as very low because the data derive from a single study with low numbers of participants in each treatment arm.

Adverse events

Number of participants with any adverse event

The multiple dose studies did not report number of participants with any adverse event for the single dose phase. McQuay 2016 reported adverse event rates of about 3% with dexketoprofen 25 mg plus tramadol 75 mg, compared with about 5% with dexketoprofen 25 mg or tramadol 75 mg alone, over up to five days. Moore 2016 reported slightly higher rates of about 9% with the combination, 15% with dexketoprofen, and 13% with tramadol, over three days.

Moore 2015 reported the number of participants with any adverse event over 24 hours, following a single dose. The absolute number of events was low, ranging from 0% to 17%, and was generally higher with tramadol and tramadol combinations.

We judged the quality of the evidence from the single dose study for participants experiencing any adverse event as very low because it was from a single study with low numbers of participants and events. However, when considered together with the results from the multiple dose studies, we judged the quality of the evidence as moderate because of the larger body of data (3 studies, 1853 participants) and consistent event rates.

Serious adverse events

The multiple dose studies did not report serious adverse events for the single dose phase. McQuay 2016 reported serious adverse events in one participant treated with the combination and one treated with dexketoprofen alone, over five days. Moore 2016 reported serious adverse events in 11 participants over three days; one was judged to be treatment related, in a participant treated with the combination. Moore 2015 reported one serious adverse event in a participant treated with tramadol alone. This participant was said to have experienced mild dizziness, but was admitted to hospital for observation.

We judged the quality of the evidence from the single dose study for participants experiencing a serious adverse event as very low because it was from a single study with few participants and there were hardly any events. When we considered all the evidence from the three studies, we judged the quality as moderate because of the larger body of data (3 studies, 1853 participants) and all three consistently reported few events.

Withdrawals

Adverse event withdrawals

There were no adverse event withdrawals during the single dose phase in McQuay 2016 or Moore 2015. Moore 2016 reported two adverse event withdrawals in each of the combination, dexketoprofen alone, and placebo treatment arms, and none in the tramadol treatment arm.

Other withdrawals

All studies reported on withdrawals for reasons other than adverse events during the single dose phase, but there were too few events for sensible analysis. There was no evidence of a difference between treatment groups.

Overall, we judged the quality of the evidence for participants experiencing a withdrawal for any reason as moderate because, while we were unable to calculate a summary statistic, the studies consistently reported few events (3 studies, 1853 participants).

Full details of all adverse events and withdrawals are in Appendix 7.

DISCUSSION

Summary of main results

We identified three studies for inclusion, which provided data from 748 participants for the comparison of dexketoprofen 25 mg plus tramadol 75 mg with placebo. There were insufficient data for analysis of any other dose combinations. We have moderate quality evidence that the combination of dexketoprofen 25 mg and tramadol 75 mg provided better analgesia than placebo. The number of participants and events (3 studies, 748 participants, 367 events) was above the threshold needed to be sure of the NNT ± 0.5 in these trials (Moore 1998), but we downgraded one level because the point estimate differed between different acute pain models. We are sure that it is better than placebo, but consider that there is modest uncertainty over the magnitude of the effect. However, the NNT of 3 is consistent with other analgesics considered effective and commonly used (Moore 2015a). Our confidence in estimates of remedication rates and adverse events is very low because they were reported in a single trial with a small number of events for each. There were insufficient data to determine whether using a lower dose of each drug in the combination could provide equivalent benefit to a higher dose of the individual components. If this were so, it could also result in fewer adverse events.

There were 744 participants for the comparison of dexketoprofen 25 mg plus tramadol 75 mg with dexketoprofen 25 mg alone, and 741 participants for the comparison of dexketoprofen 25 mg plus tramadol 75 mg with tramadol 75 mg or 100 mg alone. Dexketoprofen 25 mg plus tramadol 75 mg was significantly better than either drug alone at the same dose as in the combination.

The proportion of participants achieving at least 50% pain relief over six hours with dexketoprofen 25 mg plus tramadol 75 mg was 66%, compared to 32% with placebo, giving an NNT of 3.0 (95% CI 2.5 to 3.7). The proportion of participants achieving at least 50% pain relief over six hours with dexketoprofen 25 mg alone was 53%, giving an NNT for dexketoprofen 25 mg plus tramadol 75 mg compared with dexketoprofen alone of 7.6 (95% CI 5.0 to 16). The proportion of participants achieving at least 50% pain relief over six hours with tramadol 75 mg or 100 mg alone was 45%, giving an NNT for dexketoprofen 25 mg plus tramadol 75 mg compared with tramadol alone of 4.7 (95% CI 3.5 to 6.9).

Median time to use of rescue medication could not be calculated for the multiple dose studies because fewer than 50% of participants in any of the treatment arms had received rescue medication by the time the single dose phase finished and participants received their second dose of medication. By contrast, the median time to use of rescue medication was eight hours or less in all treatment arms in

the single dose study in dental pain. In this study, higher doses of study drug (and ibuprofen) resulted in longer times to remedication than lower doses or placebo. The number of participants using rescue medication was not reported for the single dose phase of the multiple dose studies, but was lower for the higher doses of active treatment in the single dose study.

Rates of adverse events were not reported for the single dose phase of the multiple dose studies. In the single dose dental study, rates were higher over 24 hours with active treatment than with placebo, but there were too few events to draw any conclusions. There were few serious adverse events, and only one with tramadol alone specifically reported following a single dose (stated to be mild, but admitted to hospital for observation). Withdrawals due to adverse events or other reasons were also few, and not clearly related to treatment.

The two multiple dose studies did report on adverse events and adverse event withdrawals over three days (Moore 2016), or five days (McQuay 2016), but without a placebo group for comparison. The proportion of participants experiencing any adverse event was slightly lower with the combination than with the individual drugs (tramadol alone was given at 100 mg rather than 75 mg in the combination), and was similar in rate to the single dose study. Knowing that the rate of experiencing any adverse event remains fairly constant over multiple doses and several days is of greater clinical importance than information from a single dose.

Overall completeness and applicability of evidence

This review identified only a small number of studies, with sufficient data for analysis of only one dose combination. The amount of information was limited further because the multiple dose studies did not report on all our outcomes of interest due to the nature of the study design. For the combination of dexketoprofen 25 mg plus tramadol 75 mg, the primary outcome indicated improved efficacy compared with the individual components. This is in agreement with what is already known about combination therapy (Moore 2012). The results from the dental study were excellent, but these were based on few participants in only one study, and should be interpreted with caution.

The studies included participants with three different painful conditions: total hip arthroplasty, third molar surgery, and hysterectomy. Only about a third of the available data came from participants following third molar extraction; in single dose oral studies generally, dental extraction studies predominate, typically providing about 80% of the available data (Moore 2015a). While the available evidence shows no consistent difference in effect size between different pain models (Barden 2004), few studies have been done testing single dose analgesia as part of a longer multiple dose postoperative analgesic trial. The dexketoprofen plus tramadol combination provided good pain relief (at least 50% of the maximum pain relief) for 61% to 72% of participants, while the placebo response rate varied from 10% (third molar extraction) to 41% (hip replacement).

This difference in placebo response rates may have accounted for much of the heterogeneity when these studies were pooled for analysis, so we also carried out analyses for the primary outcome using a random-effects model, despite there being only three modestly sized studies, together with a sensitivity analysis removing the dental study. These methods changed the point estimate slightly, but not significantly, and gave wider CIs; the I^2 statistic remained high, as anticipated with only two studies remaining. While it seems plausible that there could be fundamental differences in response to analgesia between participants undergoing third molar surgery under local anaesthetic or more substantial surgery under general anaesthetic, this remains to be proven and would require larger data sets for the different types of surgery, particularly in the circumstance here for the two non-dental studies with higher placebo response rates. Other analgesics have been shown to perform similarly in different types of postoperative pain of comparable severity, and clinical practice demonstrates applicability across different types of acute nociceptive pain (Barden 2004).

The included studies excluded people who had significant medical conditions that might interfere with the study or contraindications that might put them at risk from the study medication. These exclusions are typical for clinical trials, but may limit applicability of the results to a wider population.

These studies investigated treatment of acute pain for short periods of time, and these results cannot necessarily be extrapolated to longer term use. In particular, studies using a single dose or short duration treatment do not provide adequate information about adverse events over longer periods of use.

Quality of the evidence

Included studies were properly randomised and double-blind, and provided information about withdrawals and drop-outs. They recruited participants with adequate baseline pain and used clinically useful outcome measures. We did not formally assess potential bias from incomplete outcome data because this is not an issue in these short (six- to eight-hour) single dose studies that use standardised methods and ITT analysis. Selective reporting bias is also not an issue for efficacy in these studies because we use outcomes that are of proven clinical value, and where they are not reported, they can usually be calculated. In this review, all three studies reported our prespecified primary outcome. The studies themselves were of high quality and validity, but the number of studies and sample sizes for some comparisons were somewhat limited, although larger than many other comparisons in the single dose acute pain literature (Moore 2015a).

We judged the quality of the evidence for the primary outcome as moderate because there was some uncertainty about the precision of the estimate but a consistent direction of response, and size of response with active treatment. Given what is known about study size and estimates of effect (Moore 1998), we considered rating this outcome as high quality, but chose to be conservative. For other outcomes derived from a single study with few participants and events, we judged the quality of the evidence to be very low. However, when considered together with data from the multiple dose studies, we rated the quality as moderate because of consistent (low) event rates.

Potential biases in the review process

We carried out extensive searches to identify studies, and consulted the manufacturer of the combination treatment, so feel confident that no unidentified studies remain. We calculated that for dexketoprofen 25 mg plus tramadol 75 mg, an additional 1250 participants would have to have been involved in unpublished trials

with zero treatment effects for the NNT for at least 50% pain relief to increase above 8, a level we consider to be the limit of clinical utility for this pain condition and outcome (Moore 2008b). It seems highly unlikely that this amount of unidentified information could exist.

All the studies were sponsored by Menarini, but we know of no evidence to show that this is likely to influence the results (Barden 2006). There are no other known potential biases in the review process.

Agreements and disagreements with other studies or reviews

We are unaware of any previous systematic reviews of dexketoprofen plus tramadol in acute pain in adults. The results for dexketoprofen alone compared with placebo were similar, but slightly better, in an earlier review of ketoprofen and dexketoprofen, mainly due to a lower placebo response rate (Barden 2009).

AUTHORS' CONCLUSIONS

Implications for practice

For people with moderate to severe acute pain

A single oral dose of dexketoprofen 25 mg plus tramadol 75 mg provided good levels of pain relief to more people than placebo or the same dose of dexketoprofen or tramadol alone. The magnitude of the effect is similar to other analgesics generally considered effective in postoperative pain.

For clinicians

A single oral dose of dexketoprofen 25 mg plus tramadol 75 mg provided good levels of pain relief with long duration of action to more people than the same dose of dexketoprofen or tramadol alone. The magnitude of the effect is similar to other good analgesics, as reported in Cochrane reviews of individual analgesics and in two overviews. Adverse event rates were low, and possibly lower than with single drugs, but this was based on very low and moderate quality evidence and should be interpreted with caution.

For policy makers

Dexketoprofen 25 mg plus tramadol 75 mg is an effective analgesic in acute pain when compared with placebo. There is modest uncertainty about the precision of the point estimate for efficacy, but the number needed to treat for an additional beneficial outcome (NNT) of 3 is consistent with other analgesics considered effective and commonly used.

For funders

Dexketoprofen 25 mg plus tramadol 75 mg is an effective analgesic in acute pain when compared with placebo. There is modest uncertainty about the precision of the point estimate for efficacy, but the NNT of 3 is consistent with other analgesics considered effective and commonly used.

Implications for research

General

This review confirms that fixed-dose combination analgesics provide good levels of pain relief in a large proportion of people with acute pain. It is not clear from the available data whether lower doses of dexketoprofen and tramadol in the combination can provide the same level of efficacy as standard doses of the individual drugs, possibly with reduced adverse events. Studies with larger numbers of participants in treatment arms using low-dose combinations would be required to investigate this.

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. 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 studies in this review demonstrate that adherence to CONSORT and similar guidelines, and the extensive use of online supplementary material, provides a case study on good reporting of clinical trial methods and results.

ACKNOWLEDGEMENTS

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This review was part of the 'PaPaS Express' project, which aimed to produce a full Cochrane review rapidly, and test for pinch-points and weaknesses in the review process. The review was chosen for this pilot project because it is part of a series of reviews that use the same well-established and verified methods; it was known in advance that there was an adequate, but not excessive, number of relevant studies; and combination therapies may provide a way to maximise benefit while keeping doses low and minimising harm. We thank all contributors who provided rapid responses during the development of this review, including peer reviewers, CEU screening team, copy edit support, and Review Group editors. For more information, contact the Pain, Palliative and Supportive Care Review Group (PaPaS) office.

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CHARACTERISTICS OF STUDIES

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

McQuay 2016

Methods	Multicentre Randomised Double-blind (double-dummy) Placebo controlled (first dose), active comparator, parallel group Medication administered orally every 8 h over 5-day period. First dose administered after cessation of postoperative analgesia once participants able to take oral medication and PI ≥ 40/100 Imputation • Single missing values linearly interpolated • LOCF for multiple missing values, unless due to sleep, when WOCF used (single dose phase) • If rescue medication used, BOCF for following 6 h
Participants	**Inclusion criteria:** men and women aged 18 to 80 years. Standard unilateral total hip arthroplasty due to osteoarthritis. Moderate to severe pain at rest on day after surgery

McQuay 2016 *(Continued)*

	Exclusion criteria: contraindication to study drug, required analgesics other than study drug, moderate or severe renal dysfunction, severe hepatic or cardiac dysfunction, chronic opioid use, pregnant, breastfeeding, Hx GI disorder, bleeding, severe asthma, epilepsy, drug or alcohol abuse N = 641 M 295, F 346 Mean age 62 years (29 to 80) Baseline PI: moderate in 324, severe in 315
Interventions	Single dose phase Dkp/Tram 25/75 mg, n = 159 Dkp 25 mg, n = 161 Tram 100 mg, n = 160 Placebo, n = 161 • Rescue medication: metamizole 500 mg • Various non-analgesic medications restricted
Outcomes	**Primary outcomes** • From first dose: PI and PR at 30 min, and 1, 1.5, 2, 3, 4, 6, 8 h Scales: PI 0 to 100 mm VAS; PR 5-point VRS (0 = none, 4 = complete) Used to calculate SPID and TOTPAR **Secondary outcomes** • Participant Global Evaluation: 5-point VRS (1 = poor, 5 = excellent) at 24 h or use of rescue medication/withdrawal • Participants who used rescue medication • Time of rescue medication • AEs, withdrawals Imputation: BOCF for use of rescue medication, linear interpolation for missing values
Notes	Sponsor: Menarini

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization sequence stratified by baseline PI-VAS categories [moderate pain (40 to 60) and severe pain (> 60) with an imbalanced 1:3:1:3:1:3 ratio, using block size of 12]"
Allocation concealment (selection bias)	Low risk	"Interactive Voice/Web Response (IVR/IWR) system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy design"

McQuay 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-dummy design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported, all participants included. Imputation judged appropriate
Size	Unclear risk	50 to 199 participants per treatment arm (159 to 161)

Moore 2015

Methods	Multicentre Randomised Double-blind (double-dummy) Placebo controlled and active comparator Parallel group Medication administered within 4 h of surgery when PI ≥ 40/100 and 4-point VRS ≥ 2
Participants	**Inclusion criteria:** men and women aged 18 to 70 years. Outpatient surgical removal, under local anaesthesia, of ≥ 1 third molar (≥ fully or partially impacted in mandibular bone) **Exclusion criteria:** pregnant; breastfeeding; known allergy to study drug; paracetamol, aspirin, opioids, other NSAIDs; moderate or severe renal, hepatic, cardiac dysfunction; epilepsy; asthma; angioedema; other medical condition that may interfere with study, Hx GI disorder, bleeding, drug or alcohol abuse N = 606 for efficacy, 611 for safety M 247, F 359 Mean age 27 years (18 to 64) Baseline PI: 64% moderate, 35% severe (3 mild, 2 missing data)
Interventions	Dkp/Tram 12.5/37.5 mg, n = 60 Dkp/Tram 12.5/75 mg, n = 62 Dkp/Tram 25/37.5 mg, n = 63 Dkp/Tram 25/75 mg, n = 61 Dkp 12.5 mg, n = 60 Dkp 25 mg, n = 60 Tram 37.5 mg, n = 59 Tram 75 mg, n = 59 Ibu 400 mg, n = 60 Placebo, n = 62

Moore 2015 *(Continued)*

	• Rescue medication: paracetamol 1000 mg (maximum 4 doses in 24 h). Participants requested to wait ≥ 60 min before taking
Outcomes	**Primary outcomes** • PI and PR at 0, 15, 30, 45 min, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 h Scales: PI 4-point VRS (0 = none, 3 = severe); PR 5-point VRS (0 = none, 4 = complete) Used to calculate SPID and TOTPAR **Secondary outcomes** • Patient Global Evaluation: 5-point VRS (1 = poor, 5 = excellent) at 24 h or use of rescue medication/withdrawal • Participants used rescue medication • Time of rescue medication Imputation: BOCF for use of rescue medication
Notes	Sponsor: Menarini

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated" "blocked randomisation procedure, with block size of 10"
Allocation concealment (selection bias)	Low risk	"Interactive Voice/Web Response (IVR/IWR) system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy design"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-dummy design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported, all participants accounted for (loss minimal). Imputation judged appropriate
Size	Unclear risk	50 to 199 participants per treatment arm (59 to 63)

Moore 2016

Methods	Multicentre Randomised Double-blind Placebo controlled and active control Parallel groups Single and multiple dose phases

Moore 2016 *(Continued)*

	Medication administered orally every 8 h over 3-day period. First dose administered after cessation of postoperative analgesia once participants able to take oral medication and PI ≥ 40/100
Participants	**Inclusion criteria:** women aged 18 to 75 years, undergoing abdominal hysterectomy for benign conditions **Exclusion criteria:** breastfeeding, contraindication to any study drug, moderate or severe renal dysfunction, severe hepatic or cardiac dysfunction, asthma, epilepsy, bleeding disorders, chronic opioid use, surgical complications, Hx GI disorders, drug or alcohol abuse, other medical condition that might confound results N = 606 All F Mean age 48 years (25 to 73) Baseline PI: moderate 38%, severe 62%
Interventions	Dkp/Tram 25/75 mg, n = 152 Dkp 25 mg, n = 151 Tram 100 mg, n = 150 Placebo, n = 153 • Rescue medication: metamizole 500 mg • Concomitant medication restricted depending on half life of drug
Outcomes	**Primary outcomes** • First dose: PI (at rest) and PR at 30 min, and 1, 1.5, 2, 3, 4, 6, 8 h Scales: PI 0 to 100 mm VAS; PR 5-point VRS (0 = none, 4 = complete) Used to calculate SPID and TOTPAR **Secondary outcomes** • Patient Global Evaluation: 5-point VRS (1 = poor, 5 = excellent) at 8 h or use of rescue medication/withdrawal • Participants using rescue medication • Time of rescue medication • Adverse events • Withdrawals Imputation: BOCF for use of rescue medication, linear interpolation for missing values
Notes	Sponsor: Menarini

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization sequence stratified by baseline PI-VAS categories [moderate pain (40 to 60) and severe pain (> 60)] with an imbalanced 3:3:3:1:1:1 ratio, using block size of 12]"
Allocation concealment (selection bias)	Low risk	"Interactive Voice/Web Response (IVR/IWR) system"

Moore 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy design"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-dummy design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported, all participants accounted for (loss minimal). Imputation judged appropriate
Size	Unclear risk	50 to 199 participants per treatment arm (150 to 153)

BOCF: baseline observation carried forward; Dkp: dexketoprofen; F: female; GI: gastrointestinal; h: hour; Hx: history; Ibu: ibuprofen; LOCF: last observation carried forward; M: male; min: minute; N: number of participants in study; n: number of participants in treatment arm; NSAID: nonsteroidal anti-inflammatory drug; PI: pain intensity; PR: pain relief; SPID: summed pain intensity difference (see 'Glossary'; Appendix 1); TOTPAR: total pain relief (see 'Glossary'; Appendix 1); Tram: tramadol; VAS: visual analogue scale (see 'Glossary'; Appendix 1); VRS: verbal rating scale; WOCF: worst observation carried forward.

DATA AND ANALYSES

Comparison 1. Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥ 50% pain relief over 6 hours	3	748	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.74, 2.42]

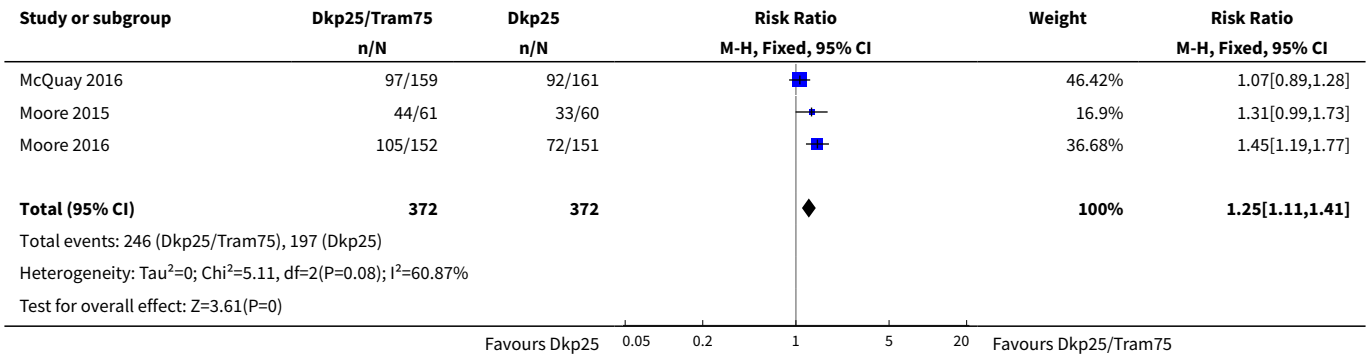
Analysis 1.1. Comparison 1 Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus placebo, Outcome 1 Participants with ≥ 50% pain relief over 6 hours.

Study or subgroup	Dkp25mg/ Tram75mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McQuay 2016	97/159	66/161		54.48%	1.49[1.19,1.86]
Moore 2015	44/61	6/62		4.94%	7.45[3.43,16.2]
Moore 2016	105/152	49/153		40.57%	2.16[1.67,2.78]
Total (95% CI)	**372**	**376**		**100%**	**2.05[1.74,2.42]**
Total events: 246 (Dkp25mg/Tram75mg), 121 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=18.75, df=2(P<0.0001); I^2=89.33%					
Test for overall effect: Z=8.55(P<0.0001)					

Comparison 2. Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus dexketoprofen 25 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥ 50% pain relief over 6 hours	3	744	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.11, 1.41]

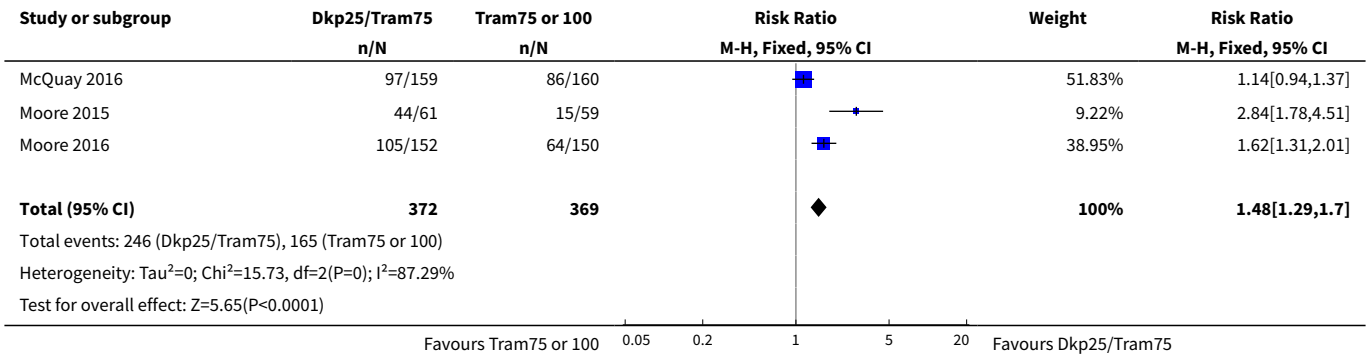
Analysis 2.1. Comparison 2 Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus dexketoprofen 25 mg, Outcome 1 Participants with ≥ 50% pain relief over 6 hours.



Comparison 3. Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus tramadol 75 mg or 100 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥ 50% pain relief over 6 hours	3	741	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.29, 1.70]

Analysis 3.1. Comparison 3 Dexketoprofen (Dkp) 25 mg/tramadol (Tram) 75 mg versus tramadol 75 mg or 100 mg, Outcome 1 Participants with ≥ 50% pain relief over 6 hours.



APPENDICES

Appendix 1. Glossary

Categorical rating scale: the most common are the four-category scale for pain intensity (none, mild, moderate, and severe) and the five-category scale for pain relief (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 pain relief, none = 0, slight = 1, moderate = 2, good or lots = 3, and complete = 4). Data from different participants 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 is checked by comparison with concurrent visual analogue scale measurements. Good correlation is 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): for pain intensity, lines with left end labelled 'no pain' and right end labelled 'worst pain imaginable', and for pain relief lines with left end labelled 'no relief of pain' and right end labelled 'complete relief of pain', seem to overcome the limitation of forcing participant descriptors into particular categories. Participants mark the line at the point that corresponds to their pain or pain relief. The scores are obtained by measuring the distance between the 'no relief of pain' 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 six hours, they would have a six hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule. 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 and baseline pain score 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* (Moore 2003).

Appendix 2. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning grade of evidence (GRADEpro GDT 2015).

- **High** = further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = 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** = any estimate of effect is very uncertain.

We decrease grade if we find:

- a serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- a high probability of reporting bias (-1).

We increase grade if we find:

- strong evidence of association - significant risk ratio of > 2 (< 0.5) based on consistent evidence from two or more; observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant risk ratio of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1);
- that all plausible confounders would have reduced the effect (+1).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if a studies use last observation carried forward imputation in circumstances where there are substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by 3 levels, to very low quality. In circumstances where there were no data reported for an outcome, we would report the level of evidence as very low quality (Guyatt 2013b).

Appendix 3. Search strategy for CENTRAL (via CRSO)

1. MESH DESCRIPTOR tramadol (739)
2. tramadol:TI,AB,KY (2093)
3. 1 or 2 (2093)
4. MESH DESCRIPTOR ketoprofen (413)
5. dexketoprofen:TI,AB,KY (123)
6. 4 or 5
7. MESH DESCRIPTOR pain EXPLODE ALL TREES (32237)
8. pain:TI,AB,KY (82416)
9. 7 or 8 (87278)
10. 3 and 6 and 9 (35)

Appendix 4. Search strategy for MEDLINE (via Ovid)

1. Tramadol/ (2479)
2. tramadol.tw. (3095)
3. 1 or 2 (3404)
4. Ketoprofen/ (2398)
5. dexketoprofen.tw. (146)
6. 4 or 5 (2425)
7. exp Pain/ (329926)
8. pain*.tw. (463630)
9. 7 or 8 (598661)
10. randomized controlled trial.pt. (416528)
11. controlled clinical trial.pt. (90709)
12. randomized.ab. (313403)
13. placebo.ab. (158663)
14. drug therapy.fs. (1858535)
15. randomly.ab. (221192)
16. trial.ab. (324199)
17. groups.ab. (1395152)
18. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3531615)
19. 3 and 6 and 9 and 18 (34)

Appendix 5. Search strategy for Embase (via Ovid)

1. Tramadol/ (15225)
2. tramadol.tw. (5926)
3. 1 or 2 (15655)
4. Ketoprofen/ (11408)
5. dexketoprofen.tw. (307)
6. 4 or 5 (11640)
7. exp Pain/ (979504)
8. pain*.tw. (735793)
9. 7 or 8 (1241008)
10. crossover-procedure/ (47133)
11. double-blind procedure/ (130965)
12. randomized controlled trial/ (404331)

13.(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw. (1451737)
14.10 or 11 or 12 or 13 (1536775)
15.3 and 6 and 9 and 14 (116)

Appendix 6. Summary of outcomes in individual studies: efficacy

Study ID	Treatment	Analgesia			Rescue medication	
		PI or PR	Number with 50% PR	PGE: very good or excellent	Median time to use (95% CI) (h)	Number using
McQuay 2016	(1) Dkp/Tram 25/75 mg (2) Dkp 25 mg (3) Tram 100 mg (4) Placebo	TOTPAR 6 (SD): (1) 13 (5.4) (2) 12 (5.2) (3) 12 (5.2) (4) 10 (5.2)	TOTPAR 6 h responders: (1) 61% = 97/159 (2) 57% = 92/161 (3) 54% = 86/160 (4) 41% = 66/161	At 8 h: (1) 56/159 (2) 44/161 (3) 51/160 (4) 18/161	Not calculable > 8 h	No data for single dose phase
Moore 2015	(1) Dkp/tram 12.5/37.5 mg (2) Dkp/tram 12.5/75 mg (3) Dkp/tram 25/37.5 mg (4) Dkp/tram 25/75 mg (5) Dkp 12.5 mg (6) Dkp 25 mg (7) Tram 37.5 mg (8) Tram 75 mg (9) Ibu 400 mg (10) Placebo	TOTPAR 6 (SD): (1) 10.2 (5.5) (2) 13.3 (7.0) (3) 12.6 (6.6) (4) 14.5 (6.1) (5) 7.9 (5.9) (6) 11.8 (5.6) (7) 4.0 (4.5) (8) 5.4 (6.1) (9) 10.5 (7.2) (10) 2.9 (4.8)	TOTPAR 6 h responders: (1) 22/60 (2) 37/62 (3) 35/63 (4) 44/61 (5) 16/60 (6) 33/60 (7) 6/59 (8) 15/59 (9) 27/60 (10) 6/62	At end of assessment period (24 h) (1) 27% = 16/60 (2) 46% = 29/62 (3) 46% = 29/63 (4) 51% = 31/61 (5) 33% = 20/60 (6) 28% = 17/60 (7) 9% = 5/59 (8) 14% = 8/59 (9) 33% = 20/60 (10) 5% = 3/62	Median (1) 4.9 (4.0 to 5.8) (2) 8.5 (5.9 to 13) (3) 7.3 (6.3 to 9.0) (4) 8.1 (6.3 to 13) (5) 3.6 (2.7 to 4.3) (6) 5.6 (4.8 to 7.6) (7) 2.2 (1.3 to 3.0) (8) 2.5 (1.4 to 3.9) (9) 7.1 (4.8 to 8.6) (10) 1.4 (1.2 to 1.8)	At 6 h: (1) 40/60 (2) 29/62 (3) 25/63 (4) 23/61 (5) 39/60 (6) 36/60 (7) 41/59 (8) 38/59 (9) 29/60 (10) 45/62
Moore 2016	(1) Dkp/tram 25/75 mg (2) Dkp 25 mg (3) Tram 100 mg (4) Placebo	TOTPAR 6 (SD): (1) 14 (4.6) (2) 11 (5.2) (3) 11 (5.5) (4) 8.9 (5.1)	TOTPAR 6 h responders: (1) 105/152 (2) 72/151 (3) 64/150 (4) 49/153	At 8 h: (1) 42/152 (2) 28/151 (3) 22/150 (4) 14/153	Not calculable > 8 h	No data for single dose phase

CI: confidence interval; Dkp: dexketoprofen; h: hour; Ibu: ibuprofen; PGE: Patient Global Evaluation; PI: pain intensity; PR: pain response; SD: standard deviation; TOTPAR: total pain relief (see 'Glossary'; Appendix 1); Tram: tramadol

Appendix 7. Summary of outcomes in individual studies: adverse events and withdrawals

Study ID	Treatment	Adverse events		Withdrawals	
		Any	Serious	Adverse event	Other
McQuay 2016	(1) Dkp/Tram 25/75 mg (2) Dkp 25 mg (3) Tram 100 mg (4) Placebo	No data for single dose phase Over 5 days (no placebo) (1) 2.8% (2) 4.7% (3) 5.1%	Over 5 days (no placebo) (1) 1/213 (1 event) (2) 1/213 (4 events) (3) 0/212	None	(1) 0/159 (2) 1/161 (withdrawal by subject) (3) 0/160 (4) 2/161 (withdrawal by subject, protocol violation)
Moore 2015	(1) Dkp/Tram 12.5/37.5 mg (2) Dkp/Tram 12.5/75 mg (3) Dkp/Tram 25/37.5 mg (4) Dkp/Tram 25/75 mg (5) Dkp 12.5 mg (6) Dkp 25 mg (7) Tram 37.5 mg (8) Tram 75 mg (9) Ibu 400 mg (10) Placebo	Over 24 h: (1) 3/61 (2) 6/63 (3) 4/63 (4) 7/61 (5) 1/60 (6) 3/61 (7) 3/59 (8) 10/60 (9) 3/61 (10) 0/62 All except one were mild or moderate in intensity	1 in (8) - mild dizziness, but admitted to hospital for observation	None	(1) 0/61 (2) 1/63 (eDiary failure) (3) 1/63 (lost to follow-up) (4) 1/61 (lost to follow-up) (5) 0/60 (6) 0/61 (7) 1/59 (lost to follow-up) (8) 0/60 (9) 0/61 (10) 0/62
Moore 2016	(1) Dkp/Tram 25/75 mg (2) Dkp 25 mg (3) Tram 100 mg (4) Placebo	No data for single dose phase Over 3 days (no placebo) (1) 9% (2) 15% (3) 13%	Over 3 days: 11 participants reported 15 SAEs; only one judged treatment related (psychiatric disorder in (1))	(1) 2/152 (2) 2/152 (3) 0/150 (4) 2/153	(1) 0/152 (2) 3/151 (3) 1/150 (4) 6/153

Dkp: dexketoprofen; Ibu: ibuprofen; SAE: serious adverse event; Tram: tramadol

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
22 September 2016	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

Draft the protocol	SD, TC
Develop and run the search strategy	SD PaPaS Information Specialist provided support
Obtain copies of studies	SD
Select which studies to include	TC, SD
Extract data from studies	TC, SD
Enter data into Review Manager 5	SD
Carry out the analysis	SD, TC
Interpret the analysis	All authors
Draft the final review	All authors
Update the review	SD

DECLARATIONS OF INTEREST

SD: none known.

TC: none known.

TP: none known; TP is an anaesthetist and manages patients with acute 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

Objectives: we included as a secondary objective, comparisons between the combination therapy and the individual components for the primary outcome. This was not specified in the protocol, but direct comparisons have been made for other combination analgesics in this series of reviews where data were available. Although the studies were not designed to show differences between active treatments, it is useful to have an indication of this comparison to consider alongside indirect evidence if and when it is available. We did not consider direct comparison for other outcomes because the studies were not designed to show these differences, and they were unlikely to be helpful.

Although we did not plan any sensitivity analyses in advance, we explored the resilience of our primary outcome to potential heterogeneity, when found, by checking for any effect of using random-effects analyses rather than fixed-effect analysis, and by testing the effect of removing one study.

Quality of the evidence: we added a sentence in 'Methods' to explain that in some circumstances the overall rating for a particular outcome may need to be adjusted, as recommended by GRADE guidelines.

We have included median time to use of rescue medication in the 'Summary of findings' table. This was omitted from the protocol.

NOTES

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