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

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[Intervention Review]

Single dose oral nefopam for acute postoperative pain in adults

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ABSTRACT

Background

Nefopam is a centrally-acting but non-opioid analgesic drug of the benzoxazocine chemical class, developed in the early 1970s. It is widely used, mainly in European countries, for the relief of moderate to severe pain as an alternative to opioid analgesic drugs, and used in rheumatic disease and other musculoskeletal disorders in the UK. This review sought to evaluate the efficacy and safety of oral nefopam in acute postoperative pain, using clinical studies of patients with established pain, and with outcomes measured primarily over 6 hours using standard methods. This type of study has been used for many decades to establish that drugs have analgesic properties.

Objectives

To assess the efficacy of single dose oral nefopam in acute postoperative pain, and any associated adverse events.

Search methods

We searched CENTRAL (Issue 2, 2009), MEDLINE (1966 to May 2009); EMBASE via Ovid (1980 to May 2009); the Oxford Pain Relief Database (1950 to 1994); and reference lists of studies found.

Selection criteria

Randomised, double-blind, placebo-controlled clinical trials of oral nefopam for relief of acute postoperative pain in adults.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. The area under the "pain relief versus time" curve was used to derive the proportion of participants with nefopam and placebo experiencing least 50% pain relief over 4 to 6 hours, using validated equations. The number-needed-to-treat-to-benefit (NNT) was calculated using 95% confidence intervals (CIs). The proportion of participants using rescue analgesia over a specified time period, and time to use of rescue analgesia, were sought as additional measures of efficacy. Information on adverse events and withdrawals was also collected.

Main results

No included studies were identified after examining in detail thirteen studies on oral nefopam in participants with established postoperative pain.

Authors' conclusions

In the absence of evidence of efficacy for oral nefopam in acute postoperative pain, its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies are lacking, use in other indications should be evaluated carefully. Given the large number of available drugs of this and similar classes, there is no urgent research agenda.

PLAIN LANGUAGE SUMMARY

Single dose oral nefopam for postoperative pain in adults

Pain is commonly experienced after surgical procedures. Acute postoperative pain of moderate or severe intensity is often used (as a model) to test whether or not drugs are effective painkillers. In this case we could find no studies that tested oral nefopam against placebo. It is possible that the studies were performed, but not reported, because they were used only to register nefopam with licensing authorities throughout the world. However, this leaves an important gap in our knowledge, and it means that we cannot be confident, at present, about using oral nefopam for acute painful conditions.

BACKGROUND

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care.

The aim of this series of reviews is to present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level.

Recent reviews include lumiracoxib (Roy 2007), paracetamol (Toms 2008), celecoxib (Derry 2008), naproxen (Derry C 2009a), diclofenac (Derry P 2009), parecoxib (Lloyd 2009), etoricoxib (Clarke 2009) and ibuprofen (Derry C 2009b).

Acute pain trials

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

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials need to be randomised and double blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following 4 to 6 hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over 4 to 6 hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first 6 hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful. An example is the relative efficacy in the third molar extraction pain model (Barden 2004).

Nefopam

This review looks at nefopam. Nefopam HCl (3,4,5,6-tetrahydro-5-methyl-1-phenyl-1h-2,5-benzoxazocine hydrochloride) has a unique heterocyclic structure and is derived from orphenadrine and diphenhydramine by cyclization of the side chain. It is unrelated chemically or pharmacologically to any other analgesic compound. It appears safe and seems to have no depressant action on the central nervous system (CNS). It has been shown to be effective when given by oral and parenteral routes. The mechanism of action of nefopam is not known, and there seems to have been little advance in knowledge since the drug began to be used in the 1970s and 1980s (Heel 1980). It may have a place in the relief of persistent moderate pain which is not responding to other analgesics.

Nefopam is available by prescription as 30 mg tablets in the UK, where 108,000 prescriptions were dispensed in 2007 (PCA 2007) by general practitioners. Nefopam comes under a variety of descriptions worldwide:

- 3M Brand of Nefopam Hydrochloride; Acupan; Ajan;
- Biocodex Brand of Nefopam Hydrochloride; Fenazoxine;
- Krewel Brand of Nefopam Hydrochloride; Nefopam Hydrochloride; Silentan Nefopam; Hydrochloride, Nefopam; Nefopam, Silentan.

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral nefopam for acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they were double blind trials of single dose oral nefopam compared with placebo for the treatment of moderate to severe postoperative pain in adults with at least 10 participants randomly allocated to each treatment group. Multiple dose studies will be included if appropriate data from the first dose were available. Cross-over studies were included provided that data from the first arm were presented separately.

The following were excluded:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies where pain relief is assessed only by clinicians, nurses or carers (i.e., not patient-reported);
- studies of less than 4 hours duration or studies that fail to present data over 4 to 6 hours post-dose.

For postpartum pain, studies were included if the pain investigated was due to episiotomy or Caesarean section irrespective of the

presence of uterine cramps; studies investigating pain due to uterine cramps alone were excluded.

Types of participants

Studies of adult participants (> 15 yrs) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity will be equated to greater than 30 mm (Collins 1997).

Types of interventions

Nefopam or matched placebo administered as a single oral dose for postoperative pain.

Types of outcome measures

Data was collected on the following:

- participant characteristics;
- patient reported pain at baseline (physician, nurse or carer reported pain will not be included in the analysis);
- patient reported pain relief expressed at least hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both);
- patient global assessment of efficacy (PGE), using a standard categorical scale;
- time to use of rescue medication;
- number of participants using rescue medication;
- number of participants with one or more adverse events;
- number of participants with serious adverse events;
- number of withdrawals (all cause, adverse events).

Search methods for identification of studies

To identify studies for inclusion in this review, the following electronic databases were searched:

- Cochrane CENTRAL (issue 2, 2009);
- MEDLINE via Ovid (to May 2009);
- EMBASE via Ovid (to May 2009);
- Oxford Pain Relief Database (Jadad 1996a).

Please see Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy.

Additional studies were sought from the reference lists of retrieved articles and reviews.

Language

No language restriction was applied.

Unpublished studies

No manufacturing or distributing pharmaceutical company was contacted for unpublished trial data.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies that might be included in the review. Disagreements were resolved by consensus or referral to a third review author.

Quality assessment

Two review authors independently assessed the included studies for quality using a five-point scale (Jadad 1996b) that considers randomisation, blinding, and study withdrawals and dropouts.

The scale used is as follows.
Is the study randomised? If yes give one point.
Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.
Is the study double blind? If yes then add one point.
Is the double blind method reported and is it appropriate? If yes add one point, if no deduct one point.
Are the reasons for patient withdrawals and dropouts described? If yes add one point.

Data management

Information was extracted by two review authors and recorded on a standard data extraction form. Information suitable for pooling was entered into RevMan 5.0.

Data analysis

QUOROM guidelines were followed (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used number of participants who received study medication in each treatment group.

Primary outcome:

Number of participants achieving at least 50% pain relief

For each study, mean TOTPAR (total pain relief) or SPID (summed pain intensity difference) for active and placebo groups were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The proportion of participants in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then converted into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. Information on the number of participants with at least 50%maxTOTPAR for active treatment and placebo was then used to calculate relative benefit (RB) and number-needed-to-treat-to-benefit (NNT).
Pain measures accepted for the calculation of TOTPAR or SPID were:

- five-point categorical pain relief (PR) scales with comparable wording to "none, slight, moderate, good or complete";
- four-point categorical pain intensity (PI) scales with comparable wording to "none, mild, moderate, severe";
- Visual analogue scales (VAS) for pain relief;
- VAS for pain intensity.

If none of these measures were available, numbers of participants reporting "very good or excellent" on a five-point categorical global scale with the wording "poor, fair, good, very good, excellent" were taken as those achieving at least 50% pain relief (Collins 2001).

Further details of the scales and derived outcomes are in the glossary (Appendix 4).

Secondary outcomes:

1. **Use of rescue medication**. Numbers of participants requiring rescue medication were used to calculate relative risk (RR) and numbers-needed-to-treat-to-prevent (NNTp) use of rescue medication for treatment and placebo groups. Median (or mean) time to use of rescue medication was used to calculate the weighted mean of the median (or mean) for the outcome. Weighting was by number of participants.
2. **Adverse events**. Numbers of participants reporting adverse events for each treatment group were used to calculate RR and numbers-needed-to-treat-to-harm (NNH) estimates for:
   a. any adverse event;
   b. any serious adverse event (as reported in the study);
   c. withdrawal due to an adverse event.
3. **Withdrawals.** Withdrawals for reasons other than lack of efficacy (participants using rescue medication - see above) and adverse events were noted, as were exclusions from analysis where data were presented.

RB or RR estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CI were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the RB did not include the number one. Homogeneity of studies was assessed visually (L'Abbe 1987).

Sub-group analyses were planned to determine the effect of dose, presenting condition (pain model: dental versus other surgery), and high versus low (two or fewer versus three or more) quality trials. A minimum of two trials and 200 participants must be available in any sensitivity analysis (Moore 1998).

RESULTS

Description of studies

Results of the search

Thirteen potential studies were found. Full copies were obtained and read to decide on inclusion.

Included studies

No studies were found matching the inclusion criteria.

Excluded studies

All the thirteen studies examined were excluded. One study as it was not dealing exclusively with postoperative pain (Campos 1980). One study of 20 mg oral nefopam was excluded as the first dose was infused preoperatively (Du Manoir 2003). One study measured pain at 1 hour only (Hedges 1978). Five studies had no placebo arm (Calmi 1985; Pandit 1989; Phillips 1979; Sidhu 1993; Tigerstedt 1977; Tigerstedt 1979). Two studies used intravenous nefopam only, one without placebo; both were preemptive (Goucke 1990; McLintock 1988). Two studies did not conform to the standard pain model (Bloomfield 1980; Gassel 1976).

Risk of bias in included studies

There were no included studies, so bias could not be evaluated.

Effects of interventions

There were no included studies, so effects could not be evaluated.

DISCUSSION

Nefopam is a widely available analgesic, by oral, rectal, and intravenous or intramuscular injection. It is disappointing that no classical analgesic studies of efficacy of oral nefopam compared with placebo in patients with established pain have been published.

It is almost certain that such studies have been performed, as they would have been required for registration purposes. Previously, large numbers of unpublished trials of this design have been included in systematic reviews of tramadol (Moore 1997c), and large numbers of analgesic trials of many designs with dexketoprofen (Moore 2008). Obtaining unpublished clinical trial data is, however, a long and complicated process, made more difficult by drugs being older, with original trial data hard to find.

There is a literature showing that nefopam has analgesic properties when used perioperatively, and nine such trials with 847 participants have recently been the subject of a systematic review (Evans 2008). Based on subsets of these nine trials, there was some evidence that nefopam reduced postoperative pain scores and opioid consumption, but with increased tachycardia (NNH 7) and sweating (NNH 13). A recent French survey showed that nefopam was only rarely used perioperatively (Fletcher 2008).

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy for oral nefopam in acute postoperative pain, its use in this indication is not justified. As trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies is lacking, use in other indications should be evaluated carefully.

Implications for research

Given the large number of available drugs of this and similar classes, there is no urgent research agenda.

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Goucke 1990 *{published data only}*

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Pandit 1989 *{published data only}*

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Phillips 1979 *{published data only}*

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Sidhu 1993 *{published data only}*

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Derry C 2009a

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bloomfield 1980	Not standard pain model
Calmi 1985	No placebo arm
Campos 1980	Not exclusively postoperative pain
Du Manoir 2003	First dose infused preoperatively
Gassel 1976	Not standard pain model
Goucke 1990	Single intramuscular injection given after induction of anaesthesia. No placebo arm
Hedges 1978	Pain relief at 1 hour only
McLintock 1988	Analgesic administration is intramuscular and pre-emptive to surgical intervention
Pandit 1989	No placebo arm
Phillips 1979	No placebo arm
Sidhu 1993	No placebo arm
Tigerstedt 1977	No placebo arm
Tigerstedt 1979	No placebo arm

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

1. Nefopam.sh

2. (Acupan OR Ajan OR Fenazoxine OR Silentan).ti,ab,kw.

3. OR/1-2

4. Pain, postoperative.sh

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$) or ("post-operative analgesi$")).ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")).ti,ab,kw.

11. OR/4-10

12. randomized controlled trial.pt.

13. controlled clinical trial.pt.

14. randomized.ab.

15. placebo.ab.

16. drug therapy.fs.

17. randomly.ab.

18. trial.ab.

19. groups.ab.

20. OR/12-19

21. humans.sh.

22. 20 AND 21

23. 3 AND 11 AND 22

Appendix 2. EMBASE search strategy (via OVID)

1. Nefopam.sh

2. (Acupan OR Ajan OR Fenazoxine OR Silentan).ti,ab,kw.

3. OR/1-2

4. Postoperative pain.sh

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$) or ("post-operative analgesi$")).ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")).ti,ab,kw.

11. OR/4-10

12. clinical trials.sh

13. controlled clinical trials.sh

14. randomized controlled trial.sh

15. double-blind procedure.sh

16. (clin$ adj25 trial$).ab

17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab

18. placebo$.ab

19. random$.ab

20. OR/12-19

21. 3 AND 11 AND 20

Appendix 3. CENTRAL search strategy

1. MESH descriptor Nefopam

2. (Acupan OR Ajan OR Fenazoxine OR Silentan).ti,ab,kw.

3. OR/1-2

4. MESH descriptor Pain, Postoperative

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$) or ("post-operative analgesi$")):ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)):ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")):ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")):ti,ab,kw.

11. OR/4-10

12. Clinical trials:pt.

13. Controlled Clinical Trial:pt.

14. Randomized Controlled Trial.pt.

15. MESH descriptor Double-Blind Method

16. (clin$ adj25 trial$):ti,ab,kw.

17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)):ti,ab,kw.

18. placebo$:ti,ab,kw.

19. random$:ti,ab,kw.

20. OR/12-19

21. 3 AND 11 AND 20

Appendix 4. Glossary

Categorical rating scale:

The commonest is the five category scale (none, slight, moderate, good or lots, and complete). For analysis numbers are given to the verbal categories (for pain intensity, none=0, mild=1, moderate=2 and severe=3, and for relief none=0, slight=1, moderate=2, good or lots=3 and complete=4). Data from different subjects is then combined to produce means (rarely medians) and measures of dispersion

(usually standard errors of means). The validity of converting categories into numerical scores was checked by comparison with concurrent visual analogue scale measurements. Good correlation was found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

VAS:

Visual analogue scale: lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain", seem to overcome this limitation. Patients mark the line at the point which corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the patient's mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. More concentration and coordination are needed, which can be difficult post-operatively or with neurological disorders.

TOTPAR:

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

SPID:

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

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

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

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
10 November 2010	Review declared as stable	The authors declare that there is unlikely to be any further studies to be included in this review and so it should be published as a 'stable review'.

CONTRIBUTIONS OF AUTHORS

MK, SD and RAM performed searching, data extraction, and analysis, including assessment of study quality. HJM helped with analysis and act as arbitrator. All review authors contributed to the writing of the final review. SD will be responsible for conducting the review update.

DECLARATIONS OF INTEREST

SD, RAM & HJM have received research support from charities, government and industry sources at various times. RAM and HJM have consulted for various pharmaceutical companies. RAM, and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. Support for this review came from Oxford Pain Research, the NHS Cochrane Collaboration Programme Grant Scheme, and NIHR Biomedical Research Centre Programme.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the protocol and the review.

NOTES

The authors declare that there is unlikely to be any further studies to be included in this review and so it should be published as a 'stable review'.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage]; Nefopam [*administration & dosage]; Pain, Postoperative [*drug therapy]

MeSH check words

Adult; Humans