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Single dose oral dihydrocodeine for acute postoperative pain (Review)

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[Intervention Review]

Single dose oral dihydrocodeine for acute postoperative pain

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 2, 2000. Dihydrocodeine is a synthetic opioid analgesic developed in the early 1900s. Its structure and pharmacokinetics are similar to that of codeine and it is used for the treatment of postoperative pain or as an antitussive. It is becoming increasingly important to assess the relative efficacy and harm caused by different treatments. Relative efficacy can be determined when an analgesic is compared with control under similar clinical circumstances.

Objectives

To quantitatively assess the analgesic efficacy and adverse effects of single-dose dihydrocodeine compared with placebo in randomised trials in moderate to severe postoperative pain.

Search methods

Published reports were identified from electronic databases (MEDLINE, EMBASE, CENTRAL, the Oxford Pain Relief Database in December 2007, the original search was conducted in October 1999). Additional studies were identified from the reference lists of retrieved reports.

Selection criteria

Inclusion criteria: full journal publication, clinical trial, random allocation of participants to treatment groups, double blind design, adult participants, baseline pain of moderate to severe intensity, postoperative administration of study drugs, treatment arms which included dihydrocodeine and placebo and either oral or injected (intramuscular or intravenous) administration of study drugs.

Data collection and analysis

Data collection and analysis: summed pain intensity and pain relief data over four to six hours were extracted and converted into dichotomous information to yield the number of participants obtaining at least 50% pain relief. This was used to calculate relative benefit and number-needed-to-treat-to-benefit (NNT) for one participant to obtain at least 50% pain relief. Single-dose adverse effect data were collected and used to calculate relative risk and number-needed-to-treat-to-harm (NNH).

Main results

Fifty-two reports were identified in the original review as possible randomised trials which assessed dihydrocodeine in postoperative pain. Four reports met the inclusion criteria; all assessed oral dihydrocodeine. Three reports (194 participants) compared dihydrocodeine with placebo and one (120 participants) compared dihydrocodeine (30 mg or 60 mg) with ibuprofen 400 mg. For a single dose of dihydrocodeine 30 mg in moderate to severe postoperative pain the NNT for at least 50% pain relief was 8.1 (95% confidence interval 4.1 to 540) when compared with placebo over a period of four to six hours. Pooled data showed significantly more participants to have reported adverse effects with dihydrocodeine 30 mg than with placebo. When compared to ibuprofen 400 mg both dihydrocodeine 30 mg and 60 mg were significantly inferior. No additional studies were found for this update.

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Authors' conclusions

A single 30 mg dose of dihydrocodeine is not sufficient to provide adequate pain relief in postoperative pain. Statistical superiority of ibuprofen 400 mg over dihydrocodeine (30 mg or 60 mg) was shown. Since the last version of this review no new relevant studies have been identified.

PLAIN LANGUAGE SUMMARY

Dihydrocodeine in a single dose in the treatment of acute postoperative pain

This review assessed the efficacy of single-dose dihydrocodeine in adults with moderate/severe postoperative pain using information from randomised placebo controlled trials. There was a lack of data that could be included in the analyses; all assessed the oral form of the drug and none assessed dihydrocodeine 60 mg. The results were not robust. The implication was that single-dose oral dihydrocodeine 30 mg was more effective than placebo, but was inferior to ibuprofen 400 mg. Dizziness, drowsiness and confusion were commonly reported.

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BACKGROUND

This is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 2, 2000) on 'Single dose dihydrocodeine for the treatment of acute postoperative pain'.

Opioids are used extensively in the management of pain and are believed capable of relieving severe pain more effectively than non-steroidal anti-inflammatory drugs (NSAIDs) (Alexander 1987). The aim of this systematic review was to assess the efficacy and safety of a single dose of dihydrocodeine in the management of postoperative pain of moderate to severe intensity.

Dihydrocodeine is a synthetic opioid analgesic developed in the early 1900s. Its structure and pharmacokinetics are similar to that of codeine (Rowell 1983) and it is used for the treatment of postoperative pain or as an antitussive. In England, 2.2 million prescriptions were written for dihydrocodeine tablets in 2006, and 4.2 million prescriptions for dihydrocodeine in combination with paracetamol (PACT 2006). This is only about one-fifth of the level of use a decade earlier. The amount of dihydrocodeine used for the treatment of postoperative pain is not known, but it is not now commonly used to treat acute pain.

It is becoming increasingly important to assess the relative efficacy and harm caused by different treatments. Relative efficacy can be determined when an analgesic is compared with control under similar clinical circumstances. Mean pain outcome values from categorical pain intensity and pain relief scales (percent of maximum possible pain intensity or pain relief; %maxSPID and %maxTOTPAR) can be converted into dichotomous information (number of participants with at least 50% pain relief) (Moore 1996; Moore 1997a; Moore 1997b). This can then be used to derive the number-needed-to-treat-to-benefit (NNT) for at least 50% pain relief. Comparison of the NNTs against placebo for different analgesics allows a rank order of relative efficacy to be established.

OBJECTIVES

To quantitatively evaluate the analgesic efficacy and adverse effects of dihydrocodeine in moderate to severe postoperative pain. To compare its efficacy and safety to that of other analgesics assessed in the same way.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they were full journal publications of single-dose, double blind, randomised controlled (placebo or active) trials (RCTs) of dihydrocodeine over four to six hours in postoperative pain. Multiple dose studies were included if they provided single-dose data. Study drugs needed to have been administered (by injection or orally) postoperatively to adult participants with moderate or severe pain at baseline.

Studies were excluded if they did not state clearly that study medication had been randomly allocated or the method of randomisation was considered inappropriate (e.g. date of birth), or they examined other pain conditions (postfracture, postpartum uterine cramps, chronic pain, muscle strain, post-trauma pain).

Abstracts, review articles, case reports, clinical observations, and unpublished data were not sought. Neither pharmaceutical companies nor authors were contacted for unpublished reports.

Full details of the individual studies are provided in the 'Characteristics of included studies' and 'Characteristics of excluded studies' sections.

Types of participants

Adult participants with established postoperative pain of moderate to severe intensity.

Types of interventions

Reports were included if they assessed participants who had been randomised to either dihydrocodeine (oral or injected) or placebo.

Types of outcome measures

Pain outcomes used were TOTPAR, SPID, VAS TOTPAR or VAS SPID over four to six hours or sufficient data provided to allow their calculation. Pain measures allowed for the calculation of TOTPAR were a standard five point pain relief scale (none, slight, moderate, good, complete) and for SPID a standard four point pain intensity scale (none, mild, moderate, severe).

Search methods for identification of studies

The following electronic databases were searched:

- Cochrane CENTRAL (Issue 3, 1999 for the original review and Issue 4, 2007 for the update);
- MEDLINE and Pre-MEDLINE from 1966 to October 1999 for the original review, and MEDLINE from January 1999 to December 2007 for the update;
- EMBASE from 1989 to October 1999 for the original review and January 1999 to December 2007 for the update;
- the Oxford Pain Relief database (handsearch records for the years 1954 to 1995 (Jadad 1996a).

The MEDLINE search strategy can be seen in Appendix 1 and was adapted for the other databases searched.

Reference lists of retrieved reports were also manually searched.

Data collection and analysis

From each study we extracted:
(i) the number of participants treated,
(ii) mean TOTPAR, SPID, VAS TOTPAR or VAS SPID,
(iii) study duration,
(iv) the dose of dihydrocodeine,
(v) the dose of active comparator (if relevant),
(vi) information on adverse effects, and
(vii) information on remedication.

Mean TOTPAR, SPID, VAS TOTPAR and VAS SPID values were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Moore 1996). Verified equations were used to estimate the proportion of participants achieving at least 50% maxTOTPAR (Moore 1997a; Moore 1997b). This was then converted in to the number of participants achieving at least 50% maxTOTPAR by multiplying the figure by the total number of participants in the treatment group. The number of participants

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with at least 50% maxTOTPAR was then used to calculate estimates of relative benefit and NNT.

Relative benefit/risk estimates with 95% confidence intervals (CI) were calculated using the fixed-effect model (Morris 1995). Homogeneity was assumed when P > 0.1 and was tested for using a chi-squared test. A statistically significant benefit of active treatment over placebo was assumed when the lower limit of the 95% CI of the relative benefit was >1. A statistically significant benefit of placebo over active treatment was assumed when the upper limit of the 95% CI of the relative benefit was <1. Number-needed-to-treat-to-harm (NNH) and NNT with 95% CIs were calculated (Cook 1995). The CI includes no benefit of one treatment over the other when the upper limit is represented as infinity. Calculations were performed with the help of Excel 5.0 on a Macintosh Performa 6320.

There was no attempt at anonymisation of the studies prior to assessment. Two review authors (JE, HM) independently carried out data abstraction and quality assessments. A consensus meeting with all review authors was held to agree on the data abstracted, the quality scores, the data to be used in the analyses, and the studies for inclusion in the review.

RESULTS

Description of studies

Fifty-two published reports of dihydrocodeine in postoperative pain (359 participants in total) were identified; one could not be obtained from the British Library (Hummel 1995). Of the retrieved studies, 18 studies were not randomised or were abstracts and were excluded. Thirty-two studies were randomised. Of the randomised studies eight were not double blind (two were single blind), five did not specify baseline pain of moderate to severe intensity, five had no extractable pain outcome data, six did not assess the analgesic properties of dihydrocodeine, three included other pain conditions (e.g. chronic/cold-induced/trauma pain) and two did not use a placebo group. These studies were excluded (see 'Characteristics of excluded studies' table).

Four studies met the inclusion criteria from the original searches. No further studies were identified in the updated searches.

Risk of bias in included studies

Each study was scored for quality using a three-item scale (see below) (Jadad 1996b); a consensus score was agreed for each study. The quality scores for individual studies are reported in the 'Characteristics of included studies' table. These scores were not used to weight the results in any way.

The three item scale is as follows:
Is the study randomised? If yes then one point
Is the randomisation procedure reported and is it appropriate? If yes then add one point, if not deduct one
Is the study double blind? If yes then one point
Is the double blind method reported and is it appropriate? If yes then add one point, if not deduct one
Are withdrawals and dropouts described? If yes add one point

Effects of interventions

Four studies (359 participants) met the inclusion criteria: three were placebo-controlled and one used ibuprofen 400 mg as an active control. All four studies examined the effects of oral dihydrocodeine. Three of the studies (Frame 1989; Galasko 1989; McQuay 1985) compared dihydrocodeine 30 mg with placebo, and one (McQuay 1993) compared dihydrocodeine (30 mg or 60 mg) with ibuprofen 400 mg. No additional studies were identified in the updated searches.

Oral dihydrocodeine versus placebo

No studies comparing dihydrocodeine 60 mg with placebo met the inclusion criteria. Three studies compared dihydrocodeine tartrate 30 mg (97 participants) with placebo (97 participants). One study investigated dental pain (Frame 1989), one orthopaedic pain (Galasko 1989), and one pain following minor day-case surgery (McQuay 1985).

The proportion of participants experiencing at least 50% pain relief with dihydrocodeine varied between 14% and 50% (mean 32%). The proportion of participants experiencing at least 50% pain relief with placebo varied between 5% and 50% (mean 20%). Dihydrocodeine 30 mg was significantly different from placebo, relative benefit 1.6 (1.01 to 2.5). For a single dose of dihydrocodeine 30 mg compared with placebo the NNT was 8.1 (4.1 to 540) for at least 50% pain relief over four to six hours in postoperative pain of moderate to severe intensity.

Adverse effects

The most frequently reported adverse effects were nausea, vomiting, headache, and central nervous system effects (dizziness/drowsiness/confusion). All were mild, transient in nature and no participants withdrew as a result.

Participants reporting any adverse effect

Information on the number of participants reporting any adverse effect was pooled. The proportion of participants who reported adverse effects was 13/67 with dihydrocodeine 30 mg and 4/69 with placebo. The relative risk was 3.4 (1.2 to 9.8) and the NNH was 7.4 (4.1 to 38).

Particular adverse effects

There was no significant difference in the reported incidence of particular (e.g. drowsiness) adverse effects with dihydrocodeine 30 mg than with placebo.

Oral dihydrocodeine versus ibuprofen

One study (McQuay 1993) compared the efficacy and safety of either dihydrocodeine tartrate 30 mg (40 participants) or 60 mg (40 participants) with ibuprofen 400 mg (40 participants) in dental pain.

The proportion of participants experiencing at least 50% pain relief with dihydrocodeine 30 mg was 8%, with dihydrocodeine 60 mg it was 15%, and with ibuprofen 400 mg (active control) it was 45%. A statistical superiority of ibuprofen 400 mg over dihydrocodeine 30 mg and dihydrocodeine 60 mg was shown, relative benefit 0.2 (0.05 to 0.5) and 0.3 (0.2 to 0.8) respectively.

Ibuprofen 400 mg was significantly more effective than dihydrocodeine 30 mg or dihydrocodeine 60 mg. The NNT for a single dose of ibuprofen 400 mg compared to dihydrocodeine 30 mg was 2.7 (1.8 to 5.0) for at least 50% pain relief over a period

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of four to six hours in postoperative pain of moderate to severe intensity. For a single dose of ibuprofen 400 mg compared to dihydrocodeine 60 mg the NNT was 3.3 (2.0 to 9.1) for at least 50% pain relief over a period of four to six hours.

Adverse effects

No single dose adverse effect data were presented (McQuay 1993).

DISCUSSION

We found no studies which investigated injected dihydrocodeine in the evaluation of postoperative pain with standard analgesic measurement methods.

For a single dose of oral dihydrocodeine tartrate 30 mg compared with placebo the NNT was 8.1 (4.1 to 540) for at least 50% pain relief over four to six hours in postoperative pain of moderate to severe intensity. This means that one in every eight participants with moderate to severe postoperative pain would experience at least 50% pain relief with dihydrocodeine 30 mg who would not have done with placebo.

A rank order of single dose analgesic efficacy in postoperative pain of moderate to severe intensity has been established by comparing orally administered analgesics from methodologically similar studies. This rank order has been published previously, both in its entirety (McQuay 1998), for third molar extraction studies only (Barden 2004), and as individual reports (Collins 1998a; Collins 1998b; Moore 1997c; Moore 1997d). It is also available on the World Wide Web (http://www.jr2.ox.ac.uk/bandolier/painres/painpag/Acutrev/Analgesics/Leagtab.html) or is available from the authors. The rank order shows the results of a number of meta-analyses which compare analgesic with placebo in acute postoperative pain. The point estimates of the NNTs of many of these analgesics are lower (better) than that of dihydrocodeine 30 mg (for example: paracetamol, paracetamol plus codeine and dextropropoxyphene plus paracetamol) although the CIs overlap. The CIs of the NNTs for ibuprofen 400 mg, tramadol 150 mg and ibuprofen 200 mg do not overlap with those of dihydrocodeine 30 mg indicating greater analgesic efficacy.

This rank order of relative efficacy against placebo is supported by a head-to-head comparison with ibuprofen (McQuay 1993). The analgesic efficacy of a single dose of oral ibuprofen 400 mg was significantly better than dihydrocodeine (30 mg or 60 mg). The NNT was 2.7 (1.8 to 5.0) for at least 50% pain relief over a period of four to six hours in postoperative pain of moderate to severe intensity. This means that for every three participants with moderate to severe postoperative pain treated with ibuprofen 400 mg one will experience at least 50% pain relief who would not have done if given dihydrocodeine 30 mg. Similarly, for a single dose of ibuprofen 400 mg compared with dihydrocodeine 60 mg the NNT was 3.3 (2.1 to 9.0) over a period of four to six hours.

Nausea, vomiting, headache, dizziness, drowsiness and confusion were the most commonly reported adverse effects with a single dose of oral dihydrocodeine 30 mg compared with placebo. Significantly more participants reported at least one adverse effect with dihydrocodeine 30 mg than with placebo; the NNH was 7.4 (4.1 to 38). This means that for every seven participants treated with dihydrocodeine 30 mg one would experience an adverse effect who would not have done with placebo.

Our results suggest dihydrocodeine to be less effective than other analgesics when administered as a single oral dose. Few of the retrieved reports investigating oral dihydrocodeine met the criteria for inclusion in this quantitative systematic review. This resulted in little participant data being available for analysis, particularly for dihydrocodeine 60 mg which is often the preferred dose. Administering dihydrocodeine in multiple doses may improve its analgesic efficacy, but may also increase the incidence of adverse effects (McQuay 1993).

AUTHORS' CONCLUSIONS

Implications for practice

The update of this review has not identified any further information to provide evidence for or against the use of single dose dihydrocodeine for acute postoperative pain. Based on the limited amount of information in the available studies, a 30 mg dose of dihydrocodeine is not sufficient to provide good pain relief and higher doses are required. When compared with ibuprofen 400 mg, fewer participants benefited with dihydrocodeine (30 mg and 60 mg).

Implications for research

The annual prescriptions for dihydrocodeine in the UK alone indicate it to be a commonly used drug. To date, there is not enough high quality data available, especially for dihydrocodeine 60 mg, on which to make policy decisions.

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CHARACTERISTICS OF STUDIES

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

Frame 1989

Methods	RCT, DB, single oral dose, parallel groups. Assessed at t = 1/2, 1 hour and then hourly for 5 hrs. Medication taken when pain of moderate to severe intensity
Participants	Impacted third molar removal n = 148 Age: Adults
Interventions	DHC 30 mg, n = 49 Placebo, n = 50
Outcomes	Measures: PI (9 point scale) nonstandard PR (5 point scale) standard Analgesic outcome: DHC 30 mg was not significantly different to placebo. 5 hr TOTPAR: DHC 30 mg: 4.2 Placebo: 2.6
Notes	Remedication allowed at t > 2 hrs. If remedicated patients were withdrawn and their PR set to zero for all further time points. Withdrawals: 18 withdrew: 9 insufficient pain, 7 did not return assessment forms, 1 did not complete assessment forms, 1 postoperative complications Adverse effects: No serious adverse effects were reported and no patients withdrew as a result. DHC 30 mg: 1/49 with 1 AE Placebo: 1/50 with 3 AE Quality score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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Galasko 1989

Methods	RCT, DB, multiple oral dose, parallel groups. Assessed at t = 1/2, 1 hour and then hourly for 6 hrs. Medication taken when pain of moderate to severe intensity
Participants	Orthopaedic surgery n = 89 Age: 18 - 80 years
Interventions	DHC 30 mg, n = 30 Placebo, n = 28
Outcomes	Measures: PI (5 point scale) nonstandard PR (5 point scale) standard VAS 100 mm (no pain - worst pain I have ever felt) Analgesic outcomes: DHC was not significantly different to placebo. Mean TOTPAR at 6 hours: DHC: 11.3 Placebo: 11.1
Notes	Remedication: Multiple dose study, 2nd dose given as required. If remedicated patients were excluded from the analysis. Withdrawals: 9 withdrew because of inadequate analgesia after the first dose. DHC 30 mg, n = 3 Placebo, n = 6 Adverse effects: No patients experienced adverse effects in the single dose analysis. Quality score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McQuay 1985

Methods	RCT, DB, multiple oral dose, parallel groups. Assessed at t = 1/2, 1 hour and then hourly for 4 hrs.

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McQuay 1985 *(Continued)*

	Medication taken when pain of moderate to severe intensity
Participants	Minor day-case surgery (general) n = 54 Age: Adults
Interventions	DHC 30 mg, n = 18 Placebo, n = 19
Outcomes	Outcome measures: PI (4 point scale) standard PR (5 point scale) standard VAS 100 mm Analgesic outcomes: 4 hr SPID and TOTPAR presented. TOTPAR: DHC was significantly better than placebo (P<0.05) DHC30 mg: 6.5 Placebo: 3.2
Notes	Remedication: Allowed after 1 hr. If remedicated patients initial PI and PR scores were used for all further time points. Withdrawals and adverse effects: Single dose analysis: All adverse effects were mild and no patients withdrew as a result. No significant difference was found between DHC and placebo . DHC 30 mg: 6/18 with 6 AE Placebo: 3/19 with 3 AE Quality score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

McQuay 1993

Methods	RCT, DB, multiple oral dose, crossover design. Self-assessed at t = 1/2. 1 hr and then hourly for 6 hrs. Medication allowed when pain of moderate to severe intensity
Participants	Lower third molar removal.

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McQuay 1993 *(Continued)*

	n = 68 Age = Adults
Interventions	DHC 30 mg, n = 40 DHC 60 mg, n = 40 Placebo, n = 40
Outcomes	Outcome measures: PI (4 point scale) standard PR (5 point scale) standard Global rating (5 point scale) standard Analgesic outcomes: TOTPAR at 6 hrs: DHC 30 mg : 3.3 DHC 60 mg: 4.7 Ibuprofen 400 mg: 10.0 Ibuprofen was significantly better than dihydrocodeine 30 mg or 60 mg (P < 0.01)
Notes	Remedication: If remedicated at t< 6 hrs the initial PI score and PR score of zero were used for all further time points. Withdrawals: 3 patients withdrew. Adverse effects: Single dose adverse effects data was not presented. Quality score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Abbreviations:
DHC = dihydrocodeine;
R = randomised;
DB = double blind;
PI = pain intensity;
PR = pain relief;
AE = adverse effect.

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

Study	Reason for exclusion
Aitken 1990	No data to extract
Beecher 1957	Abstract

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Study	Reason for exclusion
Brittain 1959	Not randomised
Brown 1993	Abstract
Cahill 1987	No data to extract: no pain outcomes
Carapeti 1998	Dihydrocodeine used as a rescue analgesic only
Daniel 1971	Included chronic pain/trauma and fracture
Eddy 1934	Not randomised controlled trial
Fassoulaki 1995	Did not assess analgesic properties of DHC. Assessed morphine consumption not pain outcomes
Fenton-Lee 1994	Not double blind. No pain outcome data to extract
Fricke 1993	Abstract
Galasko 1988	Single blind
Grace 1994	Did not assess analgesic properties of DHC. No placebo control (used suprofen)
Grainger 1977	Baseline pain not moderate or severe
Gravenstein 1956	Not randomised
Habib 1990	Single blind
Heath 1989	Baseline pain not moderate or severe
Henderson 1999	Assessed dextromethorphan not DHC. Combination of dihydrocodeine with another drug
Howard 1953	Not randomised controlled trial
Hummel 1995	Could not be obtained: no UK location
Jorgensen 1985	Not double blind
Kay 1988	No data to extract
Keats 1950	Not randomised controlled trial. No placebo control (used floctafenine)
Keats 1957a	Abstract. No placebo control (used nalbuphine)
Keats 1957b	Not double blind. No control group
Kerrick 1993	Did not assess analgesic properties of DHC
Lipton 1975	Not randomised. No placebo control (used MST + DF118)
Lomas 1976	Chronic pain
Lund 1959	Not randomised. No placebo control (used buprenorphine)
Masson 1981	Not double blind. No placebo control (used seconal). Included children (i.e. <16 yrs)

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Study	Reason for exclusion
Moore 1983	No data to extract: placebo data not presented
Morrison 1971	Did not state randomised. Not assessing analgesic response of DHC
Myers 1958	Not double blind
Riethmuller 1987	Not randomised controlled trial. Not double blind. No placebo control
Ruch 1957	Not randomised. Single blind
Seymour 1981	Abstract
Seymour 1982	Baseline pain not moderate or severe
Seymour 1983a	Baseline pain not moderate or severe
Seymour 1983b	Baseline pain not moderate or severe. Not double blind.
Sliom 1970	Not randomised. Not double blind. No placebo control; baseline pain not moderate or severe
Squirrell 1998	Did not assess analgesic properties of dihydrocodeine. Method of surgery randomised not drug. Drugs administered on demand
Traykova 1996	No placebo group
Walker 1977	No data to extract (non standard PI and PR scales)
Walters 1984	Abstract
Walters 1985	Baseline pain intensity not moderate or severe
Williams 1995	Not double blind. No pain outcome data
Wotherspoon 1991	Not postoperative pain (cold induced pain). No placebo control (naproxen sodium). Baseline pain not moderate or severe
Yadav 1984	Not double blind

DATA AND ANALYSES

Comparison 1. Dihydrocodeine 30 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least 50% pain relief	3	194	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.01, 2.50]

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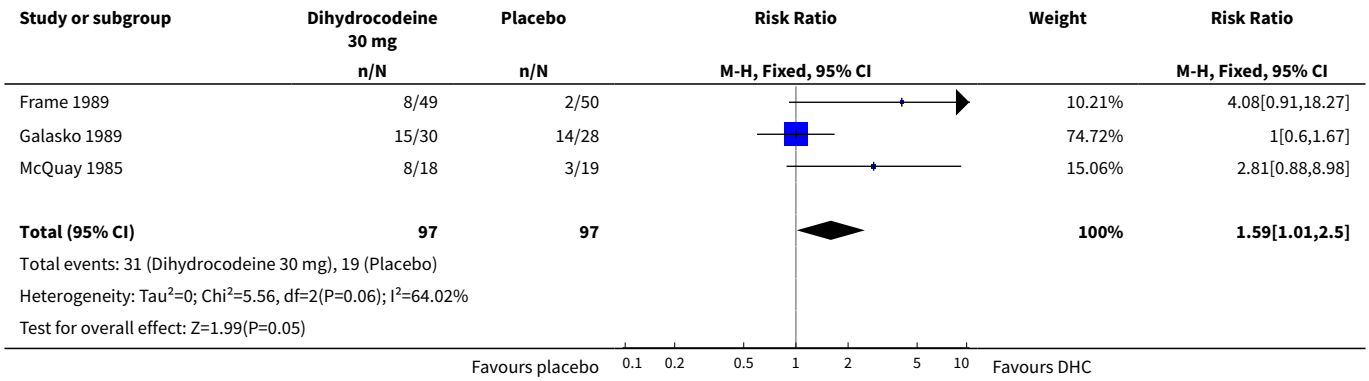
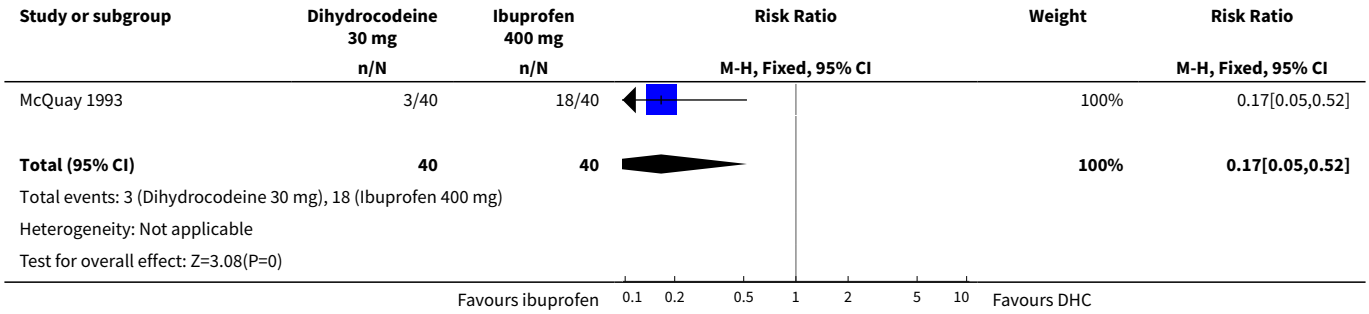
Analysis 1.1. Comparison 1 Dihydrocodeine 30 mg versus placebo, Outcome 1 Patients with at least 50% pain relief.



Comparison 2. Dihydrocodeine 30 mg versus ibuprofen 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least 50% pain relief	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.52]

Analysis 2.1. Comparison 2 Dihydrocodeine 30 mg versus ibuprofen 400 mg, Outcome 1 Patients with at least 50% pain relief.



Comparison 3. Dihydrocodeine 60 mg versus ibuprofen 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least 50% pain relief	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.15, 0.75]

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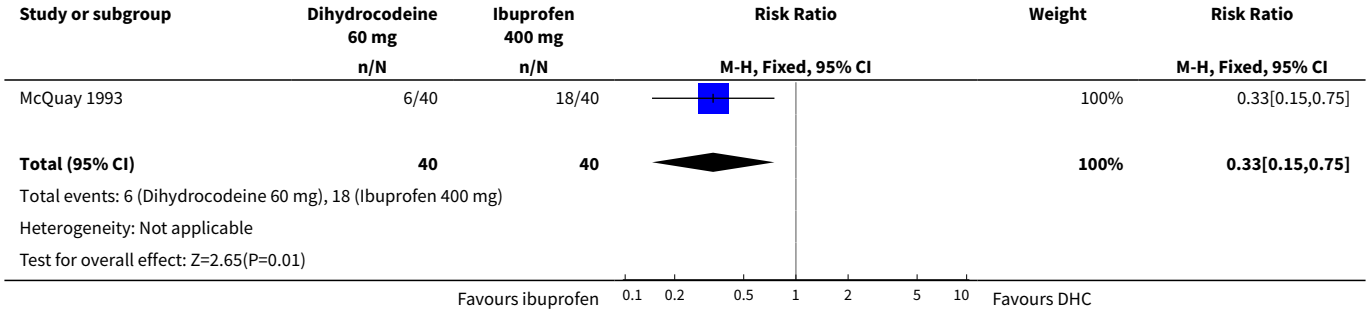
Analysis 3.1. Comparison 3 Dihydrocodeine 60 mg versus ibuprofen 400 mg, Outcome 1 Patients with at least 50% pain relief.



APPENDICES

Appendix 1. MEDLINE search strategy

Search strategy in MEDLINE
1. dihydrocodeine [single term MeSH]
2. dihydrocodeine
3. 1 OR 2
4. PAIN, POSTOPERATIVE [single term MeSH]
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")) [in title, abstract or keywords]
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)) [in title, abstract or keywords]
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")) [in title, abstract or keywords]
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)) [in title, abstract or keywords]
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 follow$ surg$")) [in title, abstract or keywords]
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 follow$ surg$"))
11. OR/4-10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized controlled trials.sh.
15. random allocation.sh.
16. double-blind method.sh.
17. single blind method.sh.
18. clinical trial.pt.
19. exp clinical trials/
20. (clin$ adj25 trial$).ti,ab.
21. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
22. placebos.sh.
23. placebo$.ti,ab.
24. random$.ti,ab.
25. research design.sh.
26. OR/12-25
26. 3 AND 11 AND 26

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.

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Date	Event	Description
5 June 2008	Review declared as stable	The review authors consider that additional relevant studies are unlikely to be conducted, and that further updates of this review are unnecessary.

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 4, 2000

Date	Event	Description
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.
4 July 2010	Amended	Contact details updated.
13 May 2009	Amended	Contact details updated.
28 May 2008	Amended	Converted to new review format.
15 January 2008	New search has been performed	Review updated - studies sought but none found
15 January 2008	New citation required but conclusions have not changed	Further studies satisfying our inclusion criteria were sought in MEDLINE (via Ovid), EMBASE (via Ovid) and Cochrane CENTRAL to December 2007. No further studies were identified, so the conclusions of the review are unchanged.
30 December 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Original review
JR: was involved with searching, data extraction, analysis and writing.
AM and HJM were involved with analysis and writing.

Update 2008
SD and AM carried out the searching and writing.

DECLARATIONS OF INTEREST

SD has no interests to declare. RAM has been a consultant for MSD. RAM and HJM have consulted for various pharmaceutical companies. RAM, HJM and JR have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times: no such support was received for this work.

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- NHS R&D Health Technology Evaluation Programmes, UK.
- NHS Cochrane Collaboration Programme Grant Scheme, UK.

NOTES

The review authors consider that additional relevant studies are unlikely to be conducted in the future, and that further updates of this review are unnecessary.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Analgesics, Non-Narcotic [administration & dosage]; Analgesics, Opioid [*administration & dosage]; Codeine [*administration & dosage] [*analogs & derivatives]; Ibuprofen [administration & dosage]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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