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

Moore RA, Derry S, Moore M, McQuay HJ

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[Intervention Review]

Single dose oral nabumetone for acute postoperative pain in adults

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ABSTRACT

Background

Nabumetone is a non-steroidal anti-inflammatory drug (NSAID) used mainly in treating pain associated with arthritis. The usual oral dose for osteoarthritis is 1000 mg daily, and higher doses are not advised in older patients. There are no known systematic reviews of its analgesic efficacy in acute postoperative pain. This review sought to evaluate the efficacy and safety of oral nabumetone 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 whether drugs have analgesic properties.

Objectives

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

Search methods

We searched *The Cochrane Library* (Issue 2, 2009), MEDLINE (May 2009); EMBASE via Ovid (May 2009); and the Oxford Pain Relief Database.

Selection criteria

Randomised, double-blind, placebo-controlled clinical trials of oral nabumetone 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 nabumetone and placebo experiencing at 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 (CI). 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 studies were identified by the searches that examined oral nabumetone in participants with established postoperative pain.

Authors' conclusions

In the absence of evidence of efficacy, at present, for oral nabumetone 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 is 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 nabumetone for postoperative pain in adults

Pain is commonly experienced after surgical procedures. Post operative pain is a good model to test whether or not drugs are effective painkillers in participants with moderate or severe pain. In this case we could find no studies that tested oral nabumetone against placebo. It is possible that the studies were conducted, but not reported, because they were used only to register nabumetone with licensing authorities throughout the world. However, this leaves an important gap in our knowledge, and it means that we cannot be confident about using oral nabumetone 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.

This is one of a series of reviews whose aim 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. Recently published reviews include paracetamol (Toms 2008), celecoxib (Derry 2008), naproxen (Derry C 2009), diclofenac (Derry P 2009) and etoricoxib (Clarke 2009).

Acute pain trials

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants tend to be 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. Hence, the use of additional or rescue analgesia is important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, 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).

Nabumetone

This review looks at nabumetone, a non-steroidal anti-inflammatory drug (NSAID). Nabumetone is used mainly in treating pain associated with arthritis. The usual oral dose for osteoarthritis is 1000 mg daily, and higher doses are not advised in older patients. Nabumetone is available in many European countries, as well as South Africa and the USA. In England in 2007 110,000 prescriptions were issued in primary care. This compares with almost 8 million prescriptions for naproxen and 4.5 million prescriptions for ibuprofen in the same period (PACT 2007).

Clinicians prescribe NSAIDs on a routine basis for a range of mild to moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins (PGs) and thromboxane A₂ (Fitzgerald 2001). PGs mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999).

Nabumetone has a number of trade names (Arthaxan, Balmox, Mebutan, Nabuser, Relafen, Relifen, Relifex Relisan and Relitone). Nabumetone is a naphthylalkanone. The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), a potent inhibitor of prostaglandin synthesis, most likely through binding to cyclooxygenases. Approximately 35% of a 1000 mg oral dose of nabumetone is converted to 6MNA and 50% is converted into unidentified metabolites that are subsequently excreted in the urine. The half life of the active metabolite, 6MNA is about 23 hours (Hedner 2004).

We could find no systematic review on the efficacy of nabumetone in acute pain. This review will look at the efficacy of nabumetone in the setting of acute postoperative pain.

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral nabumetone 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 would have been included if they were double blind trials of single dose oral nabumetone compared with placebo for the treatment of moderate to severe postoperative pain in adults with at least ten participants randomly allocated to each treatment

group. Multiple dose studies were eligible if appropriate data from the first dose were available. Cross-over studies were eligible provided that data from the first arm were presented separately. No language restriction was applied to the search for studies.

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 eligible 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 will be included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was equated to greater than 30 mm (Collins 1997).

Types of interventions

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

Types of outcome measures

Data were sought 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 event).

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 (May 2009);
- EMBASE via Ovid (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 Cochrane 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.

Quality assessment

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

Data management

It was planned that data would be extracted by two review authors and recorded on a standard data extraction form.

Data analysis

It was planned that for each study, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID ([Appendix 4](#)) values for active and placebo would be 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 would be calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions can be 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 and placebo can then be 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";
- VAS for pain relief;
- VAS for pain intensity.

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

It was planned that the number of participants reporting treatment-emergent adverse effects would be extracted for each treatment group. RB and relative risk (RR) estimates would be calculated with 95% confidence intervals (CI) using a fixed-effect

model (Morris 1995). NNT and number-needed-to-treat-to-harm (NNH) and 95% CI would be calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control is assumed when the 95% CI of the RB or RR does not include the number one. Homogeneity would be examined visually using L'Abbé plots (L'Abbé 1987).

Sub-group analyses were planned to determine the effect of dose, presenting condition (pain model), and low versus high (two versus three or more) quality trials. A minimum of two trials and 200 participants must be available in any sensitivity analysis (Moore 1998). The z test (Tramér 1997) would be used to determine if there is a significant difference between NNTs for different groups in the sensitivity analyses when the 95% CIs do not overlap.

RESULTS

Description of studies

Results of the search

One study was examined in detail by reading the abstract and the full paper (Movilia 1990). A second title was identified as possibly being relevant (Pellerin 1989), but no copy could be found either electronically or in paper format.

Included studies

No studies were found matching the inclusion criteria.

Excluded studies

The one study examined was excluded (Movilia 1990) because the trial used preemptive analgesia in which nabumetone was administered before participants had established pain.

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

Nabumetone is a widely available NSAID in many parts of the world, and it is disappointing that no classical analgesic studies were found in patients with established pain.

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 dextropropofol (Moore 2008). Obtaining unpublished clinical trial data is, however, a long and complicated process, made more difficult by drugs being older, and with original trial data being hard to find.

Nabumetone is principally used for treating chronic musculoskeletal conditions (Hedner 2004). It is regarded as having better gastrointestinal safety than other NSAIDs, with some evidence of this from randomised trials (Bannwarth 2008) and observational studies (Ashworth 2005).

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy at present for oral nabumetone 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 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 to treat postoperative pain, there is no urgent research agenda.

ACKNOWLEDGEMENTS

We wish to thank Caroline Struthers at the PaPaS Cochrane Review Group for help with searching.

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References to studies excluded from this review

Movilia 1990 {published data only}

Movilia P, Restelli L, Miriano F, Vaiani G, Grossi E. Analgesic activity of nabumetone in postoperative pain. *Drugs* 1990;**40**(Suppl 5):71-4.

References to studies awaiting assessment

Pellerin 1989 {published data only}

Pellerin I, Sommi F, Castiglioni C. Randomized double-blind study of the analgesic efficacy of nabumetone vs. diclofenac, tenoxicam and placebo for the treatment of postoperative pain. *Basi Razionali della Terapia* 1989;**19**(10):583-6.

Additional references

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Bannwarth 2008

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Barden 2004

Barden J, Edwards JE, McQuay HJ, Wiffen PJ. Relative efficacy of oral analgesics after third molar extraction. *British Dental Journal* 2004;**197**(7):407-11.

Clarke 2009

Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: [10.1002/14651858.CD004309.pub2](https://doi.org/10.1002/14651858.CD004309.pub2)]

Collins 1997

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Collins 2001

Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough?. *Pain* 2001;**91**(1-2):189-94.

Cook 1995

Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**(6977):452-4.

Cooper 1991

Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. The Design of Analgesic Clinical Trials. *Advances in Pain Research Therapy* 1991;**18**:117-24.

Derry 2008

Derry S, Moore RA, McQuay HJ. Single dose oral celecoxib for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: [10.1002/14651858.CD004233](https://doi.org/10.1002/14651858.CD004233)]

Derry C 2009

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: [10.1002/14651858.CD004234.pub2](https://doi.org/10.1002/14651858.CD004234.pub2)]

Derry P 2009

Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: [10.1002/14651858.CD004768.pub2](https://doi.org/10.1002/14651858.CD004768.pub2)]

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Hawkey 1999

Hawkey CJ. Cox-2 inhibitors. *Lancet* 1999;**353**(9149):307-14.

Hedner 2004

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Jadad 1996a

Jadad AR, Carroll D, Moore RA, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;**66**(2-3):239-46.

Jadad 1996b

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

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Moore 1996

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controlled trials of analgesics. *Pain* 1996;**66**(2-3):229-37. [DOI: [10.1016/0304-3959\(96\)03032-1](https://doi.org/10.1016/0304-3959(96)03032-1)]

Moore 1997a

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997;**69**(1-2):127-30. [DOI: [10.1016/S0304-3959\(96\)03251-4](https://doi.org/10.1016/S0304-3959(96)03251-4)]

Moore 1997b

Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997;**69**(3):311-5. [DOI: [10.1016/S0304-3959\(96\)03306-4](https://doi.org/10.1016/S0304-3959(96)03306-4)]

Moore 1997c

Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997;**69**(3):287-94. [DOI: [10.1016/S0304-3959\(96\)03291-5](https://doi.org/10.1016/S0304-3959(96)03291-5)]

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything-large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16. [DOI: [10.1016/S0304-3959\(98\)00140-7](https://doi.org/10.1016/S0304-3959(98)00140-7)]

Moore 2003

Moore RA, Edwards J, Barden J, McQuay HJ. Bandolier's Little Book of Pain. Oxford: Oxford University Press, 2003. [ISBN: 0-19-263247-7]

Moore 2005

Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of

analysing and presenting results. *Pain* 2005;**116**(3):322-31. [DOI: [10.1016/j.pain.2005.05.001](https://doi.org/10.1016/j.pain.2005.05.001)]

Moore 2006

Moore A, McQuay H. Bandolier's Little Book of Making Sense of the Medical Evidence. Oxford: Oxford University Press, 2006. [ISBN: 0-19-856604-2]

Moore 2008

Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic pain. *BMC Clinical Pharmacology* 2008;**8**:11. [DOI: [10.1186/1472-6904-8-11](https://doi.org/10.1186/1472-6904-8-11)]

Morris 1995

Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratio and standardised ratios and rates. In: Gardner MJ, Altman DG editor(s). *Statistics with Confidence - Confidence Intervals and Statistical Guidelines*. London: British Medical Journal, 1995:50-63.

PACT 2007

Prescription Cost Analysis. England 2007. [ISBN: 978-1-84636-210-1]

Toms 2008

Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: [10.1002/14651858.CD004602.pub2](https://doi.org/10.1002/14651858.CD004602.pub2)]

Tramér 1997

Tramér MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate results on meta-analysis: a case study. *BMJ* 1997;**315**:635-9.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Movilia 1990	Analgesic administration is pre-emptive to surgical intervention

Characteristics of studies awaiting assessment [ordered by study ID]

[Pellerin 1989](#)

Methods

Participants

Interventions

Pellerin 1989 (Continued)

Outcomes

Notes

Unable to obtain publication

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

[mp=title, original title, abstract, name of substance word, subject heading word]

1. nabumetone/
2. nabumeton*.mp.
3. Arthaxan or Balmox or Brl 14777 or Brl14777 or Consolan or Diosmal or Listran or (Naphthyl and Butanone) or Nabucox or Nabumeton or Nabuser or Relafen or Relifen or Relifex or Reliflex or relifex or relafen or nabucox or arthrxan or aktratol or mevedal or nabuton or naditone or nabuco or artaxan or nabuser or relifen or mebutan or balmox or elitar or relisan or relitone or dolsinal or listran or relif or nabone or nabonet or naflex or nametone.mp.
4. /or 1-3
5. Pain, Postoperative/
6. (postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.
7. (post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*).mp.
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.
9. ("post surg*" or post-surg*) and (pain* or discomfort).mp.
- 10.(pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*").mp.
- 11.(analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*").mp.
- 12.or/5-11
- 13.exp Surgical Procedures, Operative/
- 14.12 or 13
- 15.randomized controlled trial.pt.
- 16.controlled clinical trial.pt.
- 17.randomized.ab.
- 18.placebo.ab.
- 19.drug therapy.fs.
- 20.randomly.ab.
- 21.trial.ab.
- 22.groups.ab.
- 23.or/15-22
- 24.humans.sh.
- 25.23 and 24
- 26.25 and 4 and 14

Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.

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8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10.humans.sh.
- 11.9 and 10

Appendix 2. EMBASE search strategy (via Ovid)

1. Nabumetone/
2. nabumetone.mp
3. (Arthaxan or Balmox or Brl 14777 or Brl14777 or Consolan or Diosmal or Listran or (Naphthyl and Butanone) or Nabucox or Nabumeton or Nabuser or Relafen or Relifen or Relifex or Reliflex).mp
4. (relifex or relafen or nabucox or arthaxan or akratol or mevedal or nabuton or naditone or nabuco or artaxan or nabuser or relifen or mebutan or balmox or elitar or relisan or relitone or dolsinal or listran or relif or nabone or nabonet or naflex or nametone).mp
5. or/1-4
6. Postoperative pain/
7. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp.
8. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.
9. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.
- 10.(("post surg*" or post-surg*) and (pain* or discomfort)).mp.
- 11.((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.
- 12.((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.
- 13.or/7-12
- 14.exp Surgical Procedures, Operative/
- 15.13 or 14
- 16.random*.ti,ab.
- 17.factorial*.ti,ab.
- 18.(crossover* or cross over* or cross-over*).ti,ab.
- 19.placebo*.ti,ab.
- 20.(doubl* adj blind*).ti,ab.
- 21.assign*.ti,ab.
- 22.allocat*.ti,ab.
- 23.CROSSOVER PROCEDURE.sh.
- 24.DOUBLE-BLIND PROCEDURE.sh.
- 25.RANDOMIZED CONTROLLED TRIAL.sh.
- 26.or/16-25
- 27.5 and 15 and 26

Search filter for EMBASE (Ovid format) 2008

1. random*.ti,ab.
2. factorial*.ti,ab.
3. (crossover* or cross over* or cross-over*).ti,ab.
4. placebo*.ti,ab.
5. (doubl* adj blind*).ti,ab.
6. (singl* adj blind*).ti,ab.
7. assign*.ti,ab.
8. allocat*.ti,ab.
9. volunteer*.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 15 and 16

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

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18. 15 not 17
19. 14 not 18

Appendix 3. Cochrane CENTRAL search strategy

1. nabumetone:ti,ab,kw.
2. (Arthaxan or Balmox or Brl 14777 or Brl14777 or Consolan or Diosmal or Listran or (Naphthyl and Butanone) or Nabucox or Nabumeton or Nabuser or Relafen or Relifen or Relifex or Reliflex):ti,ab,kw.
3. (relifex or relafen or nabucox or arthaxan or akrotol or mevedal or nabuton or naditone or nabuco or artaxan or nabuser or relifen or mebutan or balmox or elitar or relisan or relitone or dolsinal or listran or relif or nabone or nabonet or naflex or nametone):ti,ab,kw.
4. OR/1-3
5. MESH descriptor Pain, Postoperative explode all trees
6. ((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or "post-operative analgesi*"):ti,ab,kw.
7. ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)):ti,ab,kw.
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after"):ti,ab,kw.
9. (("post surg*" or post-surg*) and (pain* or discomfort)):ti,ab,kw.
- 10.((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")):ti,ab,kw.
- 11.((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")):ti,ab,kw.
- 12.#6 OR #7 OR #8 OR #9 OR #10 OR #11
- 13.Randomized Controlled Trial:pt.
- 14.MeSH descriptor Double-Blind Method
- 15.((doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)):ti,ab,kw.
- 16.placebo\$:ti,ab,kw.
- 17.random\$:ti,ab,kw.
- 18.#13 OR #14 OR #15 OR #16 OR 17
- 19.#4 AND #12 AND #18
- 20.Limit to CLINICAL TRIALS (CENTRAL)

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 Bandalier's Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13 ([Moore 2003](#)).

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'.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 4, 2009

Date	Event	Description
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

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

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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Internal sources

- Oxford Pain Research Funds, UK.

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- NHS Cochrane Collaboration Grant, UK.
- NIHR Biomedical Research Centre Programme, UK.

Support for RAM

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 [*administration & dosage]; Butanones [*administration & dosage]; Cyclooxygenase 2 Inhibitors [*administration & dosage]; Nabumetone; Pain, Postoperative [*drug therapy]

MeSH check words

Adult; Humans