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Codeine, alone and with paracetamol (acetaminophen), for cancer pain (Review)

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[Intervention Review]

Codeine, alone and with paracetamol (acetaminophen), for cancer pain

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ABSTRACT

Background

Pain is very common in patients with cancer. Opioid analgesics, including codeine, play a significant role in major guidelines on the management of cancer pain, particularly for mild to moderate pain. Codeine is widely available and inexpensive, which may make it a good choice, especially in low-resource settings. Its use is controversial, in part because codeine is not effective in a minority of patients who cannot convert it to its active metabolite (morphine), and also because of concerns about potential abuse, and safety in children.

Objectives

To determine the efficacy and safety of codeine used alone or in combination with paracetamol for relieving cancer pain.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2014, Issue 2), MEDLINE and EMBASE from inception to 5 March 2014, supplemented by searches of clinical trial registries and screening of the reference lists of the identified studies and reviews in the field.

Selection criteria

We sought randomised, double-blind, controlled trials using single or multiple doses of codeine, with or without paracetamol, for the treatment of cancer pain. Trials could have either parallel or cross-over design, with at least 10 participants per treatment group. Studies in children or adults reporting on any type, grade, and stage of cancer were eligible. We accepted any formulation, dosage regimen, and route of administration of codeine, and both placebo and active controls.

Data collection and analysis

Two review authors independently read the titles and abstracts of all studies identified by the searches and excluded those that clearly did not meet the inclusion criteria. For the remaining studies, two authors read the full manuscripts and assessed them for inclusion. We resolved discrepancies between review authors by discussion. Included studies were described qualitatively, since no meta-analysis was possible because of the small amount of data identified, and clinical and methodological between-study heterogeneity.

Main results

We included 15 studies including 721 participants with cancer pain due to diverse types of malignancy. All studies were performed on adults; there were no studies on children. The included studies were of adequate methodological quality, but all except for one were judged to be at a high risk of bias because of small study size, and six because of methods used to deal with missing data or high withdrawal rates. Three studies used a parallel group design; the remainder were cross-over trials in which there was an adequate washout period, but only one reported results for treatment periods separately.

Twelve studies used codeine as a single agent and three combined it with paracetamol. Ten studies included a placebo arm, and 14 included one or more of 16 different active drug comparators or compared different routes of administration. Most studies investigated the effect of a single dose of medication, while five used treatment periods of one, seven or 21 days. Most studies used codeine at doses of 30 mg to 120 mg.

There were insufficient data for any pooled analysis. Only two studies reported our preferred responder outcome of 'participants with at least 50% reduction in pain' and two reported 'participants with no worse than mild pain'. Eleven studies reported treatment group mean measures of pain intensity or pain relief; overall for these outcome measures, codeine or codeine plus paracetamol was numerically superior to placebo and equivalent to the active comparators.

Adverse event reporting was poor: only two studies reported the number of participants with any adverse event specified by treatment group and only one reported the number of participants with any serious adverse event. In multiple-dose studies nausea, vomiting and constipation were common, with somnolence and dizziness frequent in the 21-day study. Withdrawal from the studies, where reported, was less than 10% except in two studies. There were three deaths, in all cases due to the underlying cancer.

Authors' conclusions

We identified only a small amount of data in studies that were both randomised and double-blind. Studies were small, of short duration, and most had significant shortcomings in reporting. The available evidence indicates that codeine is more effective against cancer pain than placebo, but with increased risk of nausea, vomiting, and constipation. Uncertainty remains as to the magnitude and time-course of the analgesic effect and the safety and tolerability in longer-term use. There were no data for children.

PLAIN LANGUAGE SUMMARY

Codeine, alone and with paracetamol (acetaminophen), for cancer pain

Codeine is an opioid medication commonly used worldwide to treat pain including cancer pain. Oral codeine, either alone or in combination with paracetamol, provided good pain relief for some people with cancer pain, based on limited amounts of information.

In this review we set out to estimate how well codeine worked, how many people had side effects, and how severe those side effects were - for example, whether they were so severe that participants stopped taking their oral codeine. We included 15 studies with 721 participants. The studies we found had methodological shortcomings: they were small and of short duration. They also reported results in different ways, so that it was not possible to combine results. In seven of the eight studies that compared codeine with placebo, codeine was better than placebo. In studies that compared codeine with another drug, the results were similar. Codeine at doses of 30 mg to 120 mg, alone or in combination with paracetamol, does seem to provide a good level of pain relief for some people with cancer pain. We cannot be certain about how many people will get this benefit, and we do not know whether, or by how much, adding paracetamol increases its effect. Codeine increases nausea, vomiting, and constipation, and may cause drowsiness or dizziness if used for more than a week. Some people will stop taking codeine because of the side effects.

More trials comparing codeine with other treatments and using patient-centred outcomes are needed. The role of codeine in mild cancer pain, in addition to moderate to severe cancer pain, should be investigated.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Codeine ± paracetamol compared with placebo for cancer pain

Patient or population: Adults with cancer pain

Settings: any

Intervention: codeine 60 mg ± paracetamol single dose

Comparison: placebo

Outcomes	Outcome with comparator (placebo)	Outcome with intervention (active)	Relative effect	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
At least 50% reduction in pain or equivalent	22/69 (32%)	39/69 (57%)	Not calculated	2 studies, 69 participants	Very low	Small numbers of studies and participants. Single dose, cross-over studies.
"Moderate" benefit At least 30% reduction in pain	No data		Not calculated			
Proportion below 30/100 mm on VAS	No data		Not calculated			
Patient Global Impression of Change much or very much improved	No data		Not calculated			
Adverse event withdrawals	No usable data. Uncommon, 2 reported in one study, unclear during which treatment period		Not calculated		Very low	
Serious adverse events	None reported, only 1 study specified no serious adverse events		Not calculated		Very low	
Death	3 deaths, all reported to be due to disease progression in the studies		Not calculated		Very low	

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.

VAS: visual analogue scale

BACKGROUND

Description of the condition

Pain is very common in patients with a diagnosis of cancer, and for many it is the most disruptive and distressing symptom. It may be due to the primary cancer itself or metastases, or to treatment (for example chemotherapy, radiation, surgery) or to a comorbid condition. A systematic review of pain prevalence in patients with cancer reported rates in excess of 50% (52% to 70%) for six different cancers. More than one third reported pain of moderate to severe intensity (van den Beuken-van Everdingen 2007). For the purposes of this review, cancer pain is defined broadly as pain of unspecified origin in any patient with cancer or a history of cancer.

Description of the intervention

Codeine is an opioid analgesic, and is the most widely used, naturally occurring narcotic in medical treatment in the world (Opiates 2013). Codeine can also be synthesised from morphine. It is most commonly administered by mouth (as tablets or syrup), but is also available for intramuscular and subcutaneous injections, and in some countries as suppositories. In many countries it is a controlled substance, but it may still be available in small quantities without prescription, in combination analgesics with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) and in cough syrups. In 2012 in England, there were almost 3.6 million prescriptions in primary care for codeine phosphate, mostly as 30 mg and 15 mg tablets, with many more for combination products (PCA 2013). The BNF 2014 suggests a dose of 30 mg to 60 mg every four hours as required for mild to moderate pain in adults. These doses are usually available on prescription only.

Codeine is used for a variety of painful states and conditions, including pain associated with cancer. Opioid analgesics, including codeine, play a significant role in major guidelines associated with the management of pain for patients diagnosed with cancer (Caraceni 2012; Jacox 1994; Miaskowski 2005; Ripamonti 2012 I; SIGN 2008; WHO 1996). In the context of these guidelines, codeine is considered an analgesic for moderate pain or for situations where simple analgesics (for example NSAIDs or paracetamol) alone are ineffective or provide suboptimal analgesia. Codeine has been used in children, although recent guidance is critical of this use (RCPCH 2013; WHO 2012).

In some clinical guidelines, codeine is referred to as a 'weak' opioid analgesic. Codeine and tramadol are defined as step II opioids on the WHO analgesic ladder. The role and utility of step II opioids in cancer pain are controversial (Ripamonti 2012 II) and there is currently a discussion as to whether step II opioids should be omitted from the ladder since low doses of step III opioids are equally, or in the case of 'poor metabolisers', more effective. The European Association for Palliative Care currently recommends both options (Caraceni 2012).

As with other opioid analgesics, codeine is associated with significant adverse effects. In acute dosing situations, concerns centre around respiratory depression and other adverse effects mediated by the central nervous system, such as excessive sedation or nausea and vomiting. The principal adverse effect associated with chronic dosing is constipation, which in most patients requires prophylactic use of stimulant laxatives (Jackson 2001). The use of codeine for postoperative pain in children is currently under serious debate due to safety issues (Kuehn 2013). As an opioid, codeine is a drug with the potential for abuse and addiction.

Codeine use in cancer pain remains consistent and in some settings may be increasing (De Conno 2003). This may be due to earlier treatment of cancer pain, codeine becoming more widely available, prescribing preferences, or other issues, such as cost. Codeine use is primarily promoted for cases of mild to moderate pain, or when simple analgesics in isolation are inadequate (Jadad 1995). The role of codeine in more severe pain is not well described. Opioid use in more severe pain may be limited by the development of constipation, which may be even more problematic for codeine than other opioids (Bennett 2003; Jackson 2001).

How the intervention might work

Codeine is a prodrug. It is metabolised to morphine in the liver. The analgesic effect of morphine is due to its action on the mu opioid receptor. Morphine is metabolised in the liver and brain, the predominant metabolites being morphine-3-glucuronide and morphine-6-glucuronide. The total production of morphine-3-glucuronide is approximately five times higher than that of morphine-6-glucuronide. Morphine-3-glucuronide has low potency at the mu receptor and is considered to be inactive in humans, while morphine-6-glucuronide is a mu receptor agonist with analgesic effect and is more potent than morphine (Paul 1989; Wittwer 2006).

In most people 5% to 10% of codeine is converted to morphine; a 30 mg dose of codeine is considered equivalent to a 3 mg dose of morphine. The ability to metabolise codeine varies between individuals. Some (up to 10% of Caucasians, 2% of Asians, and 1% of Arabs) are 'poor metabolisers' (Cascarbi 2003) with low rates of conversion, and in these people codeine is a relatively ineffective analgesic. At the other extreme, a few individuals are 'extensive metabolisers' with high rates of conversion, and this puts them at increased risk of toxicity from standard doses. There are rare case reports of deaths attributed to ultrarapid metabolism of codeine administered at recommended doses (Ciszkowski 2009; Madadi 2007).

A number of medications can interfere with the enzymes that catalyse the metabolism of codeine, and by increasing or decreasing the extent of conversion they can change the analgesic effect. The selective serotonin reuptake inhibitors fluoxetine and paroxetine (used for the treatment of depression which may present as a comorbidity along with malignant disease) as well as the serotonin and noradrenaline reuptake inhibitor duloxetine (which may be used for pain management) for example, reduce conversion, and other drugs, such as rifampicin and dexamethasone, increase it.

Why it is important to do this review

There is clearly an unmet need for pain control amongst cancer patients. Codeine is inexpensive and has a long track record. However, there is an ongoing controversy as to whether there is a place for step II opioids in the treatment of cancer pain.

A systematic review is needed to inform clinical practice and guideline development. This Cochrane review will investigate how effective codeine is in controlling cancer pain compared to placebo or other analgesics, and whether adding paracetamol to codeine confers any benefit.

The present review is one of a series of reviews whose aim is to evaluate the place of opioid analgesics in the management of cancer pain. Other important reviews include updates of oral morphine for cancer pain (Wiffen 2013), transdermal fentanyl for cancer pain (Hadley 2013), and methadone for cancer pain (Nicholson 2007), which is currently being updated. Other relevant Cochrane reviews include NSAIDs or paracetamol, alone or combined with opioids, for cancer pain (McNicol 2005), single dose oral codeine, as a single agent, for acute postoperative pain in adults (Derry 2010), and single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults (Toms 2009).

OBJECTIVES

To determine the efficacy and safety of codeine used alone or in combination with paracetamol for relieving cancer pain when compared with placebo or an alternative active treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We sought randomised, double-blind, placebo- or active-controlled studies using single or multiple doses of codeine, with or without paracetamol, for the treatment of cancer pain. Studies could use either a parallel or cross-over design and had to have at least 10 participants per treatment group. Studies including participants with pain of different (cancer and non-cancer) aetiologies were eligible for inclusion if they reported results separately for participants with cancer pain or where the majority of participants had cancer pain. We included studies reported as full journal publications. We would have also included trials with information available in the form of substantial clinical trial summaries. We did not include studies published only as short abstracts (typically conference abstracts).

Types of participants

Studies had to report on children or adults with cancer pain. We accepted any type, grade, and stage of cancer. In order to be inclusive, we accepted studies conducted in populations with cancer and non-cancer pain, as long as the majority of patients had cancer; we would have excluded them in a sensitivity analysis if they had contributed to any pooled analysis. Studies where only a minority of patients had cancer pain and where results were not reported separately for such patients were excluded.

Types of interventions

Studies had to investigate codeine, alone or in combination with paracetamol, using any formulation, dosage regimen, and route of administration. Comparators were placebo or an alternative active treatment.

Types of outcome measures

Our preferred outcome measures are based on recent guidance as provided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008), the Special Interest Group on Systematic Reviews in Pain Relief of the International Association for the Study of Pain, and the Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors (Moore 2010). We preferred responder outcomes over treatment group average outcomes; the former are more informative than the latter as there is considerable between-participant heterogeneity with regard to pain intensity and pain relief in clinical trials (Moore 2013).

Primary outcomes

- Participants with at least 50% reduction in pain (preferred outcome)
- Participants with pain intensity below 30/100 mm on the visual analogue scale (VAS) or 3/10 on the numeric rating scale (NRS) (preferred outcome)
- Patient Global Impression of Change (participants who are much or very much improved)

Secondary outcomes

- Treatment group average pain intensity or pain relief
- Functioning (any scale)
- Adverse events: any adverse events, serious adverse events
- Withdrawals: any withdrawals, lack of efficacy withdrawals, adverse event withdrawals
- Death

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library,* Issue 2 of 12, 2014;
- MEDLINE (via PubMed) from inception to 5 March 2014;
- EMBASE (via Ovid) from inception to 5 March 2014.

We developed detailed search strategies for each database searched, based on the strategy developed for MEDLINE and revised appropriately for each database. Appendix 1 details the MEDLINE search strategy, Appendix 2 the CENTRAL search strategy and Appendix 3 the EMBASE search strategy.

We applied no language restrictions.

Searching other resources

We screened the bibliographies of studies and review articles in this field for other potentially relevant studies. We also searched trials registries for details of unpublished and ongoing trials: the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). The search was performed on 5 March 2014.

Data collection and analysis

Selection of studies

Two review authors independently read the titles and abstracts of all studies identified by the searches and excluded those that clearly did not meet the inclusion criteria. For the remaining studies two authors read the full manuscripts to assess if they should be included. We resolved discrepancies between review authors by discussion. We did not anonymise studies before selection. Reasons for excluding studies are reported, unless the studies were excluded on the basis of title or abstract.

Data extraction and management

Two review authors independently extracted data using a standard form. Discrepancies were resolved by discussion before data entry into Review Manager 5 (RevMan 2012). Data extracted included:

1. publication details;
2. patient population, number of patients, age, type of cancer;
3. study design and duration;
4. description of the pharmacological intervention;
5. description of the instruments used to evaluate pain;
6. outcome measures as detailed above;
7. quality score as described below.

Assessment of risk of bias in included studies

We assessed methodological study quality using a validated scoring system, the Oxford Quality Scale (Jadad 1996). For inclusion, trials needed to score at least two points on this scale (out of a possible five points), one for randomisation and one for blinding.

We also used the 'Risk of bias' tool available in RevMan 5, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Pregnancy and Childbirth Group, with any disagreements resolved by discussion. The following were assessed for each study.

1. Random sequence generation (checking for possible selection bias). The method used to generate the allocation sequence was assessed 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).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions was assessed as to whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. The methods were assessed 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).
3. Blinding of outcome assessment (checking for possible detection bias). The methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received were assessed as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). The methods used to deal with incomplete data were assessed as: low risk (< 10% of participants did not complete the study or a 'baseline observation carried forward' analysis was used); unclear risk of bias ('last observation carried forward' analysis was used); high risk of bias ('completer' analysis was used).
5. Size of study (checking for possible biases confounded by small size). Studies were assessed as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We planned to use dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI), and would have calculated numbers needed to treat to benefit (NNT) as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to harm (NNH), and would have been calculated in the same manner.

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

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

If appropriate, we would have used continuous data to calculate the mean difference (± standard deviation (SD)) between treatment groups.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis: patients who were randomised, took the study medication, and gave a minimum of one post-baseline assessment. Where there were missing participants or information, these were assigned to a zero improvement category where possible. The method of dealing with data from withdrawals was ascertained where possible. In original studies, participants who withdrew may have been analysed using last observation carried forward (that is their level of pain when stopping the medication) or returned to their baseline observation.

We report when there are substantial numbers (> 10%) of participants missing from the analyses. There were insufficient data to conduct meta-analyses. Had meta-analyses been conducted, we would have performed sensitivity analyses to assess the impact of including studies with substantial numbers (> 10%) of participants missing from the analyses reported in the studies.

Assessment of heterogeneity

Had meta-analyses been conducted, heterogeneity would have been assessed using L'Abbé plots, a visual method for assessing differences in results of individual studies (L'Abbé 1987), and with the I^2 statistic. There could have been effects of differences between patients, environments (inpatient versus outpatient), and outcome measures. These would have been explored with subgroup and sensitivity analyses.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010). The review does not depend on what authors of the original studies chose to report or not.

Data synthesis

There were insufficient data to conduct meta-analyses; to pool data we would have required at least two studies and 200 participants

for the outcome and comparison in question (Moore 1998). If data had been available we would have performed data analysis using RevMan 5 (RevMan 2012), and we planned to carry out separate analyses for codeine used alone and codeine with paracetamol.

For dichotomous outcomes, we would have calculated the RR of benefit or harm with 95% CI using a fixed-effect model (Morris 1995); NNT or NNH would have been calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995).

For continuous outcomes (for example, group mean data for pain intensity or pain relief), we would have calculated the mean difference between the treatment groups. It was planned to meta-analyse the treatment group mean data only when the studies were similar enough to allow pooling and when the underlying individual data were normally distributed. We would have used fixed-effect model meta-analysis unless there was evidence of heterogeneity, when we would have used the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses, had they been appropriate.

- Immediate release codeine versus modified release codeine.
- Single dose versus multiple dose.
- By type of cancer.
- By age.

Sensitivity analysis

We planned to carry out the following sensitivity analyses, had they been appropriate.

- Studies including participants with cancer pain only versus studies including participants with cancer and other types of pain.
- Studies with an Oxford Quality Score ≥ 3 versus those with an Oxford Quality Score of 2.
- Studies using an enriched enrolment design versus studies using non-enriched enrolment (Straube 2008).

No sensitivity analyses were performed.

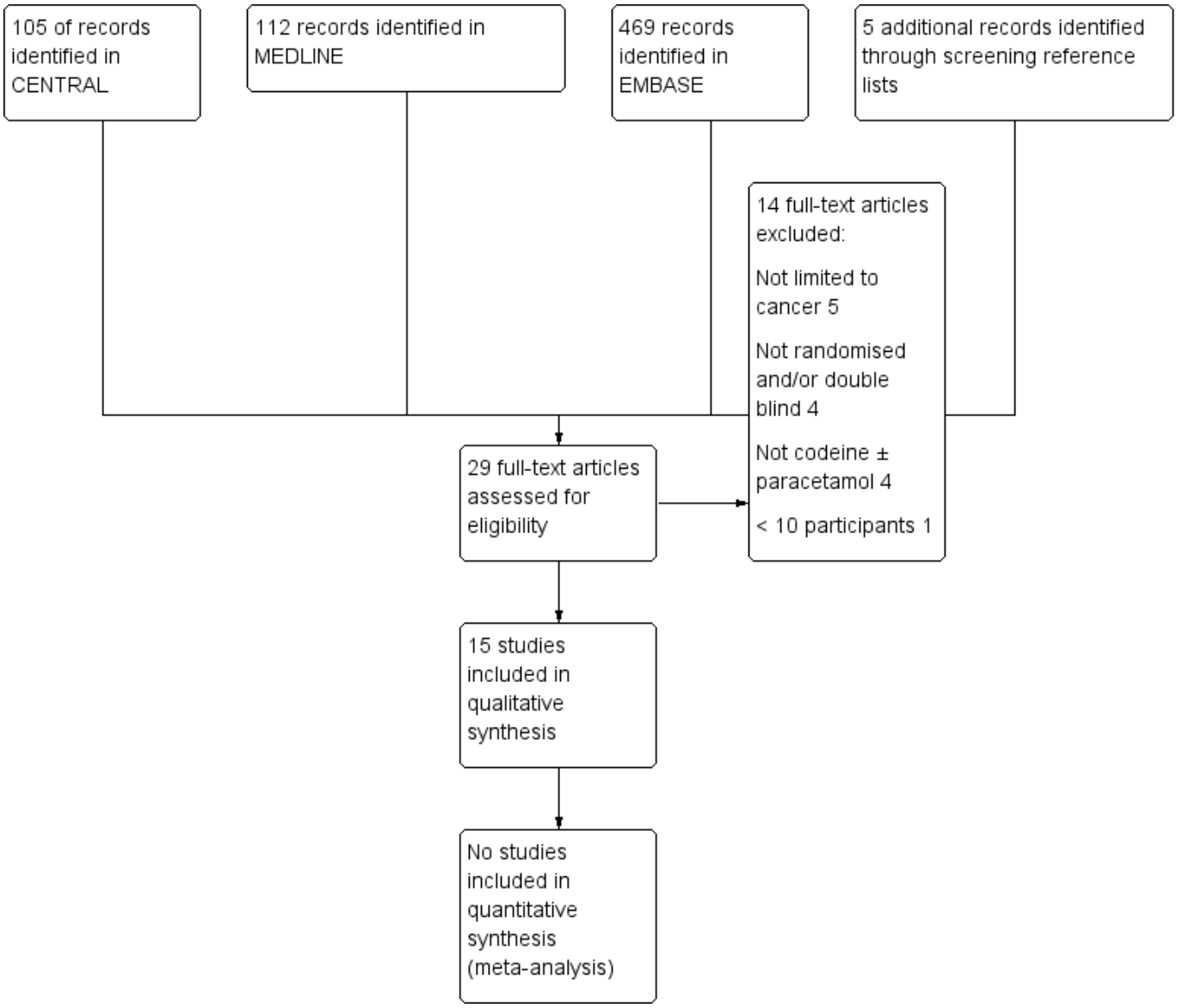
RESULTS

Description of studies

Results of the search

Electronic searches identified the following numbers of reports: MEDLINE: 112, EMBASE: 469, CENTRAL: 105. Screening reference lists identified five reports. Searching trial registries retrieved no additional relevant studies. See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 15 studies (Beaver 1978 I; Beaver 1978 II; Capretti 1970; Carlson 1990; Chen 2003; Dhaliwal 1995; Jochimsen 1978 I; Moertel 1971; Noyes 1975; Rico 2000; Rodriguez 2007; Stambaugh 1987; Staquet 1971; Staquet 1978; Staquet 1993) with a total of 721 participants with cancer pain due to diverse types of malignancy. One study (Capretti 1970) claimed to involve participants "in pain from cancer" but included one participant with Paget's disease. Another study (Staquet 1971) enrolled adults with chronic pathologic pain, most of whom had various types of cancer. Although neither study reported results separately for cancer participants, we decided to include these studies, intending to exclude them in a sensitivity analysis if they contributed to any pooled analysis, which they did not.

All studies were performed in adults; there were no studies in children. The mean age of the participants, where specified, varied between 51 and 64 years. The sex of the participants was not always stated; in the studies that reported it, the numbers were similar and overall were balanced (278 women, 268 men). One study included only women (Capretti 1970). Baseline pain intensity was at least moderate (≥ 40/100 mm) in all studies except Dhaliwal 1995, where it was not reported but likely to be mild, since the placebo group had pain intensities of 33/100 to 38/100 from days one to seven.

Three studies investigated codeine together with paracetamol (Carlson 1990; Rico 2000; Rodriguez 2007); all others investigated codeine as a single agent. Ten studies included a placebo arm (Capretti 1970; Carlson 1990; Chen 2003; Dhaliwal 1995; Jochimsen 1978 I; Moertel 1971; Noyes 1975; Stambaugh 1987; Staquet 1971; Staquet 1978). Oral codeine was compared with intramuscular codeine (Beaver 1978 I), and intramuscular codeine with intramuscular oxycodone and morphine (Beaver 1978 II), at various doses. Other active comparators for oral codeine were an investigational drug (Z 424) (Capretti 1970), ketorolac tromethamine (Carlson 1990), codeine plus ibuprofen (Chen 2003), benzopyranoperidine (Jochimsen 1978 I), aspirin (Moertel 1971), tetrahydro-

cannabinol (TCH) (Noyes 1975), ciramadol (Stambaugh 1987), alclofenac (Staquet 1971), a synthetic nitrogen analogue of tetrahydrocannabinol (NIB) (Staquet 1978), as well as piroxicam and piroxicam plus codeine (Staquet 1993). Codeine plus paracetamol was compared with hydrocodone plus paracetamol (Rodriguez 2007), tramadol plus paracetamol (Rico 2000), and tramadol alone (Rodriguez 2007).

In single-dose studies, the dose of codeine used was usually 30 mg to 180 mg (360 mg in a comparison with intramuscular opioids). In the study with one-day treatment periods, the doses of codeine were 30 mg and 60 mg. In studies with seven-day treatment periods, the dose of codeine was 100 mg to 200 mg (controlled release) every two hours, and up to 320 mg daily (mean 200 mg), while doses for the combination of codeine plus paracetamol were 240 mg plus 2400 mg, and up to 300 mg plus 5000 mg daily.

Three studies used a parallel group design (Carlson 1990; Rodriguez 2007; Staquet 1993) and the other 12 used a cross-over design. Most studies investigated the effect of a single dose of medication, usually over a period of six hours (Beaver 1978 I; Beaver 1978 II; Chen 2003; Jochimsen 1978 I; Moertel 1971; Noyes 1975; Stambaugh 1987; Staquet 1971; Staquet 1978; Staquet 1993). The other five studies used treatment periods of one day (Capretti 1970), seven days (Carlson 1990; Dhaliwal 1995; Rico 2000) or 21 days (Rodriguez 2007) for each intervention. Washout for cross-over studies was considered to be adequate.

See the Characteristics of included studies table for details.

Excluded studies

Fourteen studies were examined as full texts and excluded, most often because they investigated mixed populations with only a minority of participants having cancer, because they did not include a codeine or codeine plus paracetamol treatment arm, or because they were not randomised and double-blind. One study had fewer than 10 participants per treatment arm. See the Characteristics of excluded studies table for details. Other articles identified by the searches were excluded on the basis of their titles and abstracts without needing to obtain the full texts.

Risk of bias in included studies

Most of the included studies achieved total scores of three to five on the five-point Oxford Quality Scale (Jadad 1996); two had scores of only two (Beaver 1978 II; Capretti 1970). Points were lost because of inadequate descriptions of the method of randomisation (13 studies), not describing withdrawals (four studies) and not describing the method of double-blinding (four studies).

The 'Risk of bias' assessment (Characteristics of included studies; Figure 2; Figure 3) shows that all except one (Rodriguez 2007) of the included studies were at a high risk of bias because of small study size. Blinding of outcome assessment was largely adequate. Failure to provide details of the method used to generate the random number sequence or the method of allocation concealment is likely to reflect the age of the studies and does not necessarily indicate inadequate methods. Six studies were judged to be at high risk of bias because of imputation or withdrawal rates of >10%. See Characteristics of included studies.

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

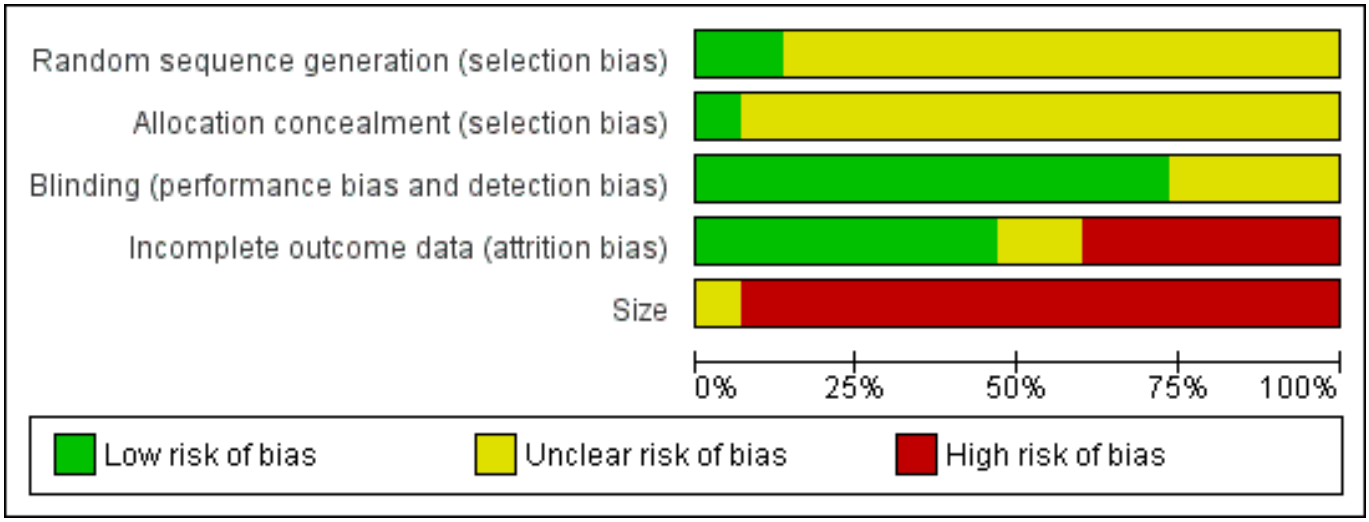


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

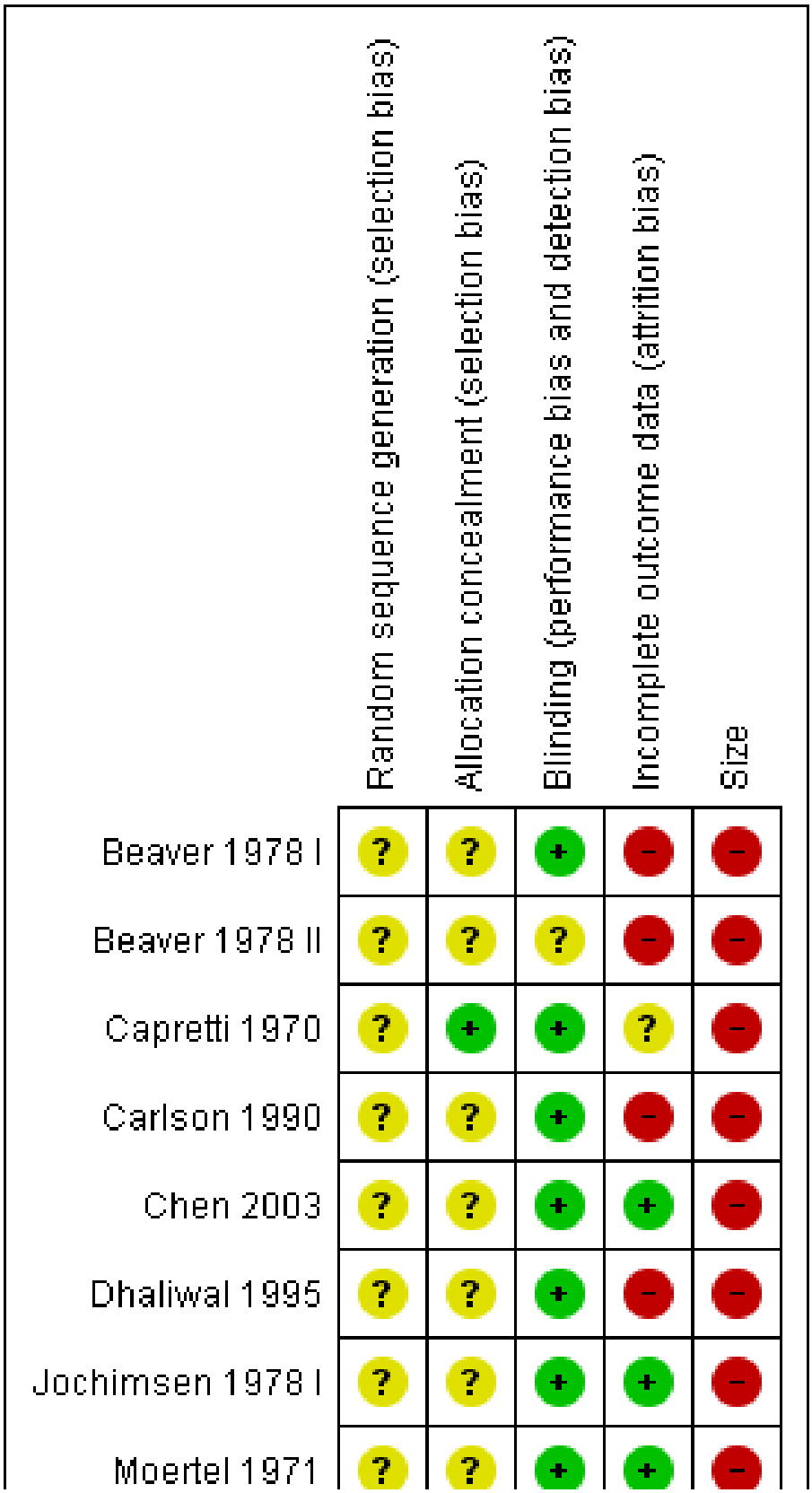
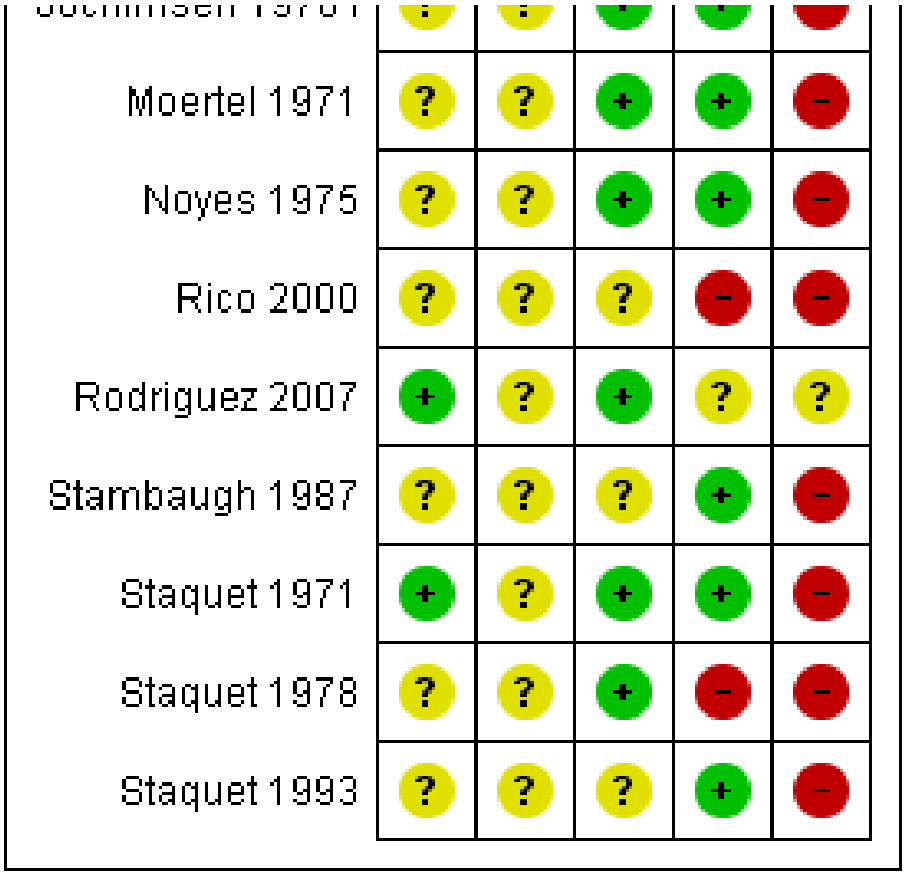


Figure 3. (Continued)



Effects of interventions

See: **Summary of findings for the main comparison**

Efficacy

Because of methodological between-study heterogeneity (participant characteristics, interventions, study design, outcomes assessed) and small numbers of participants, no meaningful pooling of results could be undertaken. Details of the results of individual studies are tabulated in Appendix 4 (efficacy), Appendix 5 (adverse events and withdrawals), and Appendix 6 (specific adverse events in multiple-dose studies).

To avoid repetition throughout the review, we have specified the route of administration only where codeine has not been administered orally.

Codeine and codeine plus paracetamol versus placebo

Participants with at least 50% reduction in pain

Only two small studies reported this outcome. Both gave single doses of study medication and reported results over six hours.

Jochimsen 1978 I reported that 17/35 participants (49%) experienced at least a 50% reduction in pain intensity with codeine 60 mg, 20/35 (57%) with codeine 120 mg, and 15/35 (43%) with placebo.

Moertel 1971 reported that 12/34 participants (35%) experienced at least a 50% reduction in pain intensity with codeine 60 mg, and 7/34 (21%) with placebo.

Participants with visual analogue score (VAS) pain intensity below 30/100 mm

This outcome was not reported in any of the included studies.

Treatment group average pain intensity or pain relief

Group mean measures of pain intensity or pain relief were given in six studies (Capretti 1970; Carlson 1990; Dhaliwal 1995; Noyes 1975; Stambaugh 1987; Staquet 1978); these were variously reported as pain intensity assessed on either a VAS, numeric rating scale (NRS), or categorical scale, pain relief measured on a categorical scale, or three- and six-hour summed pain intensity difference (SPID) or total pain relief (TOTPAR). Overall, codeine or codeine plus paracetamol was numerically superior to placebo.

Other measures

Three studies reported other measures of pain, including complete or partial pain relief (Chen 2003), maximum attained pain relief (Jochimsen 1978 I), and participants with 'substantial' pain relief (Noyes 1975). Codeine was numerically superior to placebo.

Four studies reported on the use of rescue medication, as median time to use (Carlson 1990), treatment group mean number of doses daily (Dhaliwal 1995), number of participants using it (Jochimsen 1978 I), and number using it within six hours (Stambaugh 1987). Codeine was numerically superior to placebo.

One study presented data on functioning, as a treatment group mean, using a pain disability index (Dhaliwal 1995).

No study presented data on Patient Global Impression of Change.

While there was considerable heterogeneity in the participant characteristics, interventions and outcomes assessed, all but one of the studies (Moertel 1971) demonstrated superiority of codeine over placebo in at least one outcome measure (Appendix 4).

Codeine and codeine plus paracetamol versus active comparators

Participants with at least 50% reduction in pain

Only two small studies reported this outcome. Both gave single doses of study medication and reported results over six hours.

Jochimsen 1978 I reported that 17/35 participants (49%) experienced at least a 50% reduction in pain intensity with codeine 60 mg, 20/35 (57%) with codeine 120 mg, 14/35 (40%) with benzopyranoperidine 2 mg, and 8/35 (23%) with benzopyranoperidine 4 mg.

Moertel 1971 reported that 12/34 participants (35%) experienced at least a 50% reduction in pain intensity with codeine 60 mg, and 20/34 (59%) with aspirin 650 mg.

Participants with VAS pain intensity below 30/100 mm (no worse than mild pain)

Two small studies reported the number of participants who had no worse than mild pain at the end of seven or 21 days of treatment. Since mild pain approximates to ≤ 30/100 mm on a VAS, we considered these outcomes to be equivalent (Collins 1997).

In a cross-over study with seven-day treatment periods and medication given six-hourly, Rico 2000 reported that in the first period 11/21 participants (52%) had no worse than mild pain with codeine 30 mg and 9/23 (39%) with tramadol 40 mg. In the second period 9/16 participants (56%) had no worse than mild pain with codeine and 6/12 (50%) with tramadol.

In a parallel study lasting 23 days, Rodriguez 2007 reported no worse than mild pain in 41/59 participants (69%) with codeine 150 mg plus paracetamol 2500 mg daily, 40/56 (71%) with tramadol 200 mg daily, and 45/62 (73%) with hydrocodone 25 mg plus paracetamol 2500 mg daily.

Treatment group average pain intensity or pain relief

Group mean measures of pain intensity or pain relief were given in 10 studies (Beaver 1978 I; Beaver 1978 II; Capretti 1970; Carlson 1990; Noyes 1975; Rico 2000; Stambaugh 1987; Staquet 1971; Staquet 1978; Staquet 1993); these were variously reported as pain intensity assessed on either a VAS, NRS, or a categorical scale, pain relief measured on a categorical scale, or three- and six-hour SPID or TOTPAR. Beaver 1978 I compared oral and intramuscular codeine. Active comparators in the other studies were oxycodone, morphine, alclofenac, ciramadol, ketorolac, piroxicam, piroxicam plus codeine, tramadol, THC, NIB, and an experimental drug Z 424. Overall, codeine or codeine plus paracetamol provided levels of analgesia similar to the active comparators at the doses used in both single and multiple dose studies, except that ciramadol and TCH at the higher doses (90 mg and 20 mg respectively) gave numerically better relief (Appendix 4).

Other measures

Beaver 1978 I and Beaver 1978 II tested the relative potency of oral and intramuscular formulations of codeine and of intramuscular codeine, oxycodone and morphine. The relative potency of

oral to intramuscular codeine was 0.6 for total analgesic effect, and 0.5 for peak analgesic effect. The relative potency of intramuscular codeine to oxycodone was 0.1 for total analgesic effect and 0.08 for peak analgesic effect.

Three studies reported other measures of pain, including complete or partial pain relief (Chen 2003), maximum attained pain relief (Jochimsen 1978 I), and participants with 'substantial' pain relief (Noyes 1975). Codeine gave similar results to codeine plus ibuprofen and TCH, and was numerically superior to benzopyranoperidine (Appendix 4).

Three studies reported on the use of rescue medication, as median time to use (Carlson 1990) and number using it within six hours (Jochimsen 1978 I; Stambaugh 1987). Ketorolac had a slightly longer time to use of rescue medication than codeine, while fewer participants used rescue medication with codeine than with benzopyranoperidine, and similar numbers with ciramadol and codeine.

No study presented data on functioning or Patient Global Impression of Change.

Proportion of participants with good pain relief with codeine

Summary table A shows the proportion of participants experiencing desirable pain outcomes, i.e. substantial pain relief or at most/no worse than mild pain with codeine, and Summary table B shows mean pain relief with codeine.

Summary table A: Participants experiencing desirable pain outcomes with codeine

Study ID	Number taking codeine	Dose of codeine	Duration of treatment	Outcome	Percentage with outcome
Chen 2003	18	30 mg	single dose	Partial/complete relief	100%
Jochimsen 1978 I	35	60, 120 mg	single dose	50% pain reduction	48%, 57%
Moertel 1971	34	60 mg	single dose	50% pain reduction	35%
Noyes 1975	34	60, 120 mg	single dose	Substantial pain relief (≥ 12-point reduction over 7 h, maximum 14)	23%, 47%
Rico 2000	41	Mean 200 mg daily + paracetamol 2000 mg daily	7 days	at most mild pain	51%
Rodriguez 2007	59	150 mg daily + paracetamol 2500 mg daily	21 days	at most mild pain	69%

Summary table B: Group mean values of pain relief with codeine

Study ID	Number taking codeine	Dose of codeine	Duration of treatment	Outcome	Result
Capretti 1970[1]	18	30, 60 mg	1 day	Pain relief at end of treatment (scale 0-3)	1.3, 1.3
Carlson 1990	33	240 mg + paracetamol 2400 mg daily	7 days	Mean daily pain relief (scale 0-4)	< 3 at all times
Noyes 1975	34	60, 120 mg	single dose	Sum of hourly mean pain relief (scale 0-4) over 7 h (maximum 14 = no pain)	9.4, 12.2
Stambaugh 1987	40	60 mg	single dose	Maximum mean pain relief score (scale -1 to +4)	1.6

Staquet 1971[2]	18	30 mg	single dose	Maximum mean pain relief score (scale 0 to 4)	1.4

1. Capretti 1970 included 1/18 participants with Paget's disease.

2. Staquet 1971 included a minority of participants who had chronic pain that was not due to cancer.

Adverse events, withdrawals, and deaths

Adverse event reporting was poor; only two studies reported the number of participants with any adverse event specified by treatment group (Stambaugh 1987; Staquet 1993). Only one study reported (indirectly) on the number of participants experiencing any serious adverse event (Staquet 1971). There were three deaths among the study participants, in all cases these were reported as being due to the underlying malignant diseases (Stambaugh 1987; Staquet 1978) (see Appendix 5).

Specific adverse events reported in studies with multiple dosing are tabulated in Appendix 6. There were too few data for analysis: one study used codeine 30 mg and 60 mg and compared it with two doses of an experimental drug and placebo, three studies used codeine plus paracetamol and compared it with ketorolac, tramadol (two studies), and hydrocodone plus paracetamol, while the other used controlled-release codeine and compared it with placebo. One study treated for one day, three treated for seven days and the other for 21 days. Studies varied in the permitted use of concomitant medication, such as antidepressants, which could influence frequency of adverse events. As expected, nausea, vomiting and constipation were the most commonly reported adverse events, and somnolence and dizziness were frequent in the 21-day study.

Nine studies reported data on withdrawals for any reason (Appendix 5). Withdrawals, where reported, were fewer than 10% of the study population except in the studies by Dhaliwal 1995 and Staquet 1978.

DISCUSSION

Summary of main results

Given the worldwide importance of codeine in cancer pain therapy, the amount of evidence is disappointingly small. Of the 10 placebo-controlled studies included in this review, nine demonstrated the superiority of codeine (in one instance codeine plus paracetamol) compared with placebo in the treatment of cancer pain. There are obvious shortcomings in the evidence available (small study size and other risks of bias, in addition to clinical and methodological heterogeneity between the studies precluding a meaningful pooling of results), but the available data indicate that there is an analgesic effect of codeine in at least some participants with cancer pain over and above that seen with placebo.

Although a number of different drugs or combinations of drugs were compared with codeine, no two studies made the same comparison, and the numbers involved were too small to draw any firm conclusions.

Overall completeness and applicability of evidence

We found remarkably few studies that satisfied our fairly broad inclusion criteria, and none in children. A considerable portion of the studies identified were old; eight of the 15 included studies were from the 1970s. Clinical practice has changed considerably since then and some participant characteristics may have been different in the older studies. Furthermore, different cancers may produce different types of pain (pain in different locations, pain mediated via different mechanisms); this is an important factor to consider when applying this evidence in clinical practice.

Eleven of the studies concentrated on the effects of a single dose of medication, although one also had a multiple-dose phase. Single-dose studies may not truly reflect efficacy in clinical practice where multiple dosing will be used, and do not inform adequately on adverse events.

The included studies used a variety of outcomes (Appendix 4). Few reported on our preferred responder outcomes, 'participants with at least 50% reduction in pain' and 'participants with pain intensity below 30/100 mm on the VAS' (or no worse than mild pain). Use of these responder outcomes (rather than treatment group averages) is important, especially as some participants may be codeine non-responders or poor metabolisers (Cascarbi 2003), so that significant between-patient heterogeneity in response to codeine can be expected. Information from the other outcomes was also very limited. Although codeine was numerically superior to placebo for analgesic effect in all but one study, the positive effects were generally not seen with the same assessment instruments and at the same observation times. The size of the analgesic effect of codeine in cancer pain and the time-course of the effect, therefore, cannot reliably be determined from the evidence included in this systematic review.

Adverse event reporting was poor, even at the level of reporting the number of participants per treatment arm who experienced any adverse event and serious adverse events. The five multiple dose studies all reported on individual adverse events, but they permitted concomitant use of some established pain treatments such as antidepressants and antiepileptics, which may themselves cause adverse events. Only one study specifically mentioned 'treatment emergent' (new or worsened during treatment) adverse events, which may remove events associated with the established pain treatments, but it is not clear that the reported results are restricted to treatment emergent events (Rodriguez 2007). The other studies appeared to record all adverse events, although not always in the whole population treated, (Capretti 1970; Carlson 1990; Dhaliwal 1995) or any occurrence of particular adverse events (Rico 2000).

Codeine is typically recommended at doses between 30 mg and 60 mg for use in mild to moderate pain (step II on the WHO analgesic ladder (Ventafridda 1985)). For this review, we did not identify any study specifically limited to mild to moderate pain intensity, and none reported results separately for participants with different pain intensities, so there was insufficient evidence to evaluate the suggestion that codeine use should be restricted to mild to moderate pain (Jadad 1995). On the other hand, the majority of in-

cluded studies treated pain of at least moderate intensity, for which codeine appears to be having an analgesic effect.

An analgesic effect of codeine has been shown also in postoperative pain, although codeine does not compare favourably with other commonly used analgesics in these single-dose studies (Derry 2010). Codeine and paracetamol combined, however, provided good analgesic effect in postoperative pain (Toms 2009). We identified only three studies examining codeine combined with paracetamol in cancer pain, none of which had a treatment arm using codeine alone. Therefore we do not know whether the analgesic effect is larger than that of codeine used as a single agent.

Quality of the evidence

Few studies adequately reported the method used to generate the randomisation sequence, and only one reported on the method of allocation concealment. This may reflect the age of the studies (with about half of them having been published in the 1970s and only three since 2000), rather than necessarily implying poor methodological quality. The majority did report adequately on the methods used to maintain blinding. Five studies were considered at high risk of bias from incomplete outcome data, mainly because they reported results only for participants who completed the study (and withdrawals could not be added back in) and withdrawals exceeded 10% of randomised participants. Capretti 1970 reported adverse events for only 10 of the 18 participants enrolled, without explanation. All but one study was considered at high risk of bias because there were fewer than 50 participants in each of the treatment arms (Nüesch 2010).

Potential biases in the review process

We carried out extensive searches, but there may exist some study data that we have not identified. It is possible that sufficient data exist in unidentified studies that do not show an analgesic effect of codeine to overturn the finding of this review. We have tried to be as inclusive as possible while requiring minimum criteria of randomisation, double-blinding, and size (at least 10 participants per treatment arm). We did include two studies with some participants who had pain that was not due to cancer. In Capretti 1970 one of 18 participants had Paget's disease; in Staquet 1971 the proportion of participants with cancer pain is reported only as "a majority". Our intention had been to carry out sensitivity analysis to see whether these studies gave different results, but there were no pooled analyses. Results (both as group means) from these studies, however, are consistent with other studies.

Agreements and disagreements with other studies or reviews

In agreement with the present review other reviews discussing codeine for cancer pain also found rather little and low-quality evidence. A review of opioids for cancer pain found poor evidence for codeine (Koyyalagunta 2012). That review included only studies with at least four weeks of treatment and found only one relevant study for codeine; we excluded that study because it was not double-blind (Mystakidou 2005).

Quigley found only low-quality evidence indicating that codeine was more effective than placebo for reducing cancer pain at two weeks and reducing the need for rescue medication; there was an increased incidence of nausea. There were insufficient data to compare codeine to other opioids (Quigley 2008).

A major guideline recommends the use of weak opioids such as codeine together with a non-opioid analgesic for mild to moderate cancer pain (SIGN 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence available indicates that codeine may provide good levels of pain relief for some adults with cancer pain. While it is not generally a first line drug in this context in many countries, it is an inexpensive and widely available drug with well-known adverse effects.

Implications for research

It is unlikely, for ethical and financial reasons, that randomised controlled trials of adequate size and duration will be carried out to clarify any benefit of codeine compared with placebo. We require good quality trials (randomised, double-blind, and of adequate size and duration) comparing codeine with alternative interventions, such as step II or low dose step III opioids, using patient-centred responder outcomes (participants with at least 50% (or 30%) pain relief or participants with a VAS pain score below 30 mm, or no worse than mild pain). The role of codeine in mild cancer pain, in addition to moderate to severe cancer pain, should be investigated; future studies could increase our understanding by performing separate analyses by baseline pain intensity.

Evaluation of safety and tolerability requires better reporting of treatment emergent adverse events in such trials, potentially supplemented by longer-term cohort studies. Levels of function or disability and quality of life are likely to improve if pain is relieved and adverse events are tolerable, but formal measurement of these outcomes would also help to determine the place of codeine for cancer pain.

ACKNOWLEDGEMENTS

Information about codeine and how it might work was based on what had been published in the earlier review of codeine in acute postoperative pain (Derry 2010) and has been updated for this review.

A standard protocol has been adopted by PaPaS to assess risk of bias in included studies, which is modified to satisfy the requirements of any particular review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beaver 1978 I

Methods	RCT, four-way cross-over of oral and intramuscular codeine (also of oral and intramuscular oxycodone). Single dose, 6-hour observation period
Participants	Participants with malignant tumours, with moderate or severe pain at least 3 hours after last routine analgesic medication Codeine: N = 38 (some participants completed more than one set of cross-overs) (Oxycodone: N = 14 (some participants completed more than one set of cross-overs))
Interventions	Codeine Series 1: 30 mg IM, 60 mg IM, 60 mg oral, 120 mg oral Series 2: 60 mg IM, 180 mg IM, 120 mg oral, 360 mg oral (Oxycodone: 5 mg IM, 15 mg IM, 10 mg oral, 30 mg oral)
Outcomes	Four-point PI scale (0-3) Five-point PR scale (0-4) Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3/5 Funding: Committee on Problems of Drug Dependence, National Academy of Sciences, National Research Council, "a group of interested pharmaceutical manufacturers", National Cancer Institute, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Different doses in capsules and injections were "physically indistinguishable". Double-dummy method
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Size	High risk	< 50 participants per treatment arm: n ≤ 38

Beaver 1978 II

Methods	RCT, four-way cross-over of intramuscular codeine and oxycodone and morphine (and also intramuscular morphine and oxycodone). Single dose, 6-hour observation period
Participants	Participants with malignant tumours, with moderate or severe pain at least 3 hours after last routine analgesic medication

Beaver 1978 II *(Continued)*

	Codeine N = 28 (some participants completed more than one set of cross-overs)
Interventions	Codeine Series 1: IM codeine 90 mg, codeine 180 mg, oxycodone 7.5 mg, oxycodone 15 mg, morphine 16 mg Series 2: IM codeine 90 mg, codeine 180 mg, oxycodone 15 mg, oxycodone 30 mg, morphine 16 mg
Outcomes	Four-point PI scale (0-3) Five-point PR scale (0-4) Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0. Total = 2/5 Funding: Committee on Problems of Drug Dependence, National Academy of Sciences, National Research Council, "a group of interested pharmaceutical manufacturers", National Cancer Institute, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not clearly stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Size	High risk	< 50 participants per treatment arm: n ≤ 27

Capretti 1970

Methods	RCT, five-way cross-over; duration of treatment for each drug was 1 day, with four doses of test drug taken
Participants	Hospitalised with skeletal abnormalities and pain due to malignant tumours (1 participant had Paget's Disease) N = 18 All women Mean age 55 years (23 to 77)
Interventions	Codeine 30 mg x 4 daily Codeine 60 mg x 4 daily Z 424 50 mg x 4 daily

Capretti 1970 *(Continued)*

	Z 424 100 mg x 4 daily Placebo Rescue medication not mentioned
Outcomes	Four-point PI scale (0-3) Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 2/5 Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Low risk	Pre-numbered, coded serial identical containers
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical packs
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results for all participants for efficacy, but only 55% for adverse events.
Size	High risk	< 50 participants per treatment arm: n ≤ 18

Carlson 1990

Methods	RCT, parallel group, first-dose 6-hour observation period in which patients were randomised to ketorolac, paracetamol plus codeine, or placebo. Thereafter participants receiving placebo were reassigned to one of the two active treatments and observed for 7 days with drugs taken 4 times daily
Participants	75 participants (32 women, 43 men; mean age: 62.2 years) with moderate to severe cancer pain; histologically confirmed diagnosis of cancer (most common types: genitourinary, lung, breast, gastrointestinal)
Interventions	First-dose 6-hour observation period: (1) paracetamol 600 mg plus codeine 60 mg (n = 27) (2) placebo (n = 26) (3) ketorolac tromethamine 10 mg (n = 22)
Outcomes	Four-point PI scale (0-3) Five-point PR scale (0-4) Time to remedication Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Carlson 1990 *(Continued)*

	Funding: Syntex Research, Palo Alto, California; National Cancer Institute, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical-appearing capsules"
Incomplete outcome data (attrition bias) All outcomes	High risk	Last observation carried forward analysis. Withdrawals > 10%
Size	High risk	< 50 participants per treatment arm: n ≤ 27

Chen 2003

Methods	RCT, three-way cross-over, variable observation period (until in moderate or severe pain again)
Participants	18 participants (5 women, 13 men; mean age: 54 years) with moderate or severe cancer pain
Interventions	(1) codeine 30 mg (2) placebo (3) codeine 13 mg plus ibuprofen 200 mg
Outcomes	VAS (probably 'visual analogue scale') VRS (probably 'verbal rating scale') Time to effect Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double dummy

Chen 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Size	High risk	< 50 participants per treatment arm: n = 18

Dhaliwal 1995

Methods	RCT, two-way cross-over, multiple doses, 7-day treatment phases
Participants	35 participants (30 completers: 13 women, 17 men; mean age: 64 years) with chronic cancer pain
Interventions	(1) controlled-release codeine at 100, 150 or 200 mg every 2 hours (2) placebo Rescue medication: paracetamol 300 mg plus codeine 30 mg once or twice every 4 hours
Outcomes	100 mm VAS for PI Five-point PI scale (0-4) Doses of rescue medication per day Pain disability index Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5 Funding: Purdue Frederick, Pickering, Ontario

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebos"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis. Withdrawals > 10%. Imputation for missing data not mentioned
Size	High risk	< 50 participants per treatment arm: n = 35

Jochimsen 1978 I

Methods	RCT, five-way cross-over, single dose, 6-hour observation periods

Jochimsen 1978 I *(Continued)*

Participants	37 participants (35 completers: 29 women, 6 men; mean age: 57 years) suffering from pain related to malignancies (e.g. breast and gynaecologic malignancies)
Interventions	(1) codeine 60 mg (2) codeine 120 mg (3) placebo (4) benzopyranoperidine 2 mg (5) benzopyranoperidine 4 mg Rescue with "known analgesic"
Outcomes	100 mm VAS for PI Five-point PR scale (0-4) Four-point PI scale (PI and PR may have been observer-rated; wording in the paper is ambiguous) Number of participants receiving rescue medication Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5 Funding: National Institutes of Health, USA; Abbott Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical-appearing capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 10%. Completer analysis reported
Size	High risk	< 50 participants per treatment arm: n ≤ 37

Moertel 1971

Methods	RCT, three-way cross-over, single dose, observation period at least 6 hours
Participants	34 participants with unresectable carcinoma with significant pain due to the malignant disease (13 with pancreatic cancer, 21 with colon cancer; age and sex not specified)
Interventions	(1) codeine sulphate 60 mg (2) placebo (3) aspirin 650 mg
Outcomes	"percentage scale" for PR of 0%-100%

Moertel 1971 *(Continued)*

Notes	Oxford Quality Score: R = 1, DB = 2, W = 0. Total = 3/5 Funding: National Institutes of Health, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"Each drug was prepared in a pair of identical opaque blue capsules."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Responder analysis appears to include all participants
Size	High risk	< 50 participants per treatment arm: n = 34

Noyes 1975

Methods	RCT, five-way cross-over, single dose, 7-hour observation period
Participants	36 participants (26 women, 10 men; mean age 51 years) with moderate pain from advanced cancer (13 with breast cancer, 7 with non-Hodgkin's lymphoma, 3 with Hodgkin's disease, 2 each with lung cancer, colon cancer, prostate cancer and malignant melanoma, 1 each with cervix carcinoma, carcinoid, leiomyosarcoma, carcinoma of the parotid gland and anaplastic carcinoma of unknown origin); 34 completers
Interventions	(1) codeine 60 mg (2) codeine 120 mg (3) placebo (4) THC 10 mg (5) THC 20 mg
Outcomes	Four-point PI scale (0-3) Five-point PR scale (0-4) Sum of pain reduction scores were calculated as pain reduction over 7 hours (maximum possible score estimated as 14) Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5 Funding: National Institutes of Health, USA

Risk of bias

Bias	Authors' judgement	Support for judgement

Noyes 1975 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 10%
Size	High risk	< 50 participants per treatment arm: n = 36

Rico 2000

Methods	RCT, two-way cross-over; 7-day treatment periods with 3-day washout
Participants	44 participants with oncologic pain (30 women, 14 men: 55 years; baseline pain > 6/10)
Interventions	(1) codeine 120 mg daily to max 320 mg daily (average max dose 49 ± 15 mg x 4 daily) (2) tramadol 160 mg daily to max 400 mg daily (average max dose 68 ± 24 mg x 4 daily) All participants also received paracetamol 500 mg x 4 daily
Outcomes	10 cm VAS for PI Patient preference Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5 Funding: not specifically reported. Codeine supplied by Yid Mac Farlan Smith Ltd, UK, and tramadol by Grunenthal Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not clearly stated, used the same number of drops and both had bitter taste
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis reported. Imputation not mentioned. Withdrawals > 10%

Rico 2000 *(Continued)*

Size	High risk	< 50 participants per treatment arm: n ≤ 44

Rodriguez 2007

Methods	RCT, parallel group; 2 day run in, then 21-day treatment period
Participants	177 participants (89 women, 88 men, mean age: 60 years) with persistent moderate or severe cancer pain (primarily gastric, breast, prostate, lung)
Interventions	(1) Codeine + paracetamol 150 mg + 2500 mg daily, n = 59 (2) Hydrocodone + paracetamol 25 mg + 2500 mg daily, n = 62 (3) Tramadol 200 mg daily, n = 56 If no PR (VAS ≥ 4/10) dose could be doubled. If this caused intolerable adverse events it could be reduced by 25%
Outcomes	10 cm VAS for pain intensity Five-point PR scale (0-4) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5 Funding: Universidad Libre Seccional Cali, Cali, Colombia; drugs supplied free of charge by Laboratorios Librapharma Ltda., Bogota, D.C., Colombia and Sanofi Synthelabo de Colombia S.A., Cali, Colombia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated schedule"
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"study drugs had similar characteristics such as color, shape, and dimensions and were packaged in identical containers"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned. Withdrawals not reported
Size	Unclear risk	50-200 participants per treatment arm (n ≤ 62)

Stambaugh 1987

Methods	RCT, four-way cross-over, single dose, 6-hour observation period

Stambaugh 1987 *(Continued)*

Participants	43 participants (24 women and 10 men (figure given in paper, should probably be: 19 men; mean age: 62 years) with moderate to severe pain due to primary or metastatic malignancy; 40 completers
Interventions	(1) codeine 60 mg (2) placebo (3) ciramadol 30 mg (4) ciramadol 90 mg
Outcomes	100 mm VAS for PI Four-point PI scale (0-3) Six-point PR scale (-1 to +4) Number of participants remedicating Number of participants with any adverse event Withdrawals Deaths
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5 Funding: Wyeth Laboratories, Philadelphia, Pennsylvania

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals < 10%
Size	High risk	< 50 participants per treatment arm: n = 43

Staquet 1971

Methods	RCT, three-way cross-over, repeated three times in all. Single dose with 6-hour observation period. Minimum 24 hours between study medication and no analgesics within 3 hours of administration
Participants	Study 1: 18 participants with severe pathologic pain
Interventions	(1) codeine 30 mg (2) alclofenac 500 mg (3) placebo

Staquet 1971 *(Continued)*

Outcomes	Four point PI scale (0-3) Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 3/5 Funding: not reported; first author was working for Continental Pharma, Brussels, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"accomplished by selecting Latin squares at random (with a table of random numbers)"
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical capsules containing the same volume of powder"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline observation carried forward for lack of efficacy
Size	High risk	< 50 participants per treatment arm: n = 18

Staquet 1978

Methods	RCT, three-way cross-over, single dose, 6-hour observation period
Participants	30 participants with advanced cancer with continuous moderate to severe pain (sex not specified, age range 21-75, no mean age given); 26 completers
Interventions	(1) codeine 50 mg (2) placebo (3) NIB 4 mg
Outcomes	Four-point PI scale (0-3) Withdrawals Deaths
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5 Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method used to generate sequence not clearly stated

Staquet 1978 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical capsules"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis. Pain intensity difference assigned 0 for missing data points
Size	High risk	< 50 participants per treatment arm: n = 30

Staquet 1993

Methods	RCT, parallel group. Single dose with 6-hour observation period
Participants	90 participants (30 women, 58 men analysed; 64 years) with chronic pain due to cancer. Moderate to severe pain 3 or more hours after last analgesic medication
Interventions	Codeine 60 mg, n = 30 Piroxicam 40 mg, n = 30 (29 analysed) Codeine 30 mg + piroxicam 20 mg, n = 30 (29 analysed) Rescue medication available at any time
Outcomes	Four-point PI scale (0-3) Patient global impression of efficacy (poor, fair, good, excellent) Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5 Funding: Pfizer Belgium

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not clearly stated
Allocation concealment (selection bias)	Unclear risk	Method not clearly stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method not clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline observation carried forward imputation for lack of efficacy withdrawals
Size	High risk	< 50 participants per treatment arm: n ≤ 30

DB: double-blinding
IM: intramuscular
N: number of participants in trial
n: number of participants in treatment arm
NIB: a synthetic nitrogen analogue of tetrahydrocannabinol
PI: pain intensity
PR: pain relief
R: randomisation
RCT: randomised controlled trial
THC: delta-9-tetrahydrocannabinol
VAS: visual analogue scale
W: withdrawals

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

Study	Reason for exclusion
Chary 1994	Fewer than 10 participants per treatment arm
Corgill 1965	Only a minority of participants had cancer pain
De Conno 1991	Not randomised, not double-blind
Jochimsen 1978 II	Study not stated to be randomised
Kantor 1966	Most participants had postoperative, postprocedural, or fracture pain
Martinetti 1970	Only a minority of patients had cancer pain
Minotti 1989	Not investigating codeine alone or with paracetamol
Minotti 1998	Investigates codeine plus diclofenac versus placebo plus diclofenac
Mystakidou 2005	Not double-blind
Pistevou-Gompaki 2004	Not double-blind
Sniezek 2011	Investigates postoperative pain
Stambaugh 1980	No codeine group
Sunshine 1988	Did not evaluate codeine in cancer pain
Watanabe 2008	No codeine used

APPENDICES

Appendix 1. MEDLINE (PubMed) search strategy

1. "Codeine"[mesh] (5254)
2. (codeine or ardinex or isocodeine or n-methylmorphine or “n methylmorphine”) (7004)
3. #1 OR #2 (7004)
4. "Neoplasms"[mesh] (2511639)
5. neoplasm* OR cancer* OR carcino* OR malignan* (2809398)
6. tumor* OR tumour* (1298909)

7. #4 OR #5 OR #6 (3403037)
8. "Pain"[mesh] (298062)
9. pain* (542103)
10. "Analgesia"[mesh] (31310)
11. analgesi* (486167)
12. "Analgesics, Opioid"[mesh] (27381)
13. #8 OR #9 OR #10 OR #11 OR #12 (1014939)
14. #3 AND #7 AND #13 (519)
15. randomized controlled trial [pt] (360620)
16. controlled clinical trial [pt] (86996)
17. randomized [tiab] (309269)
18. placebo [tiab] (155403)
19. clinical trials as topic [mesh: noexp] (166483)
20. randomly [tiab] (210255)
21. trial [ti] (123291)
22. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 (792250)
23. animals [mh] NOT humans [mh] (3864756)
24. #22 NOT #23 (735962)
25. #14 AND #24 (112)

We used the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format (search items 15 to 24).

Appendix 2. CENTRAL search strategy

1. MeSH descriptor: [Codeine] explode all trees (972)
2. codeine or ardinex or isocodeine or n-methylmorphine or "n methylmorphine":ti,ab (1273)
3. #1 or #2 (1667)
4. MeSH descriptor: [Neoplasms] explode all trees (49382)
5. neoplasm* or cancer* or carcino* or malignan*:ti,ab (88355)
6. tumor* or tumour*:ti,ab (23427)
7. #4 or #5 or #6 (97219)
8. MeSH descriptor: [Pain] explode all trees (31409)
9. pain*:ti,ab (56963)
10. MeSH descriptor: [Analgesia] explode all trees (5931)
11. analgesi*:ti,ab (22772)
12. MeSH descriptor: [Analgesics, Opioid] explode all trees (5063)
13. #8 or #9 or #10 or #11 or #12 (74334)
14. #3 and #7 and #13 (179)
15. Limit #14 to Trials (105)

Appendix 3. EMBASE search strategy

1. codeine/ (17226)
2. (codeine or ardinex or isocodeine or n-methylmorphine or n methylmorphine).mp. (19242)
3. 1 or 2 (19242)
4. neoplasm/ (276541)
5. (neoplasm* or cancer* or carcino* or malignan*).mp. (2934038)
6. (tumor* or tumour*).mp. (2260507)
7. 4 or 5 or 6 (3699513)
8. exp pain/ (806664)
9. pain*.mp. (836624)
10. analgesia/ (74333)
11. analgesi*.mp. (217344)
12. 8 or 9 or 10 or 11 (1148734)

13.clinical trials/ (896014)
14.controlled clinical trials/ (408807)
15.randomized controlled trial/ (367669)
16.random*.ab. (865433)
17.(clin* adj25 trial*).ab. (314441)
18.14 or 15 or 16 or 17 or 18 (1654484)
19.3 and 7 and 12 and 18 (469)

Appendix 4. Summary of outcomes in individual studies: efficacy

Study	Description of the pharmacological intervention	Participants with at least 50% reduction in pain	Participants with VAS pain intensity below 30/100 mm	Treatment group average pain intensity or pain relief	Other measures of pain intensity or pain relief	Medication/rescue medication	Patient global impression of change (participants who are much or very much improved)	Functioning (any scale)
Beaver 1978 I	Series 1 (1) codeine 30 mg IM (2) codeine 60 mg IM (3) codeine 60 mg oral (4) codeine 120 mg oral Series 2 (1) codeine 60 mg IM (2) codeine 180 mg IM (3) codeine 120 mg oral (4) codeine 360 mg oral Single dose treatments, cross-over	No data	No data	Pain relief at 1 h Series 1 (1) 1.7 (2) 2.2 (3) 1.7 (4) 1.8 Series 2 (1) 2.1 (2) 2.7 (3) 1.7 (4) 2.4	Relative potency of oral to IM codeine: Total analgesic effect 0.6 Peak analgesic effect 0.5	No data	No data	No data
Beaver 1978 II	Series 1	No data	No data	Pain relief at 1 h Series 1	Relative potency of IM codeine to IM oxycodone:	No data	No data	No data

(Continued)

	(1) codeine 90 mg IM (2) codeine 180 mg IM (3) oxycodone 7.5 mg IM (4) oxycodone 15 mg IM (5) morphine 16 mg IM Series 2 (1) codeine 90 mg IM (2) codeine 180 mg IM (3) oxycodone 15 mg IM (4) oxycodone 30 mg IM (5) morphine 16 mg IM Single dose treatments, cross-over			(1) 1.9 (2) 2.6 (3) 2.6 (4) 2.1 (5) 2.6 Series 2 (1) 1.9 (2) 2.6 (3) 2.2 (4) 3.0 (5) 2.3	Total analgesic effect 0.1 Peak analgesic effect 0.08			
Capretti 1970	(1) codeine 30 mg (2) codeine 60 mg	No data	No data	Pain relief at end of treatment (1) 1.28 (2) 1.28 (3) 1.22	No data	No data	No data	No data

(Continued)

	(3) Z 424 50 mg (4) Z 424 100 mg (5) placebo 1-day treatment, with 4 doses			(4) 1.22 (5) 0.61				
Carlson 1990	(1) paracetamol 600 mg plus codeine 60 mg (2) placebo (3) ketorolac tromethamine 10 mg 7-day treatment period with additional data from first dose, parallel groups	No data	No data	3-h SPID (1) 1.8 (2) 0.5 (3) 2.2 3-h TOTPAR (1) 4.0 (2) 1.9 (3) 4.3 6-h SPID (1) 4.0 (2) 1.6 (3) 4.6 6-h TOTPAR (1) 9.3 (2) 4.8 (3) 9.2	7-day period: Mean daily pain relief < 3 (a lot) for both treatment groups at all times	Median time to remedication (1) 4.8 h (2) 4.0 h (3) 6.0 h significant difference	No data	No data
Chen 2003	(1) codeine 30 mg (2) placebo (3) codeine 13 mg plus ibuprofen 200 mg Single-dose treatment, cross-over	No data	No data	No data	Complete relief (no pain at all) (1) 1/18 (2) 0/18 (3) 2/18 Partial relief (pain reduced to mild) (1) 17/18 (2) 11/18 (3) 15/18	No data	No data	No data

(Continued)

					Partial or complete pain relief (1) 18/18 (2) 11/18 (3) 17/18 'Time of showing effect' (min) (1) 60 ± 35 (2) 55 ± 18 (3) 48 ± 19 'Time of showing the best effect' (min) (1) 124 ± 83 (2) 104 ± 44 (3) 104 ±43 'Maintaining time' (h) (1) 5.4 ± 3.0 (2) 3.3 ± 2.5 (3) 6.8 ± 4.3			
Dhaliwal 1995	(1) controlled-release codeine at 100, 150 or 200 mg every 2 hours (2) placebo 7-day treatment phases, crossover	No data	No data	Participants had mild to moderate pain at baseline Overall mean VAS score (1) 22 ± 18 (2) 36 ± 20 Overall mean categorical PI score (1) 1.2 ± 0.8 (2) 1.8 ± 0.8	No data	Rescue medication: doses per day (overall) (1) 2.2 ± 2.3 (2) 4.6 ± 2.8	No data	Pain disability index (overall, range 0-70) (1) 25 ± 16 (2) 27 ± 16 Subscores for recreation and self-care were better with codeine
Jochimsen 1978 I	(1) codeine 60 mg	(1) 17/35 (2) 20/35 (3) 15/35	No data	No data	Maximum pain relief 3 or 4 on a scale of 0-4 (1) 14/35	Received rescue medica-	No data	No data

(Continued)

	(2) codeine 120 mg (3) placebo (4) benzopyranoperidine 2 mg (5) benzopyranoperidine 4 mg Single dose, cross-over	(4) 14/35 (5) 8/35			(2) 19/35 (3) 12/35 (4) 7/35 (5) 9/35 'Improvement' in PI score (1) 25/35 (2) 31/35 (3) 25/35 (4) 19/35 (5) 20/35 Multiple comparison test performed for PI and PR scores per treatment period: participants receiving 120 mg codeine had better responses than after placebo.	tion (after 4 h) (1) 11/35 (2) 7/35 (3) 12/35 (4) 19/35 (5) 15/35		
Moertel 1971	(1) codeine sulphate 60 mg (2) placebo (3) aspirin 650 mg Single dose, cross-over	(1) 12/34 (2) 7/34 (3) 20/34	No data	No data	No data	No data	No data	No data
Noyes 1975	(1) codeine 60 mg (2) codeine 120 mg (3) placebo (4) THC 10 mg (5) THC 20 mg Single dose, cross-over	No data	No data	Total pain relief (scored hourly during 7-h observation period, mean ± SE) (1) 9.4 ± 1.4 (2) 12 ± 1.6 (3) 6.8 ± 0.95 (4) 9.8 ± 1.4 (5) 12.9 ± 1.5 Total pain reduction (scored hourly during observation period, mean ± SE) (1) 3.6 ± 0.75	Number of participants with substantial PR (total PR scores of 12 or more) (1) 8/34 (2) 16/34 (3) 6/34 (4) 13/34 (5) 16/34	No data	No data	No data

(Continued)

				(2) 4.3 ± 0.78 (3) 1.9 ± 0.44 (4) 2.9 ± 0.62 (5) 4.7 ± 0.65				
Rico 2000	(1) codeine 30 mg + paracetamol 500 mg 6-hourly (2) tramadol 40 mg + paracetamol 500 mg 6-hourly 7-day treatment phases, crossover	No data	≤ mild pain at end of treatment period Period 1 (1) 11/21 (2) 9/23 Period 2 (1) 9/16 (2) 6/12	Mean (SD) pain intensity at end of treatment period Period 1 (1) 3.4 ± 0.5 (2) 4.1 ± 0.5 Period 2 (1) 3.3 ± 0.1 (2) 3.3 ± 0.6	No data	No data	No data	No data
Rodriguez 2007	(1) codeine 150 mg + paracetamol 2500 mg daily (2) Tramadol 200 mg daily (3) Hydrocodone 25 mg + paracetamol 2500 mg daily 21-day treatment phase, parallel groups	No data	(1) 41/59 (2) 40/56 (3) 4/62	No data	No data	No data	No data	No data

(Continued)

Stambaugh 1987	(1) codeine 60 mg (2) placebo (3) ciramadol 30 mg (4) ciramadol 90 mg Single dose, cross-over	No data	No data	6-h SPID (1) 4.0 (2) 2.1 (3) 4.5 (4) 5.6 6-h TOTPAR (1) 7.9 (2) 5.0 (3) 8.2 (4) 11.2 6-h SPAID (1) 116 (2) 60 (3) 128 (4) 168	Maximum mean pain relief score approximately 1.6 (scale -1 to +4)	Remedicating within 6 hours (1) 24/40 (2) 29/40 (3) 24/40 (4) 18/40	No data	No data
Staquet 1971	(1) codeine 30 mg (2) alclofenac 500 mg (3) placebo Single dose, cross-over	No data	No data	6-h TOTPAR (SE) (1) 7.3 ± 0.8 (2) 9.7 ± 0.8 (3) 4.6 ±0.6	Maximum mean pain relief score approximately 1.4 (scale 0 to 4)	No data	No data	No data
Staquet 1978	(1) codeine 50 mg (2) placebo (3) NIB 4 mg Single dose, cross-over	No data	No data	6-hour SPID (1) 4.8 ± 3.2 (2) 2.2 ± 2.6 (3) 4.7 ± 3.3	No data	No data	No data	No data
Staquet 1993	(1) codeine 60 mg	No data	No data	6-h SPID from graph (1) 2.7	No data	No data	Mean (SD) (1) 1.7 ±1.2	No data

(Continued)

	(2) piroxicam 40 mg (3) codeine 60 mg + piroxicam 40 mg Single dose, parallel groups	(2) 2.4 (3) 2.3	(2) 1.5 ± 1.3 (3) 1.7 ± 1.1

IM: intramuscular

NIB: a synthetic nitrogen analogue of tetrahydrocannabinol

PI: pain intensity

PR: pain relief

SE: standard error

SPAID: sum of pain analogue intensity differences

SPID: summed pain intensity difference

VAS: visual analogue scale

THC: delta-9-tetrahydrocannabinol

TOTPAR: total pain relief

Appendix 5. Summary of outcomes in individual studies: adverse events, withdrawals and deaths

Study	Description of the pharmacological intervention	Participants with any adverse event	Participants with any serious adverse event	Withdrawal (any reason)	Withdrawal (due to adverse events)	Withdrawal (due to lack of efficacy)	Death
Beaver 1978 I	Series 1 (1) codeine 30 mg IM (2) codeine 60 mg IM (3) codeine 60 mg oral (4) codeine 120 mg oral Series 2 (1) codeine 60 mg IM (2) codeine 180 mg IM (3) codeine 120 mg oral (4) codeine 360 mg oral	No data	No data	No data	No data	No data	None reported
Beaver 1978 II	Series 1 (1) codeine 90 mg IM (2) codeine 180 mg IM (3) oxycodone 7.5 mg IM (4) oxycodone 15 mg IM (5) morphine 16 mg IM Series 2 (1) codeine 90 mg IM (2) codeine 180 mg IM (3) oxycodone 15 mg IM (4) oxycodone 30 mg IM (5) morphine 16 mg IM	No data	No data	No data	No data	No data	None reported

(Continued)

Capretti 1970	(1) codeine 30 mg (2) codeine 60 mg (3) Z 424 50 mg (4) Z 424 100 mg (5) placebo 1-day treatment, with 4 doses	No data	No data	No data	No data	No data	None reported
Carlson 1990	(1) codeine 60 mg plus paracetamol 600 mg (2) placebo (3) ketorolac tromethamine 10 mg	Multidose phase (1) 19/40 (3) 21/34	None reported	Multidose phase (1) 13/40 (3) 17/34	Multidose phase (1) 4/40 (3) 8/34 (3 also had unsatisfactory pain relief)	Within 6 h ("terminated the 6-h first-dose observation period early because of inadequate pain relief") (1) 10/27 (2) 14/26 (3) 6/22 Multidose phase (1) 7/40 (3) 11/34 (3 also had unsatisfactory pain relief)	None reported
Chen 2003	(1) codeine 30 mg (2) placebo (3) codeine 13 mg plus ibuprofen 200 mg	No data	No data	0/18	0/18	0/18	None reported
Dhaliwal 1995	(1) controlled-release codeine at 100, 150 or 200 mg every 2 h (2) placebo	No data	No data	(1) 3/35 (2) 2/35	(1) 2/35 (2) 0/35	(1) 0/35 (2) 0/35	None reported
Jochimsen 1978 I	(1) codeine 60 mg (2) codeine 120 mg (3) placebo (4) benzopyranoperidine 2 mg	No data	No data	2/37 no more detail given	No data	No data	None reported

(Continued)

	(5) benzopyranoperidine 4 mg						
Moertel 1971	(1) codeine sulfate 60 mg (2) placebo (3) aspirin 650 mg	No data	No data	No data	No data	No data	None reported
Noyes 1975	(1) codeine 60 mg (2) codeine 120 mg (3) placebo (4) THC 10 mg (5) THC 20 mg	No data	No data	2/36	2/36 due to adverse reaction to THC	0/36	None reported
Rico 2000	(1) codeine 30 mg (2) tramadol 40 mg	No data	No data	First period (1) 7/21 (2) 9/23	First period (1) 3/21 (2) 0/23	None reported	None reported
Rodriguez 2007	(1) codeine 150 mg + paracetamol 2500 mg daily (2) Tramadol 200 mg daily (3) Hydrocodone 25 mg + paracetamol 2500 mg daily	No data	No data	No data	No adverse event withdrawals for codeine + paracetamol or hydrocodone + paracetamol. No data for tramadol	No data	None reported
Stambaugh 1987	(1) codeine 60 mg (2) placebo (3) ciramadol 30 mg (4) ciramadol 90 mg	(1) 10/41 (2) 5/41 (3) 7/40 (4) 10/42	No data	3/43 (including 2 deaths)	0/43	0/43	Two patients died of their disease during the study (no more details given)
Staquet 1971	(1) codeine 30 mg (2) alclofenac 500 mg (3) placebo	No data	None: "in all cases symptoms were minimal"	No data	No data	No data	None reported
Staquet 1978	(1) codeine 50 mg (2) placebo (3) NIB 4 mg	No data	No data	4/30 (including 1 death)	2/30	0/30	One death due to ter-

(Continued)

							minal cancer
Staquet 1993	(1) codeine 60 mg (2) piroxicam 40 mg (3) codeine 60 mg + piroxicam 40 mg	(1) 5/30 (2) 2/29 (3) 2/30	No data	1 participant excluded from efficacy analysis in (2) and 1 in (3) due to missing data	None	None	None

IM: intramuscular

NIB: a synthetic nitrogen analogue of tetrahydrocannabinol

THC: delta-9-tetrahydrocannabinol

Appendix 6. Specific adverse events in multidose studies

Study ID	Drug	Nausea	Vomiting	Constipation	Diar-rhoea	Dyspep-sia	Anorex-ia	Somno-lence	Dizziness
Capretti 1970	Codeine	1/10	4/10					3/10	1/10 (verti-go)
Carlson 1990	Codeine + paracetamol	12/40	5/40	1/40	0/40	4/40	1/40	3/40	2/40
	Ketorolac	7/34	3/34	1/40	6/34	5/34	1/34	1/34	4/34
Dhaliwal 1995	Codeine (controlled-release)	14/35	5/35	11/35				5/35	5/35
	Placebo	5/35	2/35	12/35				0/35	3/35
Rico 2000	Codeine + paracetamol	18/37	16/37	19/37 (mod/sev)					
	Tramadol	14/35	11/35	12/35 (mod/sev)					
Rodriguez 2007	Codeine + paracetamol	17/59	14/59	21/59	0/59		1/59	21/59	14/59
	Hydrocodone + paracetamol	17/62	10/62	18/62	3/62		4/62	23/62	12/62
	Tramadol	26/56	20/56	14/56	1/56		12/56	26/56	23/56

mod: moderate

sev: severe

Study ID	Drug	Headache	Insomnia	Dry mouth	Asthenia	Sweating	Pruritus	Hallucinations
Capretti 1970	Codeine					2/10 (hot sensation)		
Carlson 1990	Codeine + paracetamol	1/40	0/40	2/40			1/40	
	Ketorolac	7/34	2/34	0/34			0/34	
Dhaliwal 1995	Codeine (controlled-release)	8/35		7/35	5/35	3/35	2/35	
	Placebo	7/35		7/35	2/35	2/35	0/35	
Rico 2000	Codeine + paracetamol							
	Tramadol							
Rodriguez 2007	Codeine + paracetamol		0/59	9/59	0/59	5/59	7/59	4/59
	Hydrocodone + paracetamol		0/62	11/62	1/62	9/62	12/62	7/62
	Tramadol		2/56	12/56	7/56	7/56	11/56	4/56

WHAT'S NEW

Date	Event	Description
23 July 2018	Amended	See Published notes

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 9, 2014

Date	Event	Description
2 June 2016	Review declared as stable	See Published notes.
6 February 2013	Amended	This is an update of a previous version of this protocol that had been written by Kenneth C Jackson and Philip J Wiffen. In this updated version, Carmen Schremmer, Sheena Derry, Rae F Bell, Scott Strassels, and Sebastian Straube have joined the original authors.
4 October 2012	Amended	The protocol has been reactivated and is currently being updated. Carmen Schremmer, Sheena Derry, Rae F Bell, Scott Strassels, and Sebastian Straube have joined the authors of the previous protocol, Kenneth C Jackson and Philip J Wiffen.
8 June 2012	Amended	Authors have made no progress with this protocol in five years. Therefore new authors are being sought to take over this protocol.
9 November 2009	Amended	Contact details updated.
7 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Kenneth C Jackson and Philip J Wiffen had written the previous version of the protocol for this review. Sheena Derry and Sebastian Straube updated the protocol, with input from the other authors. Carmen Straube, Sebastian Straube, and Sheena Derry performed the electronic searches. Titles and abstracts of the studies identified were screened by Carmen Straube, Rae F Bell and Sheena Derry. The bibliographies of the identified articles and review articles were screened for other potentially relevant studies by Carmen Straube and Scott Strassels. The full texts of studies deemed appropriate were reviewed by Carmen Straube, Sebastian Straube, Sheena Derry and Philip Wiffen; these authors also graded the study quality and performed the data extraction. Carmen Straube, Sebastian Straube, and Sheena Derry would have performed any data analyses. Carmen Straube and Sebastian Straube drafted the manuscript for the full version of the review, the other authors contributed to the revision of the manuscript.

DECLARATIONS OF INTEREST

Carmen Straube and Kenneth C Jackson have no competing interests to declare. Scott Strassels has received research funding from Endo Pharmaceuticals and Johnson & Johnson in the past two years. Sebastian Straube has received research support from charities, academic and industry sources at various times and has received fees for presentations in the fields of pain and perinatal medicine; none of this was related to this review. Rae Frances Bell has consulted for Pfizer Norway A/S and Grunenthal A/S in a limited capacity, but this was not related to this review. Sheena Derry and Philip J Wiffen have received research support from charities, government, and industry sources at various times but none related to this review.

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Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review intended to include only placebo-controlled studies. We decided to also include active-controlled studies to be more inclusive, because of the ethical problems associated with using placebo in cancer patients (other than in single-dose studies), and to bring the review in line with other completed and planned Cochrane reviews of opioids in cancer pain. These reviews will be included in an overview when completed.

The protocol also stated that we would include only studies in cancer pain, or studies that reported results for cancer pain separately. For the full review, given the paucity of studies, we decided to also include studies where the majority of participants had cancer pain, with the intention of carrying out a sensitivity analysis to determine if this affected the results. As there were no pooled analyses, no sensitivity analysis was done.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [adverse effects] [*therapeutic use]; Analgesics, Non-Narcotic [adverse effects] [*therapeutic use]; Analgesics, Opioid [adverse effects] [*therapeutic use]; Codeine [adverse effects] [*therapeutic use]; Drug Therapy, Combination [adverse effects] [methods]; Neoplasms [*complications]; Pain [*drug therapy] [etiology]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans