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[Intervention Review]

Single dose dipyrone (metamizole) for acute postoperative pain in adults

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ABSTRACT

Background

Dipyrone (metamizole) is a nonsteroidal anti-inflammatory drug used in some countries to treat pain (postoperative, colic, cancer, and migraine); it is banned in other countries because of an association with life-threatening blood disorders. This review replaces a 2010 Cochrane review that has been withdrawn.

Objectives

To assess the analgesic efficacy and associated adverse events of single dose dipyrone for moderate to severe acute 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, and LILACS to 11 August 2015; the Oxford Pain Relief Database; two clinical trial registries; and the reference lists of articles.

Selection criteria

We included randomised, double-blind, placebo-controlled trials of single dose dipyrone for relief of established moderate to severe postoperative pain in adults. We accepted oral, rectal, intramuscular, and intravenous routes of administration.

Data collection and analysis

Two review authors independently considered studies for inclusion in the review, assessed risk of bias, and extracted data. We used summed total pain relief or pain intensity difference (TOTPAR or SPID) over four to six hours to calculate the number of participants achieving at least 50% pain relief. From derived results, we calculated the risk ratio and number needed to treat for an additional beneficial outcome (NNT), with 95% confidence intervals (CI), for one participant to experience at least 50% pain relief over four to six hours compared to placebo. We looked at use of rescue medication and time to use of rescue medication as additional measures of efficacy. We also looked for information on adverse events and withdrawals.

Main results

We included eight studies, involving 809 participants, comparing oral dipyrone 500 mg (143 participants), oral dipyrone 1000 mg (57 participants), and intramuscular dipyrone 2000 mg (35 participants) with placebo (236 participants). In addition to placebo, all studies used active controls (ibuprofen, paracetamol, aspirin, flurbiprofen, ketoprofen; 338 participants). Seven studies used the oral route of

administration, and one study used the intramuscular route. The mean age ranged from 23 to 62 years. Six studies included both men and women, and two studies included only women. All the studies were small, but were otherwise of moderate to good quality.

Over 70% of participants experienced our primary outcome of at least 50% pain relief over four to six hours with oral dipyrone 500 mg compared to 30% with placebo (five studies, 288 participants; NNT 2.4 (95% CI 1.8 to 3.1)) (moderate quality evidence). There were insufficient data to assess other doses or routes of administration of dipyrone.

Fewer participants needed rescue medication within four to six hours with dipyrone 500 mg than with placebo (7% with dipyrone versus 34% with placebo; four studies, 248 participants) (low quality evidence).

The data on numbers of participants experiencing any adverse event was inconsistently reported and no analysis was possible. No serious adverse events or adverse event withdrawals were reported (very low quality evidence).

There were too few data to compare dipyrone directly with other active treatments.

Authors' conclusions

Based on very limited information, a single dose of dipyrone 500 mg provides good pain relief to about 70% of people treated, compared to about 30% with placebo. For every five people given dipyrone 500 mg, two people would experience this level of pain relief over four to six hours who would not have done with placebo, and fewer people would need rescue medication.

We were unable to compare dipyrone directly with other active treatments, or to assess the effects of different doses or routes of administration, or the number of participants experiencing adverse events, because of insufficient data and inadequate reporting.

PLAIN LANGUAGE SUMMARY

Single dose dipyrone for the treatment of acute postoperative pain

Bottom line

Dipyrone (metamizole) at a single oral dose of 500 mg produces acceptable pain relief in about 7 out of 10 people with moderate or severe acute pain.

Background

Acute pain is short lasting and often felt soon after injury. Most people who have surgery have moderate or severe pain afterwards. Painkillers (analgesics) are tested by giving them to people who are in pain, often following the removal of wisdom teeth or other minor surgery. This pain is usually treated with painkillers taken by mouth. Results can be applied to other types of acute pain. This is one of a series of Cochrane reviews looking at how good painkillers are.

Dipyrone is a popular medicine for pain relief in some countries and is used to treat postoperative pain, colic pain (sharp pain in the tummy), cancer pain, and migraine (severe headache). Other countries (Japan, UK, USA) have banned its use because of an association with potentially life-threatening blood disorders such as agranulocytosis (deficiency of certain blood cells).

Study characteristics

We searched medical databases for studies of dipyrone used to treat pain following surgery in adults and compared with placebo (a pretend treatment). The medicines could be given by mouth, into a vein, into a muscle, or into the rectum. The evidence is current to 11 August 2015. We found eight studies, involving 809 participants treated with dipyrone, placebo, and various other painkillers. The studies were all small, but otherwise of moderate to good quality.

Key results

A single 500 mg dose of dipyrone provided effective pain relief (50% or more reduction in pain over four to six hours) for 7 in 10 (70%) participants, compared with 3 in 10 (30%) with placebo (five studies, 288 participants in the comparison; moderate quality evidence), and fewer participants need additional painkillers within four to six hours (7% with dipyrone, 34% with placebo; four studies, 248 participants; low quality evidence).

There were too few data to compare dipyrone directly with other painkillers.

There was too little information available to draw any conclusions about other doses and ways of giving dipyrone used in these studies, or about the number of people who had side effects. The studies reported no serious side effects or people withdrawing from the studies because of side effects, although not all studies provided information on these outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Oral dipyrone 500 mg compared with placebo for acute postoperative pain

Patient or population: adults with acute postoperative pain

Settings: clinic

Intervention: oral dipyrone 500 mg

Comparison: placebo

Outcomes	Probable outcome with		Relative effect and NNT or NNTp (95% CI)	Number of studies, participants, events	Quality of the evidence (GRADE)	Comments
	intervention	comparator				
At least 50% of maximum pain relief over 4 to 6 h	730 in 1000	320 in 1000	RR 2.4 (95% CI 1.8 to 3.1) NNT 2.4 (1.9 to 3.1)	5 studies, 288 participants, 151 events	Moderate	Small studies, few events
Participants remedicating within 4 to 6 h	70 in 1000	340 in 1000	RR 0.21 (0.11 to 0.40) NNTp 3.6 (2.7 to 5.4)	4 studies, 248 participants, 51 events	Low	Small studies, very few events
Participants with at least one adverse event	Insufficient data for analysis		-	-	-	-
Participants with a serious adverse event	None reported	None reported	-	5 studies, 288 participants, no events	Very low	Small studies, no events

CI: confidence interval; **h:** hour; **RR:** risk ratio; **NNT:** number needed to treat for an additional beneficial outcome; **NNTp:** number needed to treat to prevent an event.

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.

BACKGROUND

This is one of a series of reviews whose aims are:

- to increase awareness of the range of analgesics that are available for acute postoperative pain;
- 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 the UK, and dipyrrone (metamizole) because it is commonly used in Spain, Portugal, Bulgaria, Israel, Turkey, India, and Latin-American countries. Two overviews of efficacy and adverse events have examined the results (Moore 2015a; Moore 2015b). This new review of dipyrrone replaces an earlier review, which has been withdrawn and replaced with an up-to-date protocol (Derry 2010).

Description of the condition

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

Description of the intervention

Dipyrrone is a nonsteroidal anti-inflammatory drug (NSAID). It was first synthesised in 1920 in Germany and the drug was launched there in 1922. NSAIDs have pain-relieving, antipyretic, and anti-inflammatory properties, and have proven efficacy following day surgery and minor surgery. The usual adult dose of dipyrrone is 1.0 to 2.5 mg daily when given orally. It is also available for intravenous (IV), intramuscular (IM), or rectal administration. Dipyrrone (metamizole) is manufactured by a very large number of different manufacturers under 21 different generic names and hundreds of brand names (<http://www.drugs.com/international/metamizole.html>).

Dipyrrone is a controversial analgesic. It is used most commonly to treat postoperative pain, colic pain, cancer pain, and migraine, and in many countries (eg Russia, Spain, Mexico, and in many parts of South America, Asia, and Africa) it remains a popular non-opioid first-line analgesic, either by prescription only, as in Germany and Spain, or non-prescription (over the counter (OTC)), as in Bulgaria and Mexico. In other countries, it has been banned (eg the USA, the UK, Japan, Canada, and parts of Europe) because of its association with potentially life-threatening blood disorders such as agranulocytosis (a deficiency of certain blood cells). In countries where it is banned, it may still be available and widely used by immigrant populations (Bonkowsky 2002). It is sold under many different brand names, including Analgin and Novalgin, and is also known in some areas of the USA as 'Mexican aspirin'. In addition to use as a single agent, it is commonly used in combination products.

One systematic review and meta-analysis of dipyrrone use lasting less than two weeks concluded that for short-term use in the hospital setting, dipyrrone appeared to be a safe choice when compared to other widely used analgesics (Kötter 2015). However,

the main concern with dipyrrone has been an association with agranulocytosis.

There is a wealth of literature on agranulocytosis associated with dipyrrone: one large, international study found vastly differing rates of agranulocytosis in the 11 countries from which information was collected (IAAAS 1986). There are a number of published criticisms of this study (Kramer 1988). None of these criticisms mention the importance of size (of the population studied and of the analyses) for detecting true incidence rates for rare events. Size is an important criterion of study validity (Moore 1998). One report from Sweden suggested a rate of 1 case of agranulocytosis in 1439 prescriptions in a small study with high cumulative doses (Hedenmalm 2002). One case-control study in Berlin identified 10 probable dipyrrone-induced cases (of 63 drug-related cases) of agranulocytosis between 2000 and 2010, more than for any other drug (Huber 2014). One review of non-chemotherapy drug-induced agranulocytosis identified dipyrrone in six definite and five probable high quality case reports, with a median time to onset of only two days (Andersohn 2007). One case-control analysis estimated incidence of agranulocytosis at less than one per million per year; the risk increased with duration of use and disappeared 10 days after the last dose (Ibáñez 2005). One review of the clinical profile of dipyrrone concluded that the risk of agranulocytosis with short-term treatment was low and risks of serious complications were much lower than with aspirin and diclofenac and comparable to those of paracetamol (Nikolova 2013).

While the risk of agranulocytosis remains uncertain (Edwards 2002), and there may be differences between populations in their susceptibility to agranulocytosis (Mérida Rodrigo 2009), dipyrrone is one of the 10 drugs most commonly associated with it (Andersohn 2007).

The use of dipyrrone has been reported to be associated with other potentially serious adverse events, such as chronic interstitial nephritis and gastrointestinal disturbances (Zukowski 2009), as well as allergic or idiosyncratic reactions such as anaphylaxis, bronchospasm, and toxic epidermal necrolysis (Arellano 1990). One review of hospital admissions for adverse drug reactions in Brazil identified 20 dipyrrone-related admissions over an eight-month period (Lobo 2013). However, the risk of gastrointestinal bleeding with dipyrrone was low in one study of 18 hospitals in Spain and Italy (Laporte 2004). It has been reported that the excess mortality due to agranulocytosis, aplastic anaemia, anaphylaxis, and serious upper gastrointestinal complications is 0.25 per million users for dipyrrone (0.2 for paracetamol, 1.85 for aspirin, and 5.92 for diclofenac) (Andrade 1998).

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 comparison (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 necessarily have significant pain relief anyway. Approximately 18% of participants given placebo will have significant pain relief

(Moore 2006), while 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. Trials have to be randomised and double-blind. Typically, in the first few hours or days after an operation, people 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 over 12 to 24 hours for longer-acting drugs. Pain relief of half the maximum possible or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For participants 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 (BOCF)). 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 (LOCF), which gives an inflated response for the test intervention compared to placebo, but the effect of this has been shown to be negligible over four to six hours (Moore 2005). Participants 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.

How the intervention might work

NSAIDs have pain-relieving, antipyretic, and anti-inflammatory properties, and are thought to relieve pain by inhibiting cyclo-oxygenases (COX) (prostaglandin endoperoxide synthases) and thus the production of prostaglandins (Hawkey 1999). Prostaglandins occur throughout body tissues and fluids and act to stimulate pain nerve endings and inhibit the aggregation of blood platelets. Dipyrone's mechanism of action is not entirely clear but it seems to be an inhibitor of COX enzymes and thus inhibits the production of prostaglandins. It may also be associated with the endogenous opioid system (Nikolova 2013). Dipyrone, and some of its active metabolites, may also act by directly blocking ongoing inflammatory hypersensitisation (hyperalgesia).

Inhibition of prostaglandin production may be involved with some of the known problems associated with NSAIDs, including gastrointestinal, cardiovascular, renal, and hypertensive adverse effects (FitzGerald 2001; Hawkey 1999; Hawkey 2002; Patrono 2009). Interestingly, dipyrone has not been linked with gastrointestinal bleeding (Laporte 1991).

Why it is important to do this review

Although use of dipyrone is banned or restricted in many countries, it remains a drug of choice in other countries. It is important that information about its benefits and harms be carefully reviewed and made available to a worldwide audience.

OBJECTIVES

To assess the analgesic efficacy and associated adverse events of single dose dipyrone for moderate to severe acute 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 a single dose of dipyrone 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 the following.

- Review articles, case reports, and clinical observations.
- Studies of experimental pain.
- Studies where pain relief was assessed only by clinicians, nurses, or carers (ie not participant-reported).
- Studies of less than four hours' duration or studies that did not present data over a four to six hour period post dose.

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 adults (aged 15 years or older) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analogue scale (VAS), we assumed that pain intensity of greater than 30/100 mm equated to pain of at least moderate intensity (Collins 1997).

Types of interventions

Dipyrone, administered as a single dose, compared with matched placebo, administered postoperatively for pain relief. Where studies also included an active comparator, we extracted data for direct comparison. We included oral, rectal, IV, and IM routes of administration.

Types of outcome measures

We collected the following data where available.

- Participant characteristics.
- Dose and route of administration.
- Participant-reported pain at baseline (physician, nurse, or carer-reported pain was not included in the analysis).
- Participant-reported pain relief expressed at least hourly over a four to six hour period using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both).
- Patient Global Evaluation of treatment (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 causes; adverse events).

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.
- Number of participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event.
- Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication).

Search methods for identification of studies

Two review authors independently searched for studies.

Electronic searches

We searched the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL via CRSO on 11 August 2015).
- MEDLINE (via Ovid from 1946 to 11 August 2015).
- EMBASE (via Ovid from 1974 to 11 August 2015).
- LILACS (via VHL on 11 August 2015).
- Oxford Pain Relief Database on 6 February 2015 (Jadad 1996a).

See [Appendix 1](#) for the CENTRAL search strategy, [Appendix 2](#) for the MEDLINE search strategy, [Appendix 3](#) for the EMBASE search strategy, and [Appendix 4](#) for the LILACS search strategy. We did not limit the searches by language or date.

Searching other resources

We searched for additional studies in reference lists of the earlier Cochrane review, retrieved articles, and other reviews, and in two clinical trials databases (clinicaltrials.gov and apps.who.int/trialsearch/).

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. We intended to resolve disagreements 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 Review Manager 5 (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* (Chapter 8.5, Higgins 2011), and resolved any disagreements by discussion. 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 (ie any truly random process, such as random number table or computer random number generator); unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies at a high risk of bias that used a non-random process (eg odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). We assessed the method used to conceal allocation to interventions prior to assignment as to 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 (eg telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when the method was not clearly stated); and high risk of bias (eg open random allocation; unsealed or non-opaque envelopes; alternation; date of birth).
- 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 considered studies to be at low risk of bias if they stated that they were blinded and described the method used to achieve blinding (eg identical tablets; matched in appearance and smell); or at unclear risk of bias if they stated that they were blinded, but did not provide an adequate description of how this was achieved. We excluded single-blind and open studies at a high risk of bias.
- Size (checking for possible biases confounded by small size). Small studies overestimate treatment effects, probably due to methodological weaknesses (Dechartres 2013; Nüesch 2010). We considered studies to be at low risk of bias if they had 200 participants or more; at unclear risk of bias 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 (RR) to establish statistical difference. We used numbers needed to treat for an additional beneficial outcome (NNT) and pooled percentages as absolute measures of benefit or harm. We reported these with their 95% confidence intervals (CI).

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 additional 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 for an additional harmful outcome 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 LOCF 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 ([Barden 2004](#)).

Assessment of heterogeneity

We examined heterogeneity visually using L'Abbé plots ([L'Abbé 1987](#)), which is 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 (NNT of 10 or higher in this condition) ([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 (see [Appendix 5](#)) values for active and placebo groups to %maxTOTPAR or %maxSPID by division into the calculated maximum value ([Cooper 1991](#)). We then calculated the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations ([Moore 1996](#); [Moore 1997a](#); [Moore 1997b](#)). We then 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 dichotomous information on the number of participants with an outcome of interest in the active and placebo groups to calculate the RR with 95% CI, using a fixed-effect model ([Morris 1995](#)). We assumed a statistically significant difference from control when the 95% CI of the RR did not include the number '1'. We calculated NNT and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett ([Cook 1995](#)).

We accepted the following pain measures for the calculation of TOTPAR or SPID.

- Five-point categorical pain relief (PR) scales with comparable wording to 'none', 'slight', 'moderate', 'good', or 'complete'.
- Four-point categorical pain intensity (PI) scales with comparable wording to 'none', 'mild', 'moderate', or '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 5-point categorical global scale with the wording 'poor', 'fair', 'good', 'very good', or 'excellent' for the number of participants achieving at least 50% pain relief ([Collins 2001](#)).

Quality of the evidence

We have used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to assess the quality of the evidence related to the key outcomes listed in [Types of outcome measures](#), as appropriate ([Appendix 6](#); Chapter 12.2, [Higgins 2011](#)). Two review authors independently rated the quality of evidence for each outcome.

Summary of findings table

We have included 'Summary of findings' tables as set out in the PaPaS author guide ([PaPaS 2012](#)), and recommended in the Cochrane Handbook (Chapter 4.6.6, [Higgins 2011](#)). The tables include outcomes of at least 30% and at least 50% pain intensity reduction, PGIC (possibly at least substantial improvement and at least moderate improvement), serious adverse events, withdrawals due to adverse events, and death (a particular serious adverse event).

Subgroup analysis and investigation of heterogeneity

We analysed separately the data for different routes of administration. We planned subgroup analyses to determine the effect of dose and presenting condition (pain model: dental versus other postoperative pain).

Sensitivity analysis

We planned sensitivity analyses for quality score (two versus three or more) and trial size (39 or fewer versus 40 or more per treatment arm).

A minimum of two studies and 200 participants had to be available in any subgroup or sensitivity analysis ([Moore 1998](#)), which was restricted to the primary outcome (50% of maximum pain relief over a four to six hour period) and the dose with the greatest amount of data. We planned to determine significant differences between NNT or NNH for different groups in subgroup and sensitivity analyses using the z test ([Tramèr 1997](#)).

RESULTS

Description of studies

Results of the search

We identified 315 reports in CENTRAL, 231 in MEDLINE, 442 in EMBASE, and 24 in LILACS. We found no additional studies in the Oxford Pain Relief Database and in clinical trials registries. We excluded 28 studies after obtaining and reading the full report ([Figure 1](#)).

Figure 1. Study flow diagram.

Eight studies met the inclusion criteria (Bhounsule 1990; Boraks 1987; De Miguel Rivero 1997; Dos Santos Pereira 1986; Olson 1999; Pinto 1984; Rubinstein 1986; Sakata 1986). One study included one or more participants aged 14 years, but was included, subject to sensitivity analysis, because we believed that the number was small and unlikely to affect results (Pinto 1984).

Included studies

The eight included studies used both placebo and active controls (Bhounsule 1990; Boraks 1987; De Miguel Rivero 1997; Dos Santos Pereira 1986; Olson 1999; Pinto 1984; Rubinstein 1986; Sakata 1986); the active controls were oral ibuprofen 400 mg, paracetamol 500 mg or 1000 mg, aspirin 600/650 mg, flurbiprofen 50 mg, and ketoprofen 25 mg or 50 mg.

In five studies, 143 participants used oral dipyrrone 500 mg (Bhounsule 1990; Boraks 1987; Olson 1999; Pinto 1984; Rubinstein 1986), and in two studies, 58 participants used oral dipyrrone 1000 mg (Dos Santos Pereira 1986; Sakata 1986). In one study, 35 participants used IM dipyrrone 2000 mg (De Miguel Rivero 1997).

The mean age ranged from 23 to 62 years. Six studies included both men and women, and two studies included only women. One study was carried out in participants who had undergone dental surgery (Boraks 1987), three studies following orthopaedic surgery

(De Miguel Rivero 1997; Dos Santos Pereira 1986; Sakata 1986), two studies following episiotomy (Bhounsule 1990; Olson 1999), one study following tonsillectomy (Pinto 1984), and one study following urological surgery (Rubinstein 1986).

All studies used a parallel group design. One study used multiple doses of dipyrrone but reported outcomes for the first dose separately (De Miguel Rivero 1997). All studies reported single dose efficacy over four to six hours.

Full details of included studies are in the [Characteristics of included studies](#) table.

Excluded studies

The main reasons for exclusion of studies were lack of placebo, not randomised controlled trials, dipyrrone was given before the end of surgery (before pain was established), time to data collection was too short or too long, no data for single doses, and use of non-standard pain scales.

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

Risk of bias in included studies

Three studies scored the minimum of 2/5 on the Oxford Quality Scale (Bhounsule 1990; Boraks 1987; Sakata 1986), three studies

scored 3/5 (Dos Santos Pereira 1986; Olson 1999; Pinto 1984), and two studies scored 4/5 (De Miguel Rivero 1997; Rubinstein 1986).

We completed a 'Risk of bias' table for randomisation, allocation concealment, blinding, and size (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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Size
Bhounsule 1990	?	?	?	?	-
Boraks 1987	?	?	?	?	-
De Miguel Rivero 1997	?	?	+	+	-
Dos Santos Pereira 1986	?	?	+	+	-
Olson 1999	?	+	+	+	-
Pinto 1984	?	?	+	+	-
Rubinstein 1986	?	?	+	+	-
Sakata 1986	?	?	?	?	-

Allocation

All studies were randomised, but none described the method used to generate the random sequence, and only one described the method used to conceal the allocation of the sequence (Olson 1999).

Blinding

All studies were double-blind, but three did not adequately describe the method used to maintain blinding (Bhounsule 1990; Boraks 1987; Sakata 1986).

Other potential sources of bias

All the studies had fewer than 50 participants in each treatment arm, and we judged them at high risk for size.

Effects of interventions

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

Eight studies compared dipyrone (500 mg, 1000 mg, or 2000 mg) with placebo over four to six hours (Boraks 1987; Bhounsule 1990;

De Miguel Rivero 1997; Dos Santos Pereira 1986; Olson 1999; Pinto 1984; Rubinstein 1986; Sakata 1986). Only the 500 mg dose of oral dipyrone provided sufficient data for statistical analysis. [Summary of findings for the main comparison](#) presents results for this comparison.

Number of participants experiencing at least 50% pain relief

Oral dipyrone 500 mg versus placebo

Five studies compared oral dipyrone 500 mg with placebo over four to six hours (Bhounsule 1990; Boraks 1987; Olson 1999; Pinto 1984; Rubinstein 1986). There were 288 participants in the comparison.

- The proportion of participants experiencing at least 50% pain relief with dipyrone 500 mg was 73% (106/143; range 60% to 87%).
- The proportion of participants experiencing at least 50% pain relief with placebo was 32% (45/145; range 19% to 41%).
- The RR of treatment compared with placebo was 2.4 (95% CI 1.8 to 3.1); the NNT for at least 50% pain relief over four to six hours was 2.4 (95% CI 1.9 to 3.1) (Figure 4).

Figure 4. Forest plot of comparison: 1 Oral dipyrone 500 mg versus placebo, outcome: 1.1 Participants with $\geq 50\%$ pain relief over 4 to 6 hours.

Removing Pinto 1984 from the analysis, because it included an unknown number of participants aged 14 years, did not change the result.

Oral dipyrone 1000 mg versus placebo

Two studies (113 participants) compared oral dipyrone 1000 mg with placebo (Dos Santos Pereira 1986; Sakata 1986); 38/57 (67%) of participants treated with dipyrone 1000 mg experienced at least 50% pain relief over four hours compared with 10/56 (18%) participants treated with placebo. There were insufficient data for statistical analysis.

Intramuscular dipyrone 2000 mg versus placebo

One study (70 participants) compared IM dipyrone 2000 mg with placebo (De Miguel Rivero 1997); 26/35 (74%) of participants treated with IM dipyrone 2000 mg experienced at least 50% pain relief over five hours compared with 16/35 (46%) of participants treated with placebo. There were insufficient data for statistical analysis.

Oral dipyrone 500 mg versus active comparators

Three studies (156 participants) compared oral dipyrone 500 mg with paracetamol 500 mg (Pinto 1984; Rubinstein 1986) or 600

mg (Bhounsule 1990); 58/77 (75%) of participants treated with dipyrone 500 mg experienced at least 50% pain relief over four to six hours compared with 53/79 (67%) participants treated with paracetamol 500 mg or 600 mg. There were insufficient data for statistical analysis.

Two studies (120 participants) compared oral dipyrone 500 mg with aspirin 600 mg (Bhounsule 1990) or 650 mg (Boraks 1987); 39/59 (66%) of participants treated with dipyrone 500 mg experienced at least 50% pain relief over four to six hours compared with 30/61 (49%) of participants treated with aspirin 600 mg or 650 mg. There were insufficient data for statistical analysis.

Single studies compared oral dipyrone 500 mg with oral ibuprofen 400 mg (40 participants, Bhounsule 1990), flurbiprofen 50 mg (79 participants, Boraks 1987), or ketoprofen 25 mg or 50 mg (81 participants, Olson 1999). Percentages experiencing at least 50% pain relief ranged from 60% to 72% but were virtually identical for the different arms of these studies. There were insufficient data for statistical analysis.

Oral dipyrone 1000 mg versus active comparators

Two studies (115 participants) compared oral dipyrone 1000 mg with paracetamol 1000 mg (Dos Santos Pereira 1986; Sakata

1986); 38/57 (67%) of participants treated with dipyrone 1000 mg experienced at least 50% pain relief over four hours compared with 38/58 (66%) participants treated with paracetamol 1000 mg. There were insufficient data for statistical analysis.

Intramuscular dipyrone 2000 mg versus active comparators

One study (71 participants) compared IM dipyrone 2000 mg with oral ibuprofen arginine 400 mg (De Miguel Rivero 1997). Despite the differences in dose and route of administration, the numbers experiencing at least 50% pain relief were virtually identical at 26/35 (74%) with dipyrone 2000 mg and 25/36 (69%) with ibuprofen. There were insufficient data for statistical analysis.

Subgroup and sensitivity analyses of the primary outcome

There were insufficient data to carry out subgroup analyses on the primary outcome for route of administration or pain model, or to carry out sensitivity analysis for study quality.

Results for individual studies are available in Summary of efficacy outcomes in individual studies (Appendix 7).

Time to use of rescue medication

One study comparing oral dipyrone 500 mg with placebo following episiotomy reported a mean time to use of rescue medication of more than six hours for dipyrone, more than six hours for ketoprofen 25 mg and 50 mg, and 5.3 hours for placebo (Olson 1999). Another study using IM dipyrone 2000 mg following orthopaedic surgery reported a median time to use of rescue medication of 2.6 hours for dipyrone, 3.5 hours for ibuprofen arginine 400 mg, and 1.8 hours for placebo (De Miguel Rivero 1997).

Number of participants needing rescue medication

The number of participants needing rescue medication during the study period was not reported in three studies (Bhounsule 1990; De Miguel Rivero 1997; Sakata 1986). It is unclear whether there were any withdrawals for this reason in these studies.

Four studies comparing dipyrone 500 mg with placebo provided data on the number of participants using rescue medication before the end of the study (within four to six hours) (Boraks 1987; Olson 1999; Pinto 1984; Rubinstein 1986). There were 248 participants in the comparison.

- The proportion of participants using rescue medication with dipyrone 500 mg was 7% (8/123; range 0% to 15%).
- The proportion of participants using rescue medication with placebo was 34% (43/125; range 20% to 51%).
- The relative benefit of treatment compared with placebo was 0.21 (0.11 to 0.40), and the NNTp was 3.6 (2.7 to 5.4) (Analysis 1.2).

Removing Pinto 1984 from the analysis, because it included an unknown number of participants aged 14 years, did not change the result.

There were insufficient data for analysis of any other dose or route of administration of dipyrone for this outcome. However, Dos Santos Pereira 1986 reported that, for oral dipyrone 1000 mg, 1/28 participants needed rescue medication at four hours, compared to 11/29 participants with placebo. For IV dipyrone 2000 mg following orthopaedic surgery, De Miguel Rivero 1997 reported

3/33 (9%) participants needing rescue medication, compared with 4/34 (12%) participants with placebo, and 5/36 (14%) participants with ibuprofen arginine 400 mg.

Appendix 7 shows the results for individual studies.

Adverse events

One study did not mention adverse events (Sakata 1986), and another study reported only that the study medication was "well tolerated" (Dos Santos Pereira 1986). Reporting of adverse events in the other studies was inconsistent, with some reporting only those that were considered related to the test drug, or that were "clinically relevant". Few events were reported, and we could not carry out an analysis for participants experiencing one or more adverse events. They did not report any serious adverse events.

Appendix 8 shows the details of events in individual studies.

Withdrawals

None of the studies reported any adverse event withdrawals. We have reported withdrawals due to lack of efficacy above under 'Number of participants needing rescue medication'. Five studies did not specifically report on all cause withdrawals (Bhounsule 1990; Boraks 1987; Dos Santos Pereira 1986; Pinto 1984; Sakata 1986).

DISCUSSION

Summary of main results

This review found eight studies using various doses of dipyrone (500 to 2000 mg) administered by different routes (oral or IM) and following different surgical procedures, with comparisons to placebo and a variety of active comparators.

For the primary outcome of at least 50% pain relief over four to six hours, there were sufficient data from placebo-controlled comparisons to analyse only oral dipyrone 500 mg versus placebo (288 participants). The RR was 2.4 (95% CI 1.8 to 3.1), and the NNT was 2.4 (1.9 to 3.2). For every five people treated, two would experience at least 50% pain relief who would not have done so with placebo (moderate quality data). For the same comparison (248 participants), the RR for needing rescue medication within four to six hours was 0.21 (95% CI 0.11 to 0.40), and the NNTp was 3.6 (2.7 to 5.4) (low quality data). For every seven people treated, two would not need rescue medication who would have done with placebo.

There was very little information on the mean or median time to use of rescue medication, a useful indicator of the duration of analgesia. Reporting of adverse events was inconsistent, with few events reported, and no analysis was possible. The studies reported no serious adverse events or adverse event withdrawals.

Results from studies using different doses and routes of administration were all consistent with a benefit of dipyrone over placebo, but based on very few data.

For active-controlled comparisons, there were insufficient data for analysis.

Indirect comparisons of NNTs for at least 50% pain relief over four to six hours in reviews of other analgesics using identical methods indicate that dipyrone has similar efficacy to standard ibuprofen

400 mg (NNT 2.5 (2.4 to 2.6)), diclofenac potassium (NNT 2.1 (1.9 to 2.5)), and ketoprofen 12.5 mg (NNT 2.4 (1.9 to 3.1)) (Moore 2015a).

Overall completeness and applicability of evidence

The studies involved participants who had undergone a diverse range of surgical procedures, from episiotomy to total hip replacement. They probably represent the majority of adults likely to be given the drug, although the studies excluded older people, pregnant women, and people with contraindications. Only one study involved dental extractions, which is usually the most common procedure used in these single dose studies.

Quality of the evidence

Overall, the methodological quality of the studies was moderate; all studies had to be randomised and double blind to satisfy inclusion criteria, but some did not fully report on withdrawals, and few gave details of the randomisation and blinding procedures, or of how missing data were handled. Treatment group sizes were small, so that even when several studies contributed data for an outcome, the number of events was small, and confidence in the result must therefore be limited.

All studies enrolled participants with established pain following surgery, with pain levels sufficient to demonstrate reduction, or otherwise, due to treatment. Adverse event data were not well reported, with no information on whether data were collected after use of rescue medication (which may cause its own adverse events). The small size of each treatment arm and small number of studies means that this review is greatly underpowered to address the safety of dipyrone. In particular, rare, but potentially serious, adverse events such as agranulocytosis, are very unlikely to be detected in these studies.

Potential biases in the review process

We identified the included studies from a comprehensive search of published papers, and used standard methods for analysis. We excluded six studies because they used non-standard measurement scales. We judged that it was unlikely these studies could have given different results that would have changed the findings of this review.

We can estimate the number of participants in studies with zero effect (RR of 1) required in order to change the NNT for at least 50% pain relief to an unacceptably high level (in this case 10) (Moore 2008). Data from over 900 participants in studies comparing oral dipyrone 500 mg with placebo would be required, and it is unlikely that such data exist.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews or meta-analyses of dipyrone in acute postoperative pain. One narrative review reported that dipyrone has similar efficacy to other NSAIDs and IV paracetamol, has a notable spasmolytic effect, and is rarely associated with agranulocytosis and other disorders of haematopoiesis (Jage 2008). The results were almost identical to that of the previous version of this review (Derry 2010).

AUTHORS' CONCLUSIONS

Implications for practice

For people with acute postoperative pain

Dipyrone 500 mg taken by mouth provides good pain relief for about 7 in 10 people. We found little evidence for other doses or other routes of administration. This analysis was based on information from relatively few participants and the quantitative estimates were not robust; the results should be interpreted with caution. Use of dipyrone is banned or restricted in many countries because it has been associated with serious blood disorders, particularly agranulocytosis. Susceptibility to these adverse effects may vary between different populations, and the single dose studies used in this review are inadequate to assess adverse events.

For clinicians

Dipyrone 500 mg taken by mouth provides good pain relief for about 7 in 10 people. We found little evidence for other doses or other routes of administration. This analysis was based on information from relatively few participants and the quantitative estimates were not robust; the results should be interpreted with caution.

Use of dipyrone is banned or restricted in many countries because it has been associated with serious blood dyscrasias, particularly agranulocytosis. Susceptibility to these adverse effects may vary between different populations, and the single dose studies used in this review are inadequate to assess adverse events. While dipyrone may provide adequate analgesia, patients should be monitored for blood dyscrasias as recommended by the manufacturers, if resources allow. The short onset of agranulocytosis seen in case reports is cause for concern.

In many countries, other drugs for which more evidence exists are readily available, while in other countries, dipyrone may be one of only a few drugs available.

For policy makers

The potential for good levels of pain relief with dipyrone must be balanced against the potential for life-threatening adverse effects in some people. The single dose studies used in this review were inadequate to assess adverse events properly, and in particular the serious blood disorders with which dipyrone is associated. In many countries, other drugs for which more evidence exists are readily available, while in other countries, dipyrone may be one of only a few drugs available.

The need for monitoring has implications for non-prescription (over-the-counter) availability.

For funders

The potential for good levels of pain relief with dipyrone must be balanced against the potential for life-threatening adverse effects in some people. The single dose studies used in this review were inadequate to assess adverse events properly. While dipyrone may provide adequate analgesia, patients should be monitored for blood disorders as recommended by the manufacturers, if resources allow.

Implications for research

General

There were few studies that satisfied inclusion criteria for this review, so any results were not robust. Larger studies, with at least 200 participants, and studies using different doses and routes of administration of dipyrone, would be required to clarify its relative efficacy amongst other analgesics.

Information about uncommon, serious adverse events are best obtained from other study types, such as cohort and case-control studies.

Design

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

Measurement (endpoints)

Endpoints in these studies have been extensively validated, as have standard pain scoring systems. The main outcome used is one

valued by patients 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. However, there is 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bhounsule 1990

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 6 h Self assessment at 0, 0.5, 1.5, and 2 h, then hourly up to 6 h
Participants	Post-episiotomy N = 100 All F Age: not reported Baseline PI = severe
Interventions	Dipyrrone 500 mg, n = 20 Ibuprofen 400 mg, n = 20 Paracetamol 600 mg, n = 20 Aspirin 600 mg, n = 20

Single dose dipyrrone (metamizole) for acute postoperative pain in adults (Review)

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Bhounsule 1990 (Continued)

Placebo, n = 20

Outcomes	<p>PI: standard 4-point scale (0 to 3)</p> <p>PR: non-standard 4-point (1 to 4), standard wording, but non-standard numbering</p> <p>Adverse events</p>
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2/5

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	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Size	High risk	< 50 participants per treatment arm

Boraks 1987

Methods	<p>Randomised, double-blind, placebo controlled, single oral dose. Study duration 6 h</p> <p>Self assessment at 0, 0.5, and 1 h, then hourly up to 6 h</p>
Participants	<p>Dental extraction</p> <p>N = 149</p> <p>M 84, F 75</p> <p>Mean age: 27 years</p> <p>Baseline PI = moderate or severe</p>
Interventions	<p>Dipyrone 500 mg, n = 39</p> <p>Aspirin 650 mg, n = 31</p> <p>Flurbiprofen 50 mg, n = 40</p> <p>Placebo, n = 39</p>
Outcomes	<p>PI: standard 4-point scale (0 to 3)</p> <p>PR: 5-point scale (1 to 5) standard wording, but non-standard numbering</p>

Boraks 1987 (Continued)

PGE: standard 5-point scale

Adverse events

Notes Oxford Quality Score: R1, DB1, W0. Total = 2/5
Rescue medication allowed after 1 h

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	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Size	High risk	< 50 participants per treatment arm

De Miguel Rivero 1997

Methods	Randomised, double-blind, placebo controlled, single and multiple dose phases. IM route of administration for dipyron and oral route for ibuprofen arginine, with double-dummy placebo. Duration of single dose phase 5 h Self assessment at 0, 0.25, 0.5, and 1 h, then hourly up to 5 h
Participants	Orthopaedic surgery - total hip replacement N = 106 M 48, F 58 Mean age 62 years Baseline PI $\geq$ 50/100 mm
Interventions	Dipyron 2000 mg IM, n = 35 Ibuprofen arginine 400 mg oral, n = 36 Placebo, n = 35
Outcomes	PI: 100 mm VAS (no pain to unbearable pain) PGE: standard 5-point scale Use of rescue medication

De Miguel Rivero 1997 (Continued)

Adverse events

Withdrawals

Notes Oxford Quality Score: R1, DB2, W1. Total = 4/5

Rescue medication allowed after 1 h

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
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
Size	High risk	< 50 participants per treatment arm

Dos Santos Pereira 1986

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 4 h
	Self assessment at 0, 0.15, and 1 h, then hourly up to 4 h
Participants	Orthopaedic surgery
	N = 85
	M 57, F 28
	Mean age 39 years
	Baseline PI = moderate or severe
Interventions	Dipyrone 1000 mg, n = 28
	Paracetamol 1000 mg, n = 28
	Placebo, n = 29
Outcomes	PI: standard 4-point scale (0 to 3)
	PR: standard 5-point scale (0 to 4)
	PGE: non-standard 4-point scale
	Use of rescue medication

Single dose dipyrone (metamizole) for acute postoperative pain in adults (Review)

Dos Santos Pereira 1986 (Continued)

Notes Oxford Quality Score: R1, DB2, W0. Total = 3/5

Rescue medication allowed after 2 h

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	Capsules of identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Capsules of identical appearance
Size	High risk	< 50 participants per treatment arm

Olson 1999

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 6 h Self assessment at 0, 0.25, 0.5, 1.0, and 1.5 h and then hourly up to 6 h
Participants	Post-episiotomy or 2nd degree vaginal tear N = 108 All F Mean age: 24 years Baseline PI = severe
Interventions	Dipyrone 500 mg, n = 27 Ketoprofen 25 mg, n = 28 Ketoprofen 50 mg, n = 26 Placebo, n = 27
Outcomes	PI: standard 4-point scale (0 to 3) PR: standard 5-point scale (0 to 4) PGE: non-standard 4-point scale Use of rescue medication Adverse events

Olson 1999 (Continued)

Withdrawals

Notes Oxford Quality Score: R1, DB2, W1. Total = 4/5

Remedication was allowed after 1 h

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"individual randomisation envelope for each patient entering the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Observation by different person to one giving treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observation by different person to one giving treatment
Size	High risk	< 50 participants per treatment arm

Pinto 1984

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 4 h
	Self assessment at 0, 0.5, and 1 h, and then hourly up to 4 h
Participants	Post-tonsillectomy
	N = 85
	M 33, F 52
	Mean age: 23 years
	Baseline PI = moderate or severe
Interventions	Dipyrone 500 mg, n = 27
	Paracetamol 500 mg, n = 29
	Placebo, n = 29
Outcomes	PI: standard 4-point scale (0 to 3)
	PR: standard 5-point scale (0 to 4)
	PGE: non-standard 4-point scale
	Use of rescue medication
	Adverse events

Pinto 1984 (Continued)

Notes Oxford Quality Score: R1, DB2, W0. Total = 3/5

Rescue medication allowed after 2 h

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	Tablets identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Tablets identical in appearance
Size	High risk	< 50 participants per treatment arm

Rubinstein 1986

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 4 h Self assessment at 0, 0.5, and 1 h, and then hourly up to 4 h
Participants	Urological surgery N = 90 M 60, F 30 Mean age 49 years Baseline PI = moderate and severe
Interventions	Dipyrone 500 mg, n = 30 Paracetamol 500 mg, n = 30 Placebo, n = 30
Outcomes	PI: standard 4-point scale (0 to 3) PR: standard 5-point scale (0 to 4) PGE: non-standard 4-point scale Use of rescue medication Adverse events Withdrawals

Rubinstein 1986 (Continued)

Notes Oxford Quality Score: R1, DB2, W1. Total = 4/5

Rescue medication allowed after 2 h

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules of identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Capsules of identical appearance
Size	High risk	< 50 participants per treatment arm

Sakata 1986

Methods	Randomised, double-blind, placebo controlled, single oral dose. Study duration 4 h Self assessment at 0, 0.5, and 1 h, and then hourly up to 4 h
Participants	Mainly orthopaedic surgery N = 86 M 49, F 37 Mean age: 32 years Baseline PI = moderate and severe
Interventions	Dipyrone 1000 mg, n = 29 Paracetamol 1000 mg, n = 30 Placebo group, n = 27
Outcomes	PI: standard 4-point scale (0 to 3) PR: standard 5-point (0 to 4) PGE: non-standard 4-point scale
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2/5

Risk of bias

Bias	Authors' judgement	Support for judgement
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Single dose dipyrone (metamizole) for acute postoperative pain in adults (Review)

Sakata 1986 (Continued)

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	Method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not described
Size	High risk	< 50 participants per treatment arm

DB: double-blind; F: female; h: hour; IM: intramuscular; M: male; N: number of participants in study; n: number of participants in treatment arm; PGE: Patient Global Evaluation; PI: pain intensity; PR: pain relief; R: randomised; VAS: visual analogue scale; W: withdrawals.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aizawa 1972	Not randomised
Bagan 1998	No placebo
Bosch 1990	Included children
Brodner 2011	Dipyrone given intra-operatively
Casali 1981	Short study duration (3 h)
Castro 2000	Administered preoperatively
Daftary 1980	Number of participants with moderate or severe pain not stated; included mild pain; non-standard PR scale used
Ferrario 1984	Baseline pain not measured. Non-standard PI scale. Small size (N = 7)
Frantz 2009	Multiple doses; no single-dose data
Gomez Jimenez 1980	Non-standard PI scale
Gonzalez Garcia 1994	No placebo
Goutaine 1975	Not randomised or blind
Hernandez 1997	Not blind
Herrera Barroso 1982	Non-standard PI and PR scales
Ibarra-Ibarra 1993	No placebo

Study	Reason for exclusion
Lal 1973	Short study duration (30 minutes). Non-standard PI and PR scales
Martin Duce 1997	Short study duration (1 h)
Mehta 1967	Not randomised or blinded
Mendl 1992	No placebo
Mukherjee 1980	Non-standard scales
Noronha 2009	First dose administered preoperatively
Patel 1980	No placebo
Quiñones 1993	Did not present hourly pain outcome data
Reyes 1988	No single dose data
Rosas Pérez 1986	No placebo
Saray 2001	Baseline pain not measured. No single dose data
Sener 2008	Intraoperative administration, not established pain
Stankov 1995	No placebo

h: hour; N: number of participants in study; PI: pain intensity; PR: pain relief.

DATA AND ANALYSES

Comparison 1. Oral dipyrone 500 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with $\geq 50\%$ pain relief over 4 to 6 hours	5	288	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.84, 3.11]
2 Participants using rescue medication over 4 to 6 hours	4	248	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.11, 0.40]

Analysis 1.1. Comparison 1 Oral dipyrone 500 mg versus placebo, Outcome 1 Participants with $\geq 50\%$ pain relief over 4 to 6 hours.

Study or subgroup	Dipyrone 500 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhounsule 1990	12/20	6/20		13.44%	2[0.94,4.27]
Favours placebo				Favours dipyrone

Analysis 1.2. Comparison 1 Oral dipyrone 500 mg versus placebo, Outcome 2 Participants using rescue medication over 4 to 6 hours.

APPENDICES

Appendix 1. Search strategy for CENTRAL (via CRSO)

- MESH DESCRIPTOR dipyrone EXPLODE ALL TREES (173)
- (dipyrone OR metamizol*):TI,AB,KY (558)
- (adolkin OR afebrin OR aminopyrine sulphonate OR anador OR analgin OR analginum OR ascorfebrina OR baralgin OR dolemicin OR dolo buscopan OR huberdor OR inalgon OR lasain OR lialgil OR metamizol OR metamizole OR metamizole sodium OR methampyrone OR minalgin OR natrium novaminsulfonicum OR neo meubrina OR neu novalgin OR neu novalgine OR neuro-brachont OR neuro-formatin S OR nolotil OR noramidaophenum OR noraminophenazonum OR norgesic OR novalgina OR novalgine OR novamidazofen OR optalgin OR pirenil OR sulpyrinepyrethane OR trisalgina):TI,AB,KY (267)
- 1 OR 2 OR 3 (574)
- MESH DESCRIPTOR Pain, Postoperative EXPLODE ALL TREES (9224)
- ((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 (16726)
- ((post-surgical adj4 pain*) OR ("post surgical" adj4 pain*) OR (post-surgery adj4 pain*)):TI,AB,KY (106)
- ("pain-relief after surg*") OR ("pain following surg*") OR ("pain control after"):TI,AB,KY (364)
- ("post surg*" OR post-surg*) AND (pain* OR discomfort):TI,AB,KY (381)
- ((pain* adj4 "after surg*") OR (pain* adj4 "after operat*") OR (pain* adj4 "follow* operat*") OR (pain* adj4 "follow* surg*")):TI,AB,KY (762)

- 11.((analgesi* adj4 "after surg*") OR (analgesi* adj4 "after operat*") OR (analgesi* adj4 "follow* operat*") OR (analgesi* adj4 "follow* surg*"));TI,AB,KY (303)
- 12.5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 (19610)
- 13.3 and 12 (315)

Appendix 2. Search strategy for MEDLINE (via Ovid)

1. Dipyrone/ (1257)
2. (dipyrone or metamizol*).mp. (1752)
3. (adolkin or afebrin or aminopyrine sulphonate or anador or analgin or alginum or ascorfebrina or baralgin or dolemicin or dolo buscopan or huberdor or inalgon or lasain or lialgil or metamizol or metamizole or metamizole sodium or methampyrone or minalgin or natrium novaminsulfonicum or neo meubrina or neu novalgin or neu novalgine or neuro-brachont or neuro-formatin S or nolotil or noramidaophenum or noraminophenazonum or norgesic or novalgina or novalgine or novamidazofen or optalgin or pirenil or sulpyrinepyrethane or trisalgina).mp. (902)
4. OR/1-3 (1882)
5. Pain, postoperative/ (29234)
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. (47413)
7. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (334)
8. (("pain-relief after surg*") or ("pain following surg*") or ("pain control after")).mp. (598)
9. (("post surg*" or post-surg*) AND (pain* or discomfort)).mp. (1228)
- 10.((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (2753)
- 11.((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (577)
- 12.OR/5-11 (49482)
- 13.randomized controlled trial.pt. (406912)
- 14.controlled clinical trial.pt. (91324)
- 15.randomized.ab. (299530)
- 16.placebo.ab. (156120)
- 17.drug therapy.fs. (1820254)
- 18.randomly.ab. (212212)
- 19.trial.ab. (311214)
- 20.groups.ab. (1340408)
- 21.OR/13-20 (3429681)
- 22.4 AND 12 AND 21 (231)

Appendix 3. Search strategy for EMBASE (via Ovid)

1. Dipyrone/ (6920)
2. (dipyrone or metamizol*).mp (7234)
3. (adolkin or afebrin or aminopyrine sulphonate or anador or analgin or alginum or ascorfebrina or baralgin or dolemicin or dolo buscopan or huberdor or inalgon or lasain or lialgil or metamizol or metamizole or metamizole sodium or methampyrone or minalgin or natrium novaminsulfonicum or neo meubrina or neu novalgin or neu novalgine or neuro-brachont or neuro-formatin S or nolotil or noramidaophenum or noraminophenazonum or norgesic or novalgina or novalgine or novamidazofen or optalgin or pirenil or sulpyrinepyrethane or trisalgina).ti,ab (2122)
4. OR/1-3(7518)
5. Pain, postoperative/ (40435)
6. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* NEAR pain*) or (postoperative adj4 analgesi* or (post-operative adj4 analgesi*) or ("post-operative analgesi*")).mp. (78385)
7. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (849)
8. (("pain-relief after surg*") or ("pain following surg*") or ("pain control after")).mp. (923)
9. (("post surg*" or post-surg*) AND (pain* or discomfort)).mp. (3234)
- 10.((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (4252)
- 11.((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (826)
- 12.OR/5-11 (82424)

- 13.(random* or factorial* or crossover or "cross over" or cross-over).tw. (1065325)
- 14.(placebo* or (doubl* adj blind*) or (singl* adj blind*)).tw. (291579)
- 15.(allocat* or allocat*).tw. (96761)
- 16.crossover Procedure/ (43946)
- 17.double-blind procedure/ (125003)
- 18.Randomized Controlled Trial/ (382097)
- 19.OR/13-18 (1297615)
- 20.4 AND 12 AND 19 (442)

Appendix 4. Search strategy for LILACS

dipyrone OR metamizole OR adolkin OR afebrin OR aminopyrine sulphonate OR anador OR analgin OR analginum OR ascorfebrina OR baralgin OR dolemicin OR dolo buscopan OR huberdor OR inalgon OR lasain OR lisalgil OR metamizol OR metamizole OR metamizole sodium OR methampyrone OR minalgin OR natrium novaminsulfonicum OR neo meubrina OR neu novalgin OR neu novalgine OR neuro-brachont OR neuro-formatin S OR nolotil OR noramidaophenum OR noraminophenazonum OR norgesic OR novalgina OR novalgine OR novamidazofen OR optalgin OR pirenil OR sulpyrinepyrethane OR trisalgina [Words] and (postoperative AND pain\$) OR (post-operative AND pain\$) OR (post-surgical AND pain\$) OR (post AND surgical AND pain\$) OR (post-surgery AND pain\$) OR (pain-relief AND after AND surg\$) OR (pain AND following AND surg\$) or (pain AND control AND after) OR (pain\$ AND after AND surg\$) OR (pain\$ AND after AND operat\$) OR (pain\$ AND follow\$ AND operat\$) OR (pain\$ AND follow\$ AND surg\$) OR (analgesi\$ AND after AND surg\$) OR (analgesi\$ AND after AND operat\$) OR (analgesi\$ AND follow\$ AND operat\$) OR (analgesi\$ AND follow\$ AND surg\$) OR ((post AND surg\$ OR post-surg\$) AND (pain\$ or discomfort\$) [Words] and ((ensaio\$ OR ensayo\$ OR trial\$) AND (azar OR acaso OR placebo OR control\$ OR aleat\$ OR random\$ OR enmascarado\$ OR simpleciego)) OR ((simple\$ OR single OR duplo\$ OR doble\$ OR double\$) AND (cego OR ciego OR blind OR mask)) [Words]

Appendix 5. Glossary

Categorical rating scale

The most common scale used 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 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 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)

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 patient 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 end and the person's mark, usually in millimetres. The main advantages of the VAS is that it is simple and quick to score, avoids imprecise descriptive terms, and provides 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 patient 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 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 6. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning grade of evidence ([GRADEpro GDT 2016](#)).

- **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 relative risk 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 relative risk 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).

Appendix 7. Summary of efficacy outcomes in individual studies

Study ID	Treatment	Analgesia		Rescue medication	
		PI or PR	Number with 50% PR	Median time to use (h)	Number using
Bhounsule 1990	(1) dipyron 500 mg, n = 20	TOTPAR 6:	(1) 12/20	Not reported	Not reported
	(2) ibuprofen 400 mg, n = 20	(1) 13.0	(2) 13/20		
	(3) paracetamol 600 mg, n = 20	(2) 14.2	(3) 7/20		
	(4) aspirin 600 mg, n = 20	(3) 8.1	(4) 5/20		
	(5) placebo, n = 20	(4) 6.7	(5) 6/20		
		(5) 7.4			
Boraks 1987	(1) dipyron 500 mg, n = 39	-	(1) 28/39	Not reported	at 6 h:
	(2) aspirin 650 mg, n = 41		(2) 25/41		(1) 6/39
	(3) flurbiprofen 50 mg, n = 40		(3) 25/40		(2) 1/41
	(4) placebo, n = 39		(4) 16/39		(3) 4/40 (4) 20/39
De Miguel Rivero 1997	(1) dipyron 2000 mg, n = 35	VAS SPID 5:	(1) 26/35	Not reported	Not reported
	(2) ibuprofen arginine 400 mg, n = 36	(1) 196.8	(2) 25/36		
	(3) placebo, n = 35	(2) 187.0	(3) 16/35		

(Continued)

		(3) 119.8			
Olson 1999	(1) dipyrone 500 mg, n = 27	TOTPAR 6:	(1) 19/27	(1) > 6	at 6 h:
	(2) ketoprofen 25 mg, n = 28	(1) 9.6	(2) 19/28	(2) > 6	(1) 14/67
	(3) ketoprofen 50 mg, n = 26	(2) 9.1	(3) 18/26	(3) > 6	(2) 20/67
	(4) placebo, n = 27	(3) 9.3	(4) 5/27	(4) 1.3	(3) 25/66
		(4) 2.8			(4) 31/39
Pinto 1984	(1) dipyrone 500 mg, n = 27	TOTPAR 4:	(1) 21/27	Not reported	at 4 h:
	(2) paracetamol 500 mg, n = 29	(1) 10.7	(2) 24/29		(1) 2/27
	(3) placebo, n = 29	(2) 11.4	(3) 10/27		(2) 0/29
		(3) 5.6			(3) 8/29
Rubinstein 1986	(1) dipyrone 500 mg, n = 30	TOTPAR 4:	(1) 26/30	Not reported	at 4 h:
	(2) paracetamol 500 mg, n = 30	(1) 11.9	(2) 22/30		(1) 0/30
	(3) placebo, n = 30	(2) 10.1	(3) 8/30		(2) 2/30
		(3) 4.7			(3) 6/30
Sakata 1986	(1) dipyrone 1000 mg, n = 29	TOTPAR 4:	(1) 18/29	Not reported	Not reported
	(2) paracetamol 1000 mg, n = 30	(1) 8.7	(2) 17/30		
	(3) placebo, n = 27	(2) 8.4	(3) 3/27		
		(3) 2.8			
Dos Santos Pereira 1986	(1) dipyrone 1000 mg, n = 28	SPID 4:	(1) 22/28	Not reported	at 4 h:
	(2) paracetamol 1000 mg, n = 28	(1) 6.2	(2) 21/28		(1) 1/28
	(3) placebo, n = 29	(2) 6.4	(3) 7/29		(2) 0/28
		(3) 2.1			(3) 11/29

h: hour; n: number of participants in treatment arm; PI: pain intensity; PR: pain relief; SPID: summed pain intensity difference; TOTPAR: total pain relief; VAS: visual analogue scale.

Appendix 8. Summary of adverse events and withdrawals

Study ID	Treatment	Adverse events		Withdrawals	
		Any	Serious	Adverse event	Other
Bhounsule 1990	(1) dipyrone 500 mg, n = 20	None	None	None	Not reported
	(2) ibuprofen 400 mg, n = 20				
	(3) paracetamol 600 mg, n = 20				

(Continued)

	(4) aspirin 600 mg, n = 20				
	(5) placebo, n = 20				
Boraks 1987	(1) dipyron 500 mg, n = 39	(1) 4/39 (somnolence, dizziness, nausea, headache)	Not reported	None reported	Not reported
	(2) aspirin 650 mg, n = 41				
	(3) flurbiprofen 50 mg, n = 40	(2) 6/41			
	(4) placebo, n = 39	(3) 7/40			
		(4) 8/39 (somnolence, dizziness, nausea, warm feeling)			
De Miguel Rivero 1997	(1) dipyron 2000 mg, n = 35	(1) 0/35	None	None	None
	(2) ibuprofen arginine 400 mg, n = 36	(2) 1/36			
	(3) placebo, n = 35	(3) 1/35			
		(headache)			
Olson 1999	(1) dipyron 500 mg, n = 27	"No adverse events reported during this study"	None	None	None
	(2) ketoprofen 25 mg, n = 28				
	(3) ketoprofen 50 mg, n = 26				
	(4) placebo, n = 27				
Pinto 1984	(1) dipyron 500 mg, n = 27	(1) 1/27 (arterial hypertension)	None	None	Not reported
	(2) paracetamol 500 mg, n = 29				
	(3) placebo, n = 29				
Rubinstein 1986	(1) dipyron 500 mg, n = 30	(2) 1/30 (vomiting)	None	None	None
	(2) paracetamol 500 mg, n = 30				
	(3) placebo, n = 30				
Sakata 1986	(1) dipyron 1000 mg, n = 29	Not reported	Not reported	Not reported	Not reported
	(2) paracetamol 1000 mg, n = 30				
	(3) placebo, n = 27				
Dos Santos Pereira 1986	(1) dipyron 1000 mg, n = 28	"well tolerated"	Not reported	Not reported	Not reported
	(2) paracetamol 1000 mg, n = 28				
	(3) placebo, n = 29				
n: number of participants in treatment arm.					

WHAT'S NEW

Date	Event	Description
22 April 2016	Review declared as stable	See Published notes .

CONTRIBUTIONS OF AUTHORS

All review authors contributed to writing the revised protocol.

LH and SD searched for studies, selected studies for inclusion, and carried out data extraction.

RAM acted as arbitrator.

All authors were involved in analysis and writing the full review.

SD will be responsible for updating the review, if appropriate.

DECLARATIONS OF INTEREST

LH none known

SD none known

RAM has received institutional grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has attended boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015).

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

We have assessed the quality of the evidence using the GRADE approach and included a 'Summary of findings' table in the full review, which were not included in the Protocol.

NOTES

For the latest update (2016) we did not identify any potentially relevant studies that were published after 1999. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Dipyrone [*administration & dosage]; Injections, Intramuscular; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male