Published in final edited form as:
Cochrane Database Syst Rev. ; (4): CD004234. doi:10.1002/14651858.CD004234.pub2.

Single dose oral naproxen and naproxen sodium for acute postoperative pain (Review)

L Mason, **JE Edwards**, **RA Moore**, and **HJ McQuay**

Abstract

Background—Postoperative pain is often poorly managed. Treatment options include a range of drug therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) of which naproxen is one. Naproxen is used to treat a variety of painful conditions including acute postoperative pain, and is often combined with sodium to improve its solubility for oral administration. Naproxen sodium 550 mg (equivalent to 500 mg of naproxen) is considered to be an effective dose for treating postoperative pain but to date no systematic review of the effectiveness of naproxen/naproxen sodium at different doses has been published.

Objectives—To assess the efficacy, safety and duration of action of a single oral dose of naproxen or naproxen sodium for acute postoperative pain in adults.

Search strategy—We searched *The Cochrane Library*, MEDLINE, EMBASE and the Oxford Pain Relief Database for relevant studies. Additional studies were identified from the reference list of retrieved reports. The most recent search was undertaken in July 2004.

Selection criteria—Included studies were randomised, double blind, placebo-controlled trials of a single dose of orally administered naproxen or naproxen sodium in adults with moderate to severe acute postoperative pain.

Data collection and analysis—Pain relief or pain intensity data were extracted and converted into dichotomous information to give the number of patients with at least 50% pain relief over four to six hours. Relative risk estimates (RR) and the number-needed-to-treat (NNT) for at least 50% pain relief were then calculated. Information was sought on the percentage of patients experiencing any adverse event, and the number-needed-to-harm was derived. Time to remedication was also estimated.

Main results—Ten trials (996 patients) met the inclusion criteria: nine assessed naproxen sodium; one combined the results from two small trials of naproxen alone. Included studies scored well for methodological quality. Meta-analysis of six trials (500 patients) that compared naproxen

Contact address: Ms Lorna Mason, c/o Pain Research Unit, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ, UK, Tel: +44 1865 225674, Fax: +44 1865 226978.
Contribution of author(s): LM was involved with searching, data extraction, quality scoring, analysis and writing. JE was involved with searching, data extraction, analysis, quality scoring and writing. HJM was involved in writing. RAM was involved in data extraction, analysis and writing.
Editorial group: Cochrane Pain, Palliative and Supportive Care Group

POTENTIAL CONFLICT OF INTEREST
RAM and HJM have undertaken research/consultants for various pharmaceutical companies. RAM, HJM and JE have received lecture fees from pharmaceutical companies for presentations on analgesics research 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 the preparation of this systematic review.

Europe PMC Funders Author Manuscripts

sodium 550 mg with placebo gave a RR for at least 50% pain relief over 4 to 6 hours of 4.2 (95% confidence interval (CI) 2.9 to 6.0) and an NNT of 2.6 (95% CI 2.2 to 3.2). Three trials (334 patients) assessed naproxen 400 mg and naproxen sodium 440 mg, giving a RR of 4.8 (95% CI 2.75 to 8.38). Two small studies indicated that naproxen 200 mg and naproxen sodium 220 mg may provide effective postoperative pain relief. There was no significant difference between the number of patients experiencing any adverse event on treatment compared with placebo. Weighted mean time to remedication for naproxen sodium 550 mg was 7.6 hours compared with 2.6 hours for placebo.

Authors' conclusions—Naproxen sodium 550 mg, naproxen 400 mg and naproxen sodium 440 mg administered orally are effective analgesics for the treatment of acute postoperative pain in adults. A low incidence of adverse events was found but reporting was not consistent.

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Naproxen [analogs & derivatives; *therapeutic use]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

BACKGROUND

Despite the availability of a range of drug treatments, the postoperative period is often dominated by the need to find an effective way to block the inflammatory reaction and relieve patients' pain (Salvato 1992). In one US study, postsurgical pain was given as the greatest cause of concern for 57% of patients asked before surgery (Warfield 1995). The perception of presurgical patients that postoperative pain is inevitable is endorsed by studies that have shown that pain is both prevalent and poorly managed amongst hospital in-patients (Bruster 1994). A recent, extensive review of postoperative pain management found that severe pain, and poor or fair pain relief, was experienced by almost one in five hospital patients (Dolin 2002).

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) and is often prescribed as the sodium salt (naproxen sodium) to improve its solubility for oral administration. As a drug class, NSAIDs have analgesic effects, do not depress respiration and do not impair gastro-intestinal motility (BNF 2002) so are clinically useful for treating pain after minor surgery and day surgery, and can have opiate-sparing effects after more major surgery (Grahame-Smith 2002). Naproxen sodium 550 mg, equivalent to 500 mg of naproxen (Martindale 1999), is considered an effective dose for treating postoperative pain (Rasmussen 1993). Specific data for the frequency of naproxen administration for postoperative pain relief are unavailable. However, in England in 2001 there were over 1.2 million prescriptions for oral naproxen and naproxen sodium in primary care (Dep of Health 2002).

In tandem with their pain-relieving properties, conventional NSAIDs are associated with serious adverse events such as upper gastrointestinal bleeding and perforation, acute liver

Europe PMC Funders Author Manuscripts

injury, acute renal injury, heart failure, and adverse reproductive outcomes (Hernandez-Diaz 2001). However, such complications are more likely to occur with chronic use and NSAIDs generally present fewer risks if used in the short term, as in the treatment of post-operative pain (Rapoport 1999).

There may be relatively small differences between types of NSAIDs as regards their anti-inflammatory and analgesic effects, but there is considerable variation in individual patient's tolerance and responses. About 60% of patients will respond to any NSAID; of the remaining 40%, those patients who do not respond to one type may well respond to another (BNF 2002). It is therefore important to assess each NSAID to determine its relative efficacy and adverse event profile.

OBJECTIVES

The primary objective of this review was to quantitatively determine the efficacy of a single dose of oral naproxen or naproxen sodium compared with placebo for treating acute, postoperative pain in adults. The evidence relating to adverse events associated with the use of oral naproxen/naproxen sodium for postoperative pain was also assessed, and a third objective was to seek evidence for the duration of action of the drug.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Studies were included if they were randomised, double blind clinical trials in which a minimum of 10 patients assigned to each treatment group received either naproxen/naproxen sodium or a matched placebo. Studies had to provide extractable, single dose data for the first treatment given, with pain intensity recorded at 4 to 6 hours following initial administration of study treatment, using standard pain measurement scales.

Abstracts, review articles, case reports and clinical observations were not included as no evaluable data could be extracted from these types of publications.

Types of participants

Adults (aged 12 or older) with moderate to severe pain following any surgical procedure, carried out in either a day surgery or inpatient setting.

Types of intervention

Postoperative, oral administration of a single dose of naproxen or naproxen sodium or a matched placebo.

Types of outcome measures

The primary outcome was patient-reported pain relief or pain intensity measured using validated pain scales, i.e. either:

- a five-point pain relief (PR) scale with standard or comparable wording (none, slight, moderate, good, complete)

- a four-point pain intensity (PI) scale (none, mild, moderate, severe)
- a 10 cm visual analogue scale (VAS) for pain relief or pain intensity.

Extracted data were converted into dichotomous information.

Global evaluations of pain relief over 4 to 6 hours were also considered acceptable if measured on a standard five-point scale as reported by the patient. However, no such evaluations were extracted from studies included in this review.

Secondary outcome measures were;

- duration of action of treatment
- number of patients remedicating following the initial dose
- mean or median time to remedication
- reports of any adverse event
- reports of particular adverse events such as headache or vomiting
- reasons for patient discontinuation or withdrawal.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

Relevant studies were sought regardless of language, publication type or publication status.

Electronic databases

The electronic databases searched were

- *The Cochrane Library* (Issue 4 2002): the Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE and PreMEDLINE (all years from 1966 to December 2002)
- EMBASE (all years from 1980 to December 2002)
- PubMed (all years from 1966 to December 2002)

The Oxford Pain Relief Database (Jadad 1996a) at the Pain Research Unit was also searched. This comprises randomised controlled trials on pain topics derived from 40 hand searched journals for the years 1954 to 1994. Unpublished trials held in-house, including individual patient data, were also searched.

No additional hand searching was conducted for this review. Reference lists of retrieved articles were searched.

Search terms

Naproxen and “naproxen sodium”, together with registered brand names, were sought. The following search strategy was used in MEDLINE and modified for other databases to find relevant trials;

Europe PMC Funders Author Manuscripts

1. Naproxen, naproxen sodium and 88 brand names (Martindale 1999) separated by the OR command.

   AND

2. Randomised control trial (MeSH term) OR Random* OR blind OR double-blind OR double-masked OR masked OR trial

   AND

3. Postoperative pain (MeSH term) OR Pain* OR Analgesi*

   AND

4. operat* OR postoperat* OR post-operat* OR post-surg* OR surgery OR surgical OR dental OR molar OR extraction OR hernia OR thoracotomy OR urological OR orthop?edic OR post-orthop?edic OR postorthop?edic OR hysterectomy OR tonsillectomy OR c?esarean OR episiotomy OR laparoscop* OR cholecystectomy

The brand names and preparations used in the search strategy were:

Acusprain, Aleve, Alganil, Aliviomas, Alpoxen, Alprofen, Anaprox, Antalgin, Aperdan, Apo-Napro-Na, Apranax, Arthrosin, Arthroxen, Artroxen, Axer, Clinosyn, Continus, Denaxpren, Diparene, Dysmenalgit, Femex, Floginax, Flogogin, Floxalin, Genoxen, Gibinap, Gibixen, Gynestral, Ilagane, Inza, Laraflex, Laser, Ledox, Leniatril, Lundiran, Madaprox, Miranax, Miranax, Nafasol, Naparatec, Napflam Napmel, Naprel, Napren, Naprex, Naprium, Naprius, Naprobene, Naprocoat, Naprodol, Napro-Dorsch, Naprogesic, Naprokes, Naprorex, Naproscript, Naprosyn, Naprosyne, Naproval, Naprovite, Natrioxen, Naxen, Nitens, Novo-Naprox, Numidan, Numide, Nu-Naprox, Nycopren, Piproxen, Pranoxen, Praxenol, Prexan, Primeral, Pronaxen, Prosaid, Proxen, Proxine, Rheuflex, Rimoxyn, Rofanten, Sobronil, Synalgo, Synflex, Ticoflex, Timpron, Traumox, Valrox, Xenar, Xenopan.

Pharmaceutical companies and individual authors were not contacted.

METHODS OF THE REVIEW

Selection of studies

Studies were selected on the basis that they met the inclusion criteria. References of studies potentially meeting the inclusion criteria for this review were independently assessed from the abstracts by at least two reviewers. If insufficient information was given to determine if a paper should be included, or the abstract was not present, the full paper was retrieved for assessment. Disagreements as to whether a study met the selection criteria were settled by discussion. Reasons for excluding trials from the review are provided below in the ‘Characteristics of excluded studies’ table.

Data extraction

We extracted the following from each study:

- number of patients treated

- patient characteristics (gender, age, surgical procedure undertaken, etc)
- baseline pain intensity
- mean total pain relief (TOTPAR) and/or mean summed pain intensity difference (SPID)
- study duration
- treatment dose
- information on adverse events
- number of patients remedicating and time to remedication
- reasons for patient withdrawal and number of withdrawals

Data synthesis

In acute pain trials the outcome most often reported is total pain relief (TOTPAR) or summed pain intensity difference (SPID) over 4 to 6 hours, and these were the two primary outcomes of interest. Data on time to remedication and adverse events were also collected.

QUOROM guidelines were followed (Moher 1999). The number of patients randomised into each treatment group (intention to treat) was used in the efficacy analysis. Mean TOTPAR or SPID over 4 to 6 hours were either extracted or calculated from pain data within each trial and converted into %maxTOTPAR and/or %maxSPID using verified equations (Cooper 1991; Moore 1996; Moore 1997a; Moore 1997b). These data were used to calculate the number of patients with at least 50% pain relief for both naproxen and placebo. Relative risk (RR) estimates with 95% confidence intervals were calculated using Meta-view 4.1 in Review Manager (version 4.1) and a fixed effect model (Morris 1995). A statistically significant benefit of the active treatment over placebo was assumed when the lower limit of the 95% confidence interval (CI) of the relative benefit was more than one. A statistically significant benefit of placebo over the active treatment was assumed when the upper limit of the 95% CI of the relative benefit was less than one.

The number-needed-to-treat (NNT) and the number-needed-to-harm (NNH) were calculated, with 95% confidence intervals (Cook 1995). The NNT is the number of patients that need to be treated for one patient to benefit from the active treatment who would not have benefited from placebo (McQuay 1998). NNTs allow indirect comparisons of different analgesics by looking at relative efficacy, and are a useful surrogate for direct comparisons between different interventions (Song 2003). Number-needed-to-harm (NNH) and the relative risk were calculated in the same way as for NNTs, ie, using the number of patients in each treatment group reporting any adverse event, and for specific events such as headache, dizziness, drowsiness, etc.

The number of patients remedicating and mean time to first remedication (weighted by number of patients) were calculated as follows. For each trial, the number of patients receiving active treatment was multiplied by the percentage remedicating within 12 hours. These values were summed and divided by the total number of patients taking active

treatment in all trials using remedication as an outcome. These calculations were performed using Microsoft Excel X for the Macintosh.

Homogeneity of trials was assessed visually (L'Abbé 1987) because heterogeneity tests have been shown to be unhelpful (Gavaghan 2000; Higgins 2002). Funnel plots were not used to assess publication bias as these have also been shown to be unhelpful (Sterne 2000; Tang 2000). The z test (Tramèr 1997) was used to determine if there was a significant difference between NNTs for different doses of active treatment, or between NNTs for equivalent doses of naproxen and naproxen sodium.

Sensitivity analysis

Sensitivity analysis for naproxen versus naproxen sodium was not performed due to insufficient data.

DESCRIPTION OF STUDIES

Fifty-nine potential papers were identified by the search strategy. One of these (Frezza 1985) could not be obtained from the British Library. Forty-eight trials were excluded for at least one of the following reasons:

- thirty-one did not use a placebo control;
- seven did not report 4 to 6 hour pain scores;
- six did not measure baseline pain or patients did not have moderate to severe baseline pain;
- six reports provided no extractable analgesic efficacy data;
- six studies were not double blind;
- two used inappropriate pain scales; and
- one was not randomised.

Full details of all excluded trials can be seen in the 'Characteristics of excluded studies' table.

Ten studies with information from a total of 996 patients met the selection criteria and were included in the analysis.

Two of the included studies were unpublished at the time of this review. These studies were conducted by the pharmaceutical company Merck & Co Inc, Rahway, New Jersey, USA, and they provided data from trials where naproxen sodium 550 mg was used as an active comparator in acute dental pain studies of rofecoxib (Merck 1997a; Merck 1997b).

In the 10 included trials, 582 patients received active treatment (505 naproxen sodium; 77 naproxen) and 414 received placebo.

One study (Mahler 1976) reported on two trials conducted at two separate hospitals, both trials assessing two different doses of active treatment (naproxen 200 mg and naproxen 400

mg). These two trials are the only included studies to assess naproxen rather than naproxen sodium. The results from these two clinically homogeneous trials were combined to give a weighted mean TOTPAR for naproxen 200 mg (40 patients), naproxen 400 mg (37 patients), and placebo (40 patients) because the number of patients recruited at one of the sites was very small. In the meta-analysis this information was pooled with the data for 220 mg and 440 mg doses of naproxen sodium respectively.

Six other included trials (500 patients) assessed naproxen sodium 550 mg; two trials (257 patients) assessed naproxen sodium 440 mg; and one trial (122 patients) used naproxen sodium 220 mg. Trial participants were male and female ranging from 14 to 72 years of age. Of the 996 participants, 682 (68%) patients underwent dental surgery, the remainder undergoing either orthopaedic or general surgery. Full details can be found in the 'Characteristics of included studies' table.

METHODOLOGICAL QUALITY

Quality assessment

To be included in this review, studies had to have a randomised, double-blind design. Included studies were additionally assessed for methodological quality using the validated three-item scale devised by Jadad 1996b. The scoring system for this quality assessment scale is described below, and the quality scores for each included study is given in the 'Characteristics of included studies' table. Quality assessments were made independently by two reviewers and disagreements settled by discussion.

Scoring system

Question 1: Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?

Question 2: Was the study described as double-blind?

Question 3: Was there a description of withdrawals and drop outs?

Score as follows:

- Either give a score of 1 point for each 'yes' or 0 points for each 'no'. There are no in-between marks.
- Give 1 additional point if
  - for Question 1 the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, coin tossing, etc);

    and / or
  - if for Question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc).
- Deduct 1 point if

- for Question 1 the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc);

  and / or

- for Question 2 the study was described as double-blind but the method of blinding was inappropriate (eg, comparison of tablet versus injection with no double dummy).

All the studies included in this review scored three or more; one study received a score of five.

Meta-analysis of individual trials is useful because it can help to reduce the effect that chance plays on the final result, giving a more precise estimate of drug efficacy than looking at individual clinical trials alone (Ionnadis 2001; Moore 1998). It does this by combining data from trials that are clinically homogeneous and reach a certain standard of trial design. Randomisation, blinding and placebo control are important factors for reducing bias and chance effects (Kalso 2000). Inclusion of reports of low quality in meta-analysis is likely to give misleading results (Moher 1999), and therefore assessments of report quality are important for determining whether trials should be included or excluded.

RESULTS

Naproxen sodium 550 mg versus placebo

In six trials comprising a total of 500 patients (Brown 1997; Forbes 1986; Gottesdiener 1999; Merck 1997a; Merck 1997b; Reicin 2001) 252 received naproxen sodium 550 mg and 248 received placebo.

The mean response rate (percentage of patients with at least 50% pain relief) for naproxen sodium was 50% (127 patients out of 252), ranging from 30% to 72% in individual trials. The mean placebo response rate was 12% (30 patients out of 248), ranging from 6% to 19%.

Meta-analysis of dichotomous data using RevMan Analyses 1.0.2 showed that naproxen sodium 550 mg was significantly better than placebo in giving at least 50% pain relief over six hours for postoperative pain of moderate to severe intensity: RR 4.18 (95% CI 2.93 to 5.97). The NNT was 2.6 (95% CI 2.2 to 3.2).

Naproxen 400 mg and naproxen sodium 440 mg versus placebo

In three trials comprising a total of 334 patients (Fricke 1993; Kiersch 1994; Mahler 1976) 37 received naproxen 400 mg, 173 received naproxen sodium 440 mg, and 124 received placebo.

The mean response rate for naproxen 400 mg and naproxen sodium 440 mg was 49% (103 out of 210 patients), ranging from 46% to 53% in individual trials. The mean placebo response rate was 11% (14 out of 124 patients), ranging from 5% to 23%.

Europe PMC Funders Author Manuscripts

Meta-analysis of dichotomous data using RevMan Analyses 1.0.2 showed that naproxen 400 mg and naproxen sodium 440 mg are significantly better than placebo in giving at least 50% pain relief over six hours for postoperative pain of moderate to severe intensity: RR 4.8 (95% CI 2.75 to 8.4). The NNT was 2.7 (2.2 to 3.5).

Naproxen 200 mg and naproxen sodium 220 mg versus placebo

In two trials comprising 202 patients (Kiersch 1993; Mahler 1976) 40 received naproxen 200 mg, 80 received naproxen sodium 220 mg, and 82 received placebo.

The mean response rate for naproxen 200 mg and naproxen sodium 220 mg was 45% (54 out of 120 patients), ranging from 30% to 53% in individual trials. The mean placebo response rate was 16% (13 out of 82 patients), ranging from 10% to 23%.

Meta-analysis of dichotomous data using RevMan Analyses 1.0.2 showed that naproxen 200 mg and naproxen sodium 220 mg were significantly better than placebo in giving at least 50% pain relief over six hours for postoperative pain of moderate to severe intensity: RR 2.9 (95% CI 1.6 to 5.2). The NNT was 3.4 (95% CI 2.4 to 5.8).

Adverse events and study withdrawals

Seven included studies reported adverse events for single dose data (Brown 1997; Forbes 1986; Gottesdiener 1999; Kiersch 1993; Kiersch 1994; Merck 1997a; Merck 1997b). Five of the trials that assessed the effectiveness of naproxen sodium 550 mg provided sufficient evaluable data for statistical pooling of their results (Brown 1997; Forbes 1986; Gottesdiener 1999; Merck 1997a; Merck 1997b). Forty-seven out of 197 patients (24%) given naproxen sodium 550 mg reported at least one adverse event. Fifty-two out of 195 patients (27%) given placebo reported at least one adverse event. There was no significant difference between treatment and placebo: RR 0.89 (95% CI 0.6 to 1.3). One patient given naproxen sodium 440 mg had severe vomiting (Fricke 1993). In another trial (Kiersch 1993) seven adverse events were “serious” in patients receiving naproxen sodium 220 mg. Investigators in both trials did not regard these events as being related to the study medication.

Patient withdrawals and exclusions were not reported consistently. Trials often reported the total number of exclusions or withdrawals without stating which treatment groups these referred to. Neither was it clear when withdrawals occurred, ie, before assessment of analgesia at 4 to 6 hours, or at some other point before the end of the trial. Four trials did not give specific information for the number of exclusions and patient withdrawals for a single dose of naproxen or naproxen sodium (Forbes 1986; Mahler 1976; Merck 1997a; Merck 1997b). Of the remaining six trials, 45 out of 354 patients assigned to treatment with naproxen sodium were reported to have withdrawn or been excluded. Half of these (40 out of 81) were in one trial using naproxen sodium 220 mg (Kiersch 1993) in which the reasons for discontinuation were not stated.

Adverse event-related withdrawals for naproxen and naproxen sodium were described in three trials (Fricke 1993; Kiersch 1994; Reicin 2001). These adverse events were:

- one report of postoperative vomiting (Fricke 1993);
- one report of a headache (not deemed due to study medication by the investigator) (Kiersch 1994);
- two out of 55 patients on naproxen sodium 550 mg and three out of 53 patients on placebo withdrew due to a clinically adverse event on day one of the study (Reicin 2001).

Remedication

Number of patients who remedicated by 12 hours—Time to remedication data were pooled from four trials (Forbes 1986; Merck 1997a; Merck 1997b; Reicin 2001) to give the percentage of study participants remedicating by 12 hours, weighted by the number of participants. This was 63% (114 out of 181 patients) for naproxen sodium 550 mg and 78% (140 out of 180 patients) for placebo.

Time to remedication—Results from five trials (Forbes 1986; Gottesdiener 1999; Merck 1997a; Merck 1997b; Reicin 2001) were pooled to give the mean time to remedication, weighted by the number of patients. For naproxen sodium 550 mg this was 7.6 hrs (206 patients), and for placebo it was 2.6 hours (205 patients).

DISCUSSION

A single oral dose of 550 mg naproxen sodium has an NNT of 2.6 (95% CI 2.2 to 3.2) for at least 50% pain relief over six hours in postoperative pain of moderate to severe intensity, compared with placebo. This means that for approximately every three patients given naproxen sodium 550 mg, one will achieve at least a 50% reduction in postoperative pain of moderate to severe intensity who would not have done so if given placebo. This analysis included the most patients and is the most clinically relevant because 550 mg is the commonly prescribed dose.

For a single oral dose of naproxen 400 mg and naproxen sodium 440 mg the NNT was 2.7 (95% CI 2.2 to 3.5). For naproxen 200 mg and naproxen sodium 220 mg, the NNT was 3.4 (95% CI 2.4 to 5.8). Doses of less than 500 mg of naproxen are not commonly prescribed for acute postoperative pain and are therefore of limited clinical value. The results for naproxen 200 mg and naproxen sodium 220 mg, and naproxen 400 mg and naproxen sodium 440 mg are also less reliable than those for naproxen sodium 550 mg because these analyses included fewer trials and smaller numbers of patients. Combining studies into a meta-analysis may be better than relying on the results from a single trials but meta-analysis based on limited data may still not overcome the effects of chance (Moore 1998).

NNTs for naproxen sodium 550 mg; naproxen 400 mg and naproxen sodium 440 mg; naproxen 200 mg and naproxen sodium 220 mg were similar but there was insufficient information from trials using 440 mg (or equivalent) doses or 220 mg (or equivalent) to comment on dose response. No increased analgesic effect was experienced when the dose was increased but, from the limited information available, it is not possible to know whether

there is no dose response; whether any additional efficacy is minimal; or whether the effect was missed.

The relative efficacies of over 50 analgesics in acute postoperative pain have been compiled: see www.jr2.ox.ac.uk/bandolier/painres/painpag/acutrev/analgesics/leagtab.html Published versions can be found in Collins 1998; Edwards 1999a; and Moore 1997a. The number of patients in each meta-analysis from which NNTs have been derived varies considerably, and should be taken into account when comparing NNTs. A low NNT with a narrow confidence interval suggests greater efficacy, and the greater the number of patients in the meta-analysis the more robust the NNT.

An NNT of 2.6 for naproxen sodium 550 mg is slightly higher (worse) than that for ibuprofen 400 mg (2.4; 95% CI 2.3 to 2.6), but lower (better) than that for paracetamol 1000 mg (3.8; 95% CI 3.4 to 4.4) and intramuscular morphine 10 mg (2.9; 95% CI 2.6 to 3.6). This meta-analysis did not compare naproxen and naproxen sodium directly with other analgesics. However, indirect comparisons such as these are valid. A recent study of 44 meta-analyses has shown that, in most cases, results of adjusted indirect comparisons are not significantly different from those of direct comparisons, with validity of indirect comparisons depending on the internal validity and similarity of the individual trials (Song 2003).

The mean time to remedication for naproxen sodium 550 mg was 7.6 hours. This is similar to that of ibuprofen 400 mg at 7.4 hours, but shorter than for COX-2 selective inhibitors like rofecoxib 50 mg, at 13.6 hours, the latter figure derived from mainly dental pain trials (Barden 2002). Remedication in trials is a useful marker for determining the duration of adequate analgesia.

The major efficacy outcomes were total pain relief over 4 to 6 hours (TOTPAR) and time to remedication in trials conducted after third molar extraction and other types of surgery. Seven of 10 trials giving pain relief data, and three of four giving time to remedication, were performed in third molar extraction studies. Analysis has shown that NNTs calculated for the outcome of 50% pain relief over 4 to 6 hours (in circumstances where oral analgesics were appropriate) are the same in both these surgical categories (Barden 2003). Whether time to remedication is similar after dental extraction and other postoperative circumstances is not yet known.

There was no significant difference between the number of patients reporting any adverse event for naproxen and naproxen sodium compared with placebo. Trials reporting adverse effects did so less rigorously than for efficacy data and the methodology for reporting adverse events varied between studies. This is not unusual for adverse event reporting in acute pain studies (Edwards 1999b). Details regarding patient withdrawals and exclusions were also absent from trial reports.

AUTHORS' CONCLUSIONS

Implications for practice

Naproxen sodium 550 mg (equivalent to naproxen 500 mg) and naproxen sodium 440 mg (equivalent to naproxen 400 mg) are effective analgesics in adults with acute (moderate to severe) post-operative pain. The NNT for naproxen sodium 550 mg compares favourably with other analgesics for postoperative pain relief. A low incidence of adverse events was found but these were poorly reported.

Implications for research

Further trials of naproxen 400 mg and naproxen sodium 440 mg would clarify their efficacy as compared with the standard prescribed doses of naproxen 500 mg and naproxen sodium 550 mg. Better reporting of information, particularly for adverse events, withdrawals and exclusions, is required.

Acknowledgments

This work was supported by the Pain Research funds of the Oxford Pain Relief Trust. We would like to thank Merck & Co Inc, Rahway, New Jersey, USA for providing unpublished data for inclusion in this review.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Pain Research Unit funds UK

TABLES

Characteristics of included studies

Study	Brown 1997
Methods	RCT, DB, single oral dose and multiple dose data. 5 parallel groups. Pain assessed at 0.25, 0.5 hrs, then hourly up to 12 hours by patient. Moderate to severe baseline pain
Participants	N = 218, 16-72 yrs, M&F, major abdominal or orthopaedic surgery

Interventions	Naproxen sodium 550 mg, n = 46;
	placebo, n = 43;
	bromfenac 25 mg, n = 44; bromfenac 50 mg, n = 43;
	IM ketorolac 30 mg, n = 30

Outcomes	Std 4 point PI scale, std 5 point PR scale, non-std 5 point global scale. 6 hr TOTPAR: naproxen Na = 7.48 placebo = 3.91

Notes	Patients reporting any adverse event: naproxen Na = 7 placebo = 8 Remedication allowed after 1hr, then PI & PR = 0. Multiple dose results only show 4 exclusions. Quality score: R = 1 DB = 2 W = 1 Total = 4
Allocation concealment	A – Adequate

Study	Forbes 1986
Methods	RCT, DB, single oral dose. 5 parallel groups. Pain assessed at hourly intervals up to 12 hours by patient. Moderate to severe baseline pain
Participants	N = 268, 15 – 34 yrs, M&F, 3rd molar extraction

Interventions	Naproxen sodium 550 mg, n = 38;
	placebo, n = 42;
	codeine sulfate 60 mg, n = 44;
	naproxen 550 mg & codeine 60 mg, n = 38;
	aspirin 650 mg, n = 36

Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale. 6 hr TOTPAR: naproxen Na = 12.76 placebo = 4.07 6hr SPID: naproxen Na = 7.13 placebo = 1.31 Median time to remedicaton: placebo = 5.3 hrs naproxen Na = 8.3 hrs Remedication by 12 hrs: placebo = 81% naproxen Na = 60%
Notes	Patients reporting any adverse event: naproxen Na = 7 placebo = 7 46 patients did not take study medication. 24 had invalid efficacy data. Quality score: R =2 DB = 2 W = 1 Total = 5
Allocation concealment	A – Adequate

Study	Fricke 1993
Methods	RCT, DB, single oral dose on day 1, 3 parallel groups, pain assessed at 20, 30, 40 and 60 mins, then hourly up to 12 hours by patient. Moderate to severe baseline pain.
Participants	N = 207, 15+ yrs, M&F, removal of impacted 3rd molars
Interventions	Naproxen sodium 440 mg n = 81; placebo n = 39; ibuprofen 400 mg n = 81
Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale. 6 hr TOTPAR: naproxen Na =11.6 placebo = 2.9 6hr SPID:

	naproxen Na = 4.8 placebo = −1.4
Notes	Patients reporting any adverse events: naproxen Na = 7 placebo = 1 one withdrawal in naproxen Na group due to severe vomiting (not due to study medication). Remedication allowed after 2 hours, then PI = baseline & PR = 0. Two withdrawals due to adverse events. Quality score: R =1 DB = 1 W = 1 Total = 3
Allocation concealment	A – Adequate

Study	Gottesdiener 1999
Methods	RCT, DB, single oral dose. 5 parallel groups. Pain assessed at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0 hrs then hourly up to 12 hours by patient. Moderate to severe baseline pain
Participants	N=196, 18-50 yrs, M&F, removal of 2 or more 3rd molars, one of which was impacted
Interventions	Naproxen sodium 550 mg, n = 25; placebo, n = 25; DFP 5 mg, n = 48; DFP 25 mg , n = 50; DFP 50 mg, n = 48 (DFP is an experimental COX-2 NSAID)
Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale. 6 hr TOTPAR: placebo = 3.4 naproxen Na = 13.0 6 hr SPID: placebo = −0.98 vnaproxen Na = 6.45
Notes	Patients reporting any adverse event: naproxen Na = 6 placebo = 12 Remedication allowed after 90 minutes, last PI and PR carried forward. If remedicated before 90 minutes, patient excluded. Median time to remedicaton: placebo = 1.6 hrs naproxen Na = 8.0 hrs No. remedicating: placebo = 92%, naproxen Na = 60% No exclusions Quality score: R =1 DB = 2 W = 1 Total = 4
Allocation concealment	A – Adequate

Study	Kiersch 1993
Methods	RCT, DB, single oral dose on day 1, 3 parallel groups, pain assessed at 20, 30, 40 and 60 m, then hourly up to 12 hours by patient. Moderate to severe baseline pain.
Participants	N = 203, 15 to 56 yrs, M&F, removal of impacted 3rd molars
Interventions	Naproxen sodium 220 mg, n = 81; placebo, n = 39; ibuprofen 200 mg, n = 81
Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale.

	6 hr TOTPAR: naproxen Na = 11.5 placebo = 3.7 Median time to remedication: naproxen Na = 9.4 hrs placebo = 2.0 hrs
Notes	Patients reporting any adverse event: naproxen Na = 21 placebo = 5 Severe events in 2 pateints on placebo and 7 on NS but not deemed due to study medications. Remedication allowed after 2 hours. 2 exclusions due to protocol violations. Quality score: R =1 DB = 1 W = 1 Total = 3
Allocation concealment	A – Adequate

Study	Kiersch 1994
Methods	RCT, DB, single oral dose on day 1, 3 parallel groups, pain assessed at 20, 30, 40 and 60 mins, then hourly up to 12 hours by patient. Moderate to severe baseline pain.
Participants	N=232, 14-39 yrs, M&F, removal of impacted 3rd molars
Interventions	Naproxen sodium 440 mg, n = 92; placebo, n = 45; acetaminophen 1000 mg, n = 89
Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale. 6 hr TOTPAR: placebo = 3.1, naproxen Na = 10.5 Median time to remedication: naproxen Na = 9.9 hrs placebo = 2.0 hrs
Notes	Patients reporting any adverse event: naproxen Na = 31 placebo = 13 4 did not receive study med (1 in ns group due to severe vomiting postsurgery, prior to naproxen Na administration). Remedication allowed after 2 hours. Quality score: R =1 DB = 2 W = 1 Total = 4
Allocation concealment	A – Adequate

Study	Mahler 1976
Methods	RCT, DB, single oral dose on day 1, 4 parallel groups in 2 trials at 2 hospitals, patient assessed pain hourly up to 6 hours. Moderate to severe baseline pain.
Participants	N = 197, M&F, adults, orthopaedic or general surgery
Interventions	Data combined for hospital 1 & 2: naproxen 200 mg, n = 40; naproxen 400 mg, n = 37; placebo, n = 40; aspirin 600 mg, n = 39; aspirin 1200 mg, n = 41
Outcomes	Std 4 point PI scale, std 5 point PR scale. used weighted mean 6 hr TOTPAR: Naproxen 200 mg = 7.4, Naproxen 400 mg = 10.4 placebo = 6.2

Notes	Single and multiple dose adverse events combined for both hospitals. Remedication allowed after 2 hours. Naproxen 400 mg group remedicated with placebo. Quality score: R =1 DB = 2 W = 0 Total = 3
Allocation concealment	A – Adequate

Study	Merck 1997a
Methods	RCT, DB, single oral dose, 6 parallel groups, pain assessed up to 24 hours. Moderate to severe baseline pain.
Participants	N = 228, adult M&F, extraction of 2 or more 3rd molars
Interventions	Naproxen sodium 550 mg, n = 39; placebo, n = 38; MK-0966 7.5 mg, n = 38; MK-0966 25 mg, n = 38; MK-0966 50 mg, n =38; MK-0966 100 mg, n = 38
Outcomes	Std 4 point PI scale, std 5 point PR scale. 6 hr TOTPAR: placebo = 2.59 naproxen Na = 15.04 Median time to remedication: Naproxen Na = 12.0 hrs placebo = 1.6 hrs Remedication by 12 hours: placebo = 57% naproxen Na = 43%
Notes	Patients reporting any adverse events: naproxen Na = 9 placebo = 12 Quality score: R =1 DB = 2 W = 0 Total = 3 Currently unpublished
Allocation concealment	A – Adequate

Study	Merck 1997b
Methods	RCT, DB, single oral dose on day 1, 5 parallel groups, patient assessed up to 24 hours. Moderate to severe baseline pain.
Participants	N=312, adult M&F, extraction of 2 or more 3rd molars
Interventions	Naproxen sodium 550 mg n = 49; placebo n = 47; MK-0966 12.5 mg n = 72; MK-0966 25 mg n = 72; MK-0966 50 mg n = 72
Outcomes	Std 4 point PI scale, std 5 point PR scale. 6 hr TOTPAR: placebo = 2.59 naproxen Na = 15.04 Median time to remedication: naproxen Na = 5.4 hrs placebo = 1.5 hrs. Remedication by 12 hours: placebo = 76% naproxen Na = 75%

Notes	Patients reporting any adverse events: naproxen Na = 18 placebo = 13 Quality score: R =1 DB = 2 W = 0 Total = 3 Currently unpublished
Allocation concealment	A – Adequate

Study	Reicin 2001
Methods	RCT, DB, single oral dose on day 1, 4 parallel groups, patient assessed pain at 0.5, 1.0, 1.5, 2.0 hrs then hourly up to 12 hours. Assessments also on day 2-5. Moderate to severe baseline pain.
Participants	N = 218, 18+ yrs, M&F, major orthopedic surgery.
Interventions	Naproxen sodium 550 mg, n = 55; placebo, n = 53; rofecoxib 50/25 mg, n=56; rofecoxib 50/50 mg, n=54
Outcomes	Std 4 point PI scale, std 5 point PR scale, std 5 point global scale. 6 hr TOTPAR: placebo = 5.4 naproxen Na = 9.8 Median time to remedicaton: placebo = 2.8 hrs naproxen Na = 5.9 hrs Remedication by 12 hrs: placebo = 93% naproxen Na = 69%
Notes	On day 1, discontinuation due to adverse event: naproxen Na = 3.6%, placebo = 5.7% Remedication allowed after 1 hour, then no further evaluations taken. By day five, 6 discontinued on naproxen sodium 550 mg, 18 discontinued on placebo. Quality score: R =2 DB = 1 W = 1 Total = 4
Allocation concealment	A – Adequate

DB - double blind

DFP - an experimental, COX-2 inhibitor (a type of non-steroidal anti-inflammatory drug)

F - female

IM - intramuscular

M - male

Na - sodium

PI - pain intensity

PR - pain relief

RCT - randomised controlled trial

std - standard

TOTPAR - total pain relief

Europe PMC Funders Author Manuscripts

Characteristics of excluded studies

Study	Reason for exclusion
Angle 2002	Inappropriate pain scales and no 4-6 hour efficacy data
Aromaa 1978	No placebo arm
Baumgartner 1987	No placebo arm and not double blind
Brown 1984	Inappropriate pain scales and no extractable efficacy data
Brown 1990	No extractable data
Bucheli 1994	No placebo arm
Bunemann 1994	Baseline pain includes mild pain and no 4-6 hour efficacy data
Buttram 1984	No placebo arm
Coli 1992	No placebo arm
Commisionat 1983	No placebo arm
DiPrima 1986	Not double blind and treatment administered pre-operatively
Drez 1987	No placebo
Filtzer 1980	Placebo used ‘when necessary’
Galasko 1988	No placebo arm and single blind
Gallardo 1980	3 hour study therefore no 4-6 hour data
Gallardo 1981	3 hour study therefore no 4-6 hour data
Gaston 1996	No extractable efficacy data and placebo group also given codeine
Goldberg 1988	No placebo arm
Henderson 1994	No placebo arm
Kristensen 1986	No placebo arm
Mugnier 1984	No extractable efficacy data
Ogilvie-Harris 1985	No baseline pain measurement and no analgesic outcome measures
Ouelette 1986	No placebo arm
Ozkal 1996	No placebo arm
Parabita 1993	No placebo arm
Patella 1984	No baseline pain measurement
Pedersen 1993	No baseline pain measurement and no 4-6 hour efficacy data
Peters 1996	No placebo arm
Polati 1998	No placebo arm
Precious 1997	Not double blind and no placebo arm
Rasmussen 1993	No baseline pain measurement
Rossi 1981	Not double blind and no extractable efficacy data
Rossi 1988	Not double blind and no placebo arm
Ruedy 1973a	No placebo arm
Ruedy 1973b	No placebo arm
Sacchetti 1978	No placebo arm
Salvato 1992	No placebo arm
Scoren 1987	No placebo arm

Europe PMC Funders Author Manuscripts

Study	Reason for exclusion
Selcuk 1998	No placebo arm
Sindet-Pedersen 1986	No placebo arm
Sisk 1990	No baseline pain measurement and cross over study design
Stetson 1973	No placebo arm
Stromsoe 1987	No extractable 4-6 hour efficacy data
Ujpal 1999	No placebo arm
Van der Zwan 1982	Not randomised and no extractable 4-6 hour efficacy data
Vargas Busquets 1988	No placebo arm
Wibin 1980	No placebo arm
Zuckerman 1993	No placebo arm

ADDITIONAL TABLES

Table 01
Remedication data - placebo

Study	No. patients	Time to remed. (hrs)	% remed. by 12 h
Gottesdiener 1999	25	1.6	92 (by 24 hrs)
Forbes 1986	42	5.29	81
Reicin 2001	53	2.8	93
Merck 1997a	38	1.6	57
Merck 1997b	47	1.5	76

Table 02
Remedication data - naproxen sodium 550 mg

Study	No. patients	Time to remed. (hrs)	% remed. by 12 hrs
Gottesdiener 1999	25	8.0	60 (by 24 hrs)
Forbes 1986	38	8.3	60
Reicin 2001	55	5.9	69
Merck 1997a	39	12.0	43
Merck 1997b	49	5.4	75

ANALYSES

Comparison 01
No. Patients with at least 50% pain relief

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Naproxen sodium 550 mg	6	500	Relative Risk (Fixed) 95% CI	4.18 [2.93, 5.97]
02 Naproxen/naproxen sodium 400/440 mg	3	334	Relative Risk (Fixed) 95% CI	4.80 [2.75, 8.38]

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
03 Naproxen/naproxen sodium 200/220 mg	2	202	Relative Risk (Fixed) 95% CI	2.87 [1.60, 5.15]

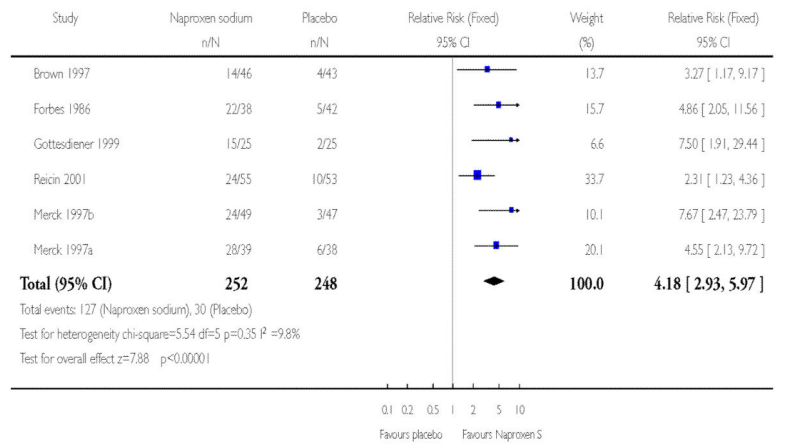
Comparison 02
Adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Naproxen sodium 550 mg	5	392	Relative Risk (Fixed) 95% CI	0.89 [0.63, 1.25]
02 Naproxen/naproxen sodium 400/440 mg	2	257	Relative Risk (Fixed) 95% CI	1.32 [0.78, 2.24]
03 Naproxen/naproxen sodium 200/220 mg	1	122	Relative Risk (Fixed) 95% CI	2.21 [0.90, 5.43]

GRAPHS AND OTHER TABLES

Analysis 01.01
Comparison 01 No. Patients with at least 50% pain relief, Outcome 01 Naproxen sodium 550 mg

Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 01 No. Patients with at least 50% pain relief
Outcome: 01 Naproxen sodium 550 mg

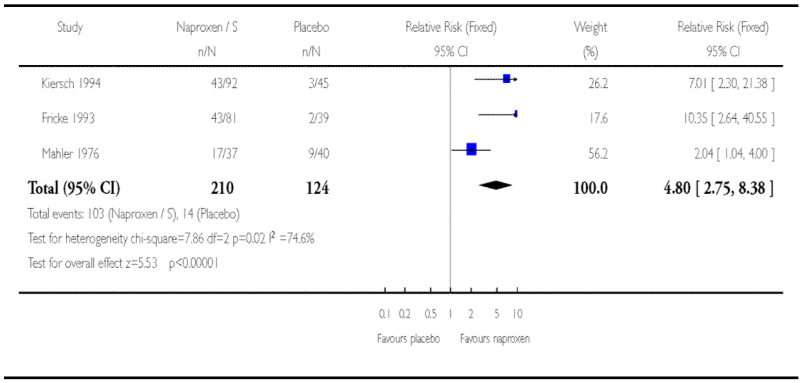


Europe PMC Funders Author Manuscripts

Analysis 01.02

Comparison 01 No. Patients with at least 50% pain relief, Outcome 02 Naproxen/naproxen sodium 400/440 mg

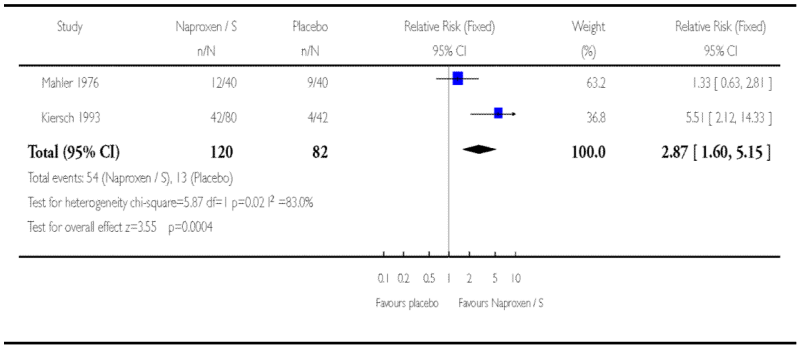
Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 01 No. Patients with at least 50% pain relief
Outcome: Outcome: 02 Naproxen/naproxen sodium 400/440 mg



Analysis 01.03

Comparison 01 No. Patients with at least 50% pain relief, Outcome 03 Naproxen/naproxen sodium 200/220 mg

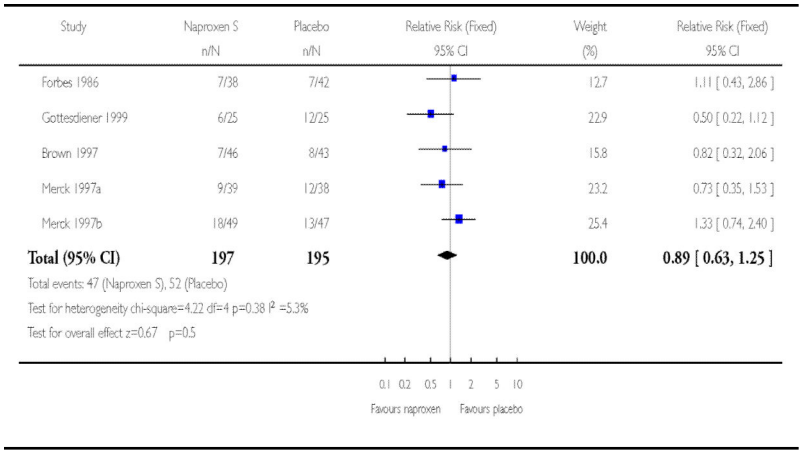
Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 01 No. Patients with at least 50% pain relief
Outcome: 03 Naproxen/naproxen sodium 200/220 mg



Analysis 02.01

Comparison 02 Adverse events, Outcome 01 Naproxen sodium 550 mg

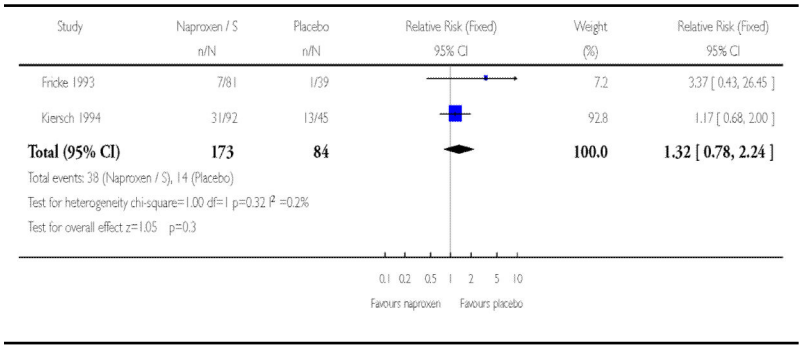
Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 02 Adverse events
Outcome: 01 Naproxen sodium 550 mg



Analysis 02.02

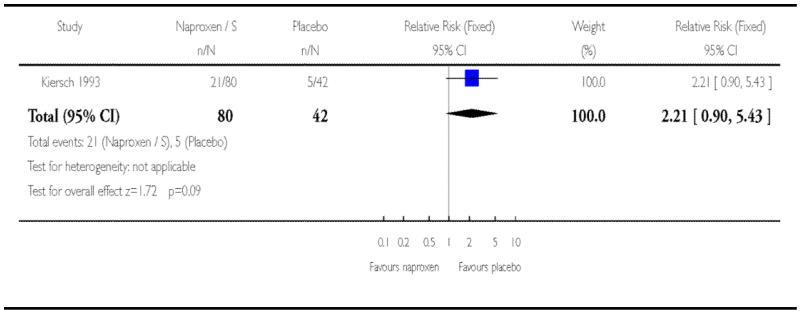
Comparison 02 Adverse events, Outcome 02 Naproxen/ naproxen sodium 400/440 mg

Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 02 Adverse events
Outcome: 02 Naproxen/naproxen sodium 400/440 mg



Analysis 02.03
Comparison 02 Adverse events, Outcome 03 Naproxen/ naproxen sodium 200/220 mg

Review: Single dose oral naproxen and naproxen sodium for acute postoperative pain
Comparison: 02 Adverse events
Outcome: 03 Naproxen/naproxen sodium 200/220 mg



References to studies included in this review

Brown 1997 {published data only} . Brown CR, Moodie J, Phillips EB. Bromfenac sodium, naproxen sodium, and ketorolac in moderate to severe postoperative pain. Journal of Pharmaceutical Care in Pain and Symptom Control. 1997; 5:21–35.

Forbes 1986 {published data only} . Forbes JA, Keller CK, Smith JW, Zeleznock JR, Sevelius H, Beaver WT. Analgesic effect of naproxen sodium, codeine, a naproxen-codeine combination and aspirin on the postoperative pain of oral surgery. Pharmacotherapy. 1986; 6:211–8. [PubMed: 3540871]

Fricke 1993 {published data only} . Fricke JR, Halladay SC, Francisco CA. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. Current Therapeutic Research. 1993; 54(6):619–27.

Gottesdiener 1999 {published data only} . Gottesdiener K, Mehlisch DR, Huntington M, Yuan W, Brown P, Gertz B, Mills S. Efficacy and tolerability of the specific cyclooxygenase-2 inhibitor DFP compared with naproxen sodium in patients with postoperative dental pain. Clinical Therapeutics. 1999; 21(8):1301–12. [PubMed: 10485502]

Kiersch 1993 {published data only} . Kiersch TA, Halladay SC, Koschik M. A double-blind, randomized study of naproxen sodium, ibuprofen, and placebo in postoperative dental pain. Clinical Therapeutics. 1993; 5:845–54. [PubMed: 8269451]

Kiersch 1994 {published data only} . Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen, and placebo in postoperative dental pain. Clinical Therapeutics. 1994; 16(3):394–404. [PubMed: 7923306]

Mahler 1976 {published data only} . Mahler DL, Forrest WH, Brown CR, Shroff PF, Gordon HE, Brown BW, James KE. Assay of aspirin and naproxen analgesia. Clinical Pharmacology and Therapeutics. 1976; 19(1):18–23. [PubMed: 1106936]

Merck 1997a {unpublished data only} . A randomized placebo and active comparator controlled dose-finding trial of the effect of MK-0966 in the treatment of postoperative dental pain. Protocol No. 027-01/single center. Merck & Co Inc; Rahway, New Jersey, USA: 1997.

Merck 1997b {unpublished data only} . A randomized placebo and active comparator controlled dose-finding trial of the effect of a 12.5% formulation of MK-0966 in the treatment of postoperative dental pain. Protocol No. 051-01/single center. Merck & Co Inc; Rahway, New Jersey, USA: 1997.

Reicin 2001 {published data only} . Reicin A, Brown J, Jove M, deAndrade R, Bourne M, Krupa D, et al. Efficacy of single-dose and multidose rofecoxib in the treatment of post-orthopedic surgery pain. American Journal of Orthopedics. 2001; 30:40–8. [PubMed: 11198829]

References to studies excluded from this review

Angle 2002 . Angle PJ, Halpern SH, Leighton BL, Szalai JP, Gnanendran K, Kronberg JE. A randomized controlled trial examining the effect of naproxen on analgesia during the second day after cesarean delivery. Anesthesia and Analgesia. 2002; 95(3):741–5. [PubMed: 12198063]

Aromaa 1978 . Aromaa U, Asp K. A comparison of naproxen, indomethacin and acetylsalicylic acid in pain after varicose vein surgery. Journal of International Medical Research. 1978; 6:152–6. [PubMed: 344088]

Baumgartner 1987 . Baumgartner H, Kuttelwascher M, McCaskey D, Winters L. The comparative efficacy of naproxen sodium and pirprofen in the treatment of post-operative pain. Journal of International Medical Research. 1987; 15:179–87. [PubMed: 3301458]

Brown 1984 . Brown CR, Sevelius H, Wild V. A comparison of single doses of naproxen sodium, morphine sulphate and placebo in patients with postoperative pain. Current Therapeutic Research. 1984; 35(4):511–8.

Brown 1990 . Brown CR, Moodie JE, Dickie G, Wild VM, Smith BA, Clarke PJ, et al. Analgesic efficacy and safety of single-dose oral and intramuscular ketorolac tromethamine for postoperative pain. Pharmacotherapy. 1990; 10(6):59S–70S. [PubMed: 2082315]

Bucheli 1994 . Bucheli R, Davlos V, Neto N, Naranjo I, Calderon D, Alamo C, Lopez-Munoz F. A randomized, double-blind study of the efficacy and safety of microcapsulated butibufen and naproxen in the treatment of post-episiotomy pain. Current Therapeutic Research. 1994; 55:1527–37.

Bunemann 1994 . Bunemann L, Thorshauge H, Herlevsen P, Iversen D, Nielson FB. Analgesia for outpatient surgery: placebo versus naproxen sodium (a non-steroidal anti-inflammatory drug) given before or after surgery. European Journal of Anaesthesiology. 1994; 11:461–4. [PubMed: 7851352]

Buttram 1984 . Buttram VC, Gravlee LC, Hale RW, Lifshitz S. Naproxen sodium vs. a combination of aspirin, phenacetin, caffeine and codeine phosphate for pain after major gynecologic surgery. A multicenter comparison. Journal of Reproductive Medicine. 1984; 29(3):189–92. [PubMed: 6374136]

Coli 1992 . Coli A, Lari S, Di Fiore M, Perin S, Urso R. Sodium naproxen in postoperative pain in orthopedics. Comparison of 2 different doses. Minerva Anestesiologica. 1992; 58:441–5. [PubMed: 1508357]

Commisionat 1983 . Commissionat Y, Benoit P, M'Hamsadji. Comparative study of the anti-inflammatory and analgesic action of sodium naproxen and indomethacin in the post-operative period of tooth extraction. L'Information Dentaire. 1983; 65(35):3241–5.

DiPrima 1986 . DiPrima JG, Keating SE, DeVincentis AF. The use of naproxen in controlling postoperative pain in podiatric surgery. Journal of Foot Surgery. 1986; 25(4):273–7. [PubMed: 3525655]

Drez 1987 . Drez D, Ritter M, Rosenberg TD. Pain relief after arthroscopy: naproxen sodium compared to propoxyphene napsylate with acetaminophen. Southern Medical Journal. 1987; 80:440–3. [PubMed: 2882607]

Filtzer 1980 . Filtzer HS. A double-blind randomized comparison of naproxen sodium, acetaminophen and pentazocine in postoperative pain. Current Therapeutic Research. 1980; 27:293–301.

Galasko 1988 . Galasko CSB, Courtney P, Jayne M, Coxhead PF, Russell S. Comparison of the efficacy of naproxen sodium and dihydrocodeine tartrate in the treatment of post-operative pain. Current Medical Research and Opinion. 1988; 10(10):656–62. [PubMed: 3371081]

Gallardo 1980 . Gallardo F, Rossi E. Double blind evaluation of naproxen and ibuprofen in periodontal surgery. Pharamacology and Therapeutics in Dentistry. 1980; 5:69–72.

Europe PMC Funders Author Manuscripts

Gallardo 1981 . Gallardo F, Lobo R, Pino M, Martino LE. Double blind evaluation of naproxen and ibuprofen in oral surgery outpatients. IRCS Medical Science. 1981; 9:440–1.

Gaston 1996 . Gaston G. A double-blind, randomized, parallel-group study of the pharmacokinetics and onset of action of Naprelan in patients following oral surgery. American Journal of Orthopedics. 1996; 25:37–41. [PubMed: 8886216]

Goldberg 1988 . Goldberg MA, McLaughlin GE, Kieffer DA, Stern L, Hiroso H, Akeson W, Hewson GF. Naproxen sodium: comparative efficacy and tolerability of two dosages for pain after joint surgery. Orthopedics. 1988; 11(4):575–80. [PubMed: 3290870]

Henderson 1994 . Henderson RC. A double-blind comparison of diclofenac potassium and naproxen sodium in the treatment of pain due to orthopedic skeletal surgery. Today's Therapeutic Trends. 1994; 12(1):81–95.

Kristensen 1986 . Kristensen S, Tveteras K, Outzen KE, Poulsen HB. Treatment of pain after tonsillectomy. Comparison between naproxen (Naprosyn) and acetylsalicylic acid (Kalcatyl). Ugeskr Laeger. 1986; 148(44):2832–5. [PubMed: 3538591]

Mugnier 1984 . Mugnier A, Schneck G, Champion P, Mignon H. Post-operative pain: Comparative study of naproxen-sodium and paracetamol in the treatment of pain following dental extraction. Presse-Medicale. 1984; 13(7):429–31.

Ogilvie-Harris 1985 . Ogilvie-Harris DJ, Bauer M, Corey P. Prostaglandin Inhibition and the rate of recovery after arthroscopy meniscectomy. The Journal of Bone and Joint Surgery. 1985; 67-B(4): 567–71. [PubMed: 3839796]

Ouelette 1986 . Ouellette RD, Feinberg A, Laraja R, Rothenberg RE, Welch GW. Naproxen sodium vs acetaminophen plus codeine in postsurgical pain. Current Therapeutic Research Clinical and Experimental. 1986; 39(5):839–45.

Ozkal 1996 . Ozkal S, Gurbuzer B, Dogan N, Kizilkaya E, Yucel O. Clinical and ultrasonographic evaluation of the effect of two non-opioid analgesic for postoperative pain and edema. Agri Dergisi. 1996; 8(1):31–7.

Parabita 1993 . Parabita GF, Zanetti U, Scalvini F, Rossi D, Scaricabarozzi I. A controlled clinical study of the efficacy and tolerability of nimesulide vs naproxen in maxillo-facial surgery. Drugs. 1993; 46(1):171–3. [PubMed: 7506163]

Patella 1984 . Patella V, Moretti B, Pesce V. Controlled double blind study on the analgesic effect of suprofen on post-surgical patients. Bollettino Chimico Farmaceutico. 1984; 123(10):71S–76S. [PubMed: 6397213]

Pedersen 1993 . Pedersen P, Nielson KD, Jensen PE. The efficacy of Na-naproxen after diagnostic and therapeutic arthroscopy of the knee joint. Arthroscopy. 1993; 9(2):170–3. [PubMed: 8461075]

Peters 1996 . Peters AA, Witte EH, Damen AC, Holm JP, Drogendijk AC, Velde EA, Trimbos J. Pain relief during and following outpatient curettage and hysterosalpingography: a double blind study to compare the efficacy and safety of tramadol versus naproxen. Gynecology and Reproductive Biology. 1996; 66(1):51–6.

Polati 1998 . Polati E, Finco G, Salgarelli A, De Santis D, Gilli E, Barzoi G, et al. Management of postoperative pain in stomatology with ibuprofen L-arginine and naproxen. Minerva Stomatologica. 1998; 47:287–92. [PubMed: 9738364]

Precious 1997 . Precious DS, Multari J, Finley GA, McGrath P. A comparison of patient-controlled and fixed schedule analgesia after orthognathic surgery. Journal of Oral & Maxillofacial Surgery. 1997; 55:33–40. [PubMed: 8994466]

Rasmussen 1993 . Rasmussen S, Thomsen S, Madsen SN, Rasmussen PJS, Simonsen O. The clinical effect of naproxen sodium after arthroscopy of the knee: a randomized, double-blind, prospective study. Arthroscopy. 1993; 9:375–80. [PubMed: 8216567]

Rossi 1981 . Rossi E, Gallardo F. Analgesic efficacy of naproxen and ibuprofen in patients undergoing mucogingival surgery. IRCS Medical Science. 1981; 9:272–3.

Rossi 1988 . Rossi S, Tadini R, Rizzi F. Naproxen sodium compared with ketoprofen lysine and lysine acetylsalicylate in the management of post-operative pain in gynecologic surgery. Minerva Ginecologica. 1988; 40:329–35. [PubMed: 3143952]

Ruedy 1973a . Ruedy J. A comparison of the analgesic efficacy of naproxen and acetylsalicylic acid-codeine in patients with pain after dental surgery. Scandanavian Journal of Rheumatology. 1973; 2:60–3.

Ruedy 1973b . Ruedy J, McCullough W. A comparison of the analgesic efficacy of naproxen and propoxyphene in patients with pain after orthopedic surgery. Scandanavian Journal of Rheumatology. 1973; 2:56–9.

Sacchetti 1978 . Sachetti G, Ferrati GC. Kinetics of analgesic response in man; an example with two non-steroidal anti-inflamatory analgesic drugs. Journal of International Medical Research. 1978; 6:312–16. [PubMed: 357233]

Salvato 1992 . Salvato A, Boldani M, Sinion M. Tiaprofenic acid in the acute treatment of postsurgical pain in dentistry. A comparative study versus nimesulide and naproxen sodium. Current Therapeutic Research. 1992; 51:937–45.

Scoren 1987 . Scoren RD, Corn H, Rhodes P, Schwarz M, Segal PL, Marks MH. Pain following periodontal surgery: Treatment with a nonnarcotic analgesic compared with two codeine combinations. Current Therapeutic Research. 1987; 42:463–71.

Selcuk 1998 . Selcuk E, Gomel M, Apaydin S, Kose T, Tuglular I. The postoperative analgesic efficacy and safety of piroxicam (FDDF) and naproxen sodium. International Journal of Clinical Pharmacological Research. 1988; 18:21–9.

Sindet-Pedersen 1986 . Sindet-Pedersen S, Peterson JK, Gotzsche PC, Christensen HA. A double-blind, randomized study of naproxen and acetylsalicylic acid after surgical removal of impacted lower third molars. International Journal of Oral & Maxillofacial Surgery. 1986; 15:389–94. [PubMed: 3091717]

Sisk 1990 . Sisk AL, Grover BJ. A comparison of preoperative and postoperative naproxen sodium for suppression of postoperative pain. Journal of Oral & Maxillofacial Surgery. 1990; 48:674–8. [PubMed: 2358942]

Stetson 1973 . Stetson JB, Robinson K, Wardell WM, Lasagna L. Analgesic activity of oral naproxen in patients with postoperative pain. Scandanavian Journal of Rheumatology. 1973; (Supplement 2):50–5.

Stromsoe 1987 . Stromsoe K, Bjerkholt H. Effects of naproxen on the postoperative course. A study of the effects of naproxen on the immediate post-operative period in the surgical treatment of crural fractures. Tidsskr Nor Laegeforen. 1987; 107(6):548–50. [PubMed: 3554604]

Ujpal 1999 . Ujpal M, Biczo A, Huszar L, Temesvari A, Tothfalusi L, Szabo G. Comparative study of the analgesic effect of Apranax and Cataflam after oral surgical procedures. Fogorv Sz. 1999; 92:374–8. [PubMed: 10641420]

Van der Zwan 1982 . Van der Zwan J, Boering G, Wesseling H, Smit Sibinga C, Van der Weele L. The lower third molar and antiphlogistics. International Journal of Oral Surgery. 1982; 11:340–50. [PubMed: 6820006]

Vargas Busquets 1988 . Vargas Busquets MA, Keoshian LA, Kelleher R, Jervis WH, Hentz VR. Naproxen sodium versus acetaminophen-codeine for pain following plastic surgery. Current Therapeutic Research. 1988; 43(2):311–16.

Wibin 1980 . Wibin E. Clinical trial of naproxen in general surgery. Ars Medici Internationaal Tijdschrift Voor Praktische Therapie. 1980; 9(10):917–27.

Zuckerman 1993 . Zuckermann M, Panconesi R, Scaricabarozzi I, Nava ML, Bechi P. Clinical efficacy and tolerability of nimesulide compared with naproxen in the treatment of posthaemorrhoidectomy pain and inflammation. Drugs. 1993; 46(1):177–9. [PubMed: 7506165]

References to studies awaiting assessment

Frezza 1985 . Frezza R, Bolognesi P, Bernardi F. Comparison of the action of 3 nonsteroidal anti-inflammatory agents in the control of post-operative pain. Effectiveness of NSAID against pain. Attualita Dentale. 1985; 1(30):40–2. [PubMed: 3869471]

Additional references

Barden 2002 . Barden J, Edwards JE, McQuay HJ, Moore R. Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review. NHS Centre for Reviews and Dissemination BMC Anesthesiology. 2002; 2(1):4.

Barden 2003 . Barden J, Edwards JE, McQuay HJ, Moore RA. Pain and analgesic response after third molar extraction and other postsurgical pain. Pain. in press.

BNF 2002 . BMJ. Non-steroidal anti-inflammatory drugs. In: Mehta, DK., editor. British National Formulary. Vol. 43. British Medical Journal; London: Mar. 2002 p. 482

Bruster 1994 . Bruster S, Jarman B, Bosanquet N, Weston D, Erens R, Delbanco TL. National Survey of hospital patients. BMJ. 1994; 309:1542–6. [PubMed: 7819893]

Collins 1998 . Collins SL, Moore RA, McQuay HJ, Wiffen PJ. Oral ibuprofen and diclofenac in postoperative pain: a quantitative systematic review. European Journal of Pain. 1998; 2:285–91. [PubMed: 10700324]

Cook 1995 . Cook RJ, Sacket DL. The number needed to treat: a clinically useful measure of treatment effect. British Medical Journal. 1995; 310:452–4. [PubMed: 7873954]

Cooper 1991 . Cooper, SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max, MB.; Portenoy, RK.; Laska, EM., editors. The design of analgesic clinical trials (Advances in Pain and Research Therapy. Vol. 18. Raven Press; New York: 1991. p. 117-24.

Dep of Health 2002 . Department of Health. Prescription Cost Analysis. Government Statistical Service; London: p. 288 [accessed November 2002]

Dolin 2002 . Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. British Journal of Anaesthesia. 2002; 89:409–23. [PubMed: 12402719]

Edwards 1999a . Edwards JE, Oldman A, Smith L, et al. Oral aspirin in postoperative pain: a quantitative systematic review. Pain. 1999; 81:289–97. [PubMed: 10431716]

Edwards 1999b . Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved. Lessons from acute postoperative pain. Journal of Pain and Symptom Management. 1999; 18:427–37. [PubMed: 10641469]

Fricke 1993 . Fricke JR, Halladay SC, Francisco CA. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. Current Therapeutic Research. 1993; 54(6):619–27.

Gavaghan 2000 . Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. Pain. 2000; 85:415–24. [PubMed: 10781914]

Grahame-Smith 2002 . Grahame-Smith, DG.; Aronson, JK. Oxford textbook of clinical pharmacology and drug therapy. 3rd Edition. Oxford University Press; Oxford: 2002.

Hernandez-Diaz 2001 . Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. American Journal of Medicine. 2001; 110(3A):20S–7S. [PubMed: 11173046]

Higgins 2002 . Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. Journal of Health Services Research and Policy. 2002; 7:51–61. [PubMed: 11822262]

Ionnadis 2001 . Ioannidis JPA, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. Proc Natl Acad Sci U S A. 2001; 98(3):831–6. [PubMed: 11158556]

Jadad 1996a . Jadad AR, Carroll D, Moore A, McQuay HJ. Developing a database of published reports of randomised clinical trials in pain research. Pain. 1996; 66:239–46. [PubMed: 8880846]

Jadad 1996b . Jadad AR, More RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomised clinical trials: is blinding necessary? Controlled Clinical Trials. 1996; 17:1–12. [PubMed: 8721797]

Kalso 2000 . Kalso E, Moore RA. Five Easy pieces on evidence based medicine (2). European Journal of Pain. 2000; 4:321–4. [PubMed: 10985878]

L'Abbé 1987 . L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Annals of International Medicine. 1987; 107:224–33.

Martindale 1999 . Parfitt, K., editor. Martindale, The Complete Drug Reference. Vol. 32. Pharmaceutical Press; London: 1999. Analgesics Anti-inflammatory drugs and Antipyretics; p. 61-2.

McQuay 1998 . McQuay, H.; Moore, A. An evidence-based resource for pain relief. Oxford University Press; Oxford: 1999. Combining data and interpreting the results; p. 35-7.

Moher 1999 . Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of meta-analyses of randomised controlled trials: the QUOROM statement. The Lancet. 1999; 354:1896–1900.

Moore 1996 . Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. Pain. 1996; 66:229–37. [PubMed: 8880845]

Moore 1997a . Moore A, Collins S, Carroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review. Pain. 1997; 70:193–201. [PubMed: 9150293]

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; 69:311–5. [PubMed: 9085306]

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. [PubMed: 9870574]

Morris 1995 . Morris, JA.; Gardner, MJ. Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. In: Gardner, MJ.; Altman, DG., editors. Statistics with confidence - confidence intervals and statistical guidelines. BMJ; London: 1995. p. 50-63.

Rapoport 1999 . Rapoport RJ. The safety of NSAIDs and related drugs for the management of acute pain: maximising benefits and minimising risks. Cancer Control. 1999; 6(2):18–21. [PubMed: 12118235]

Song 2003 . Song F, Altman DG, Glenny A, Deeks JJ. Validity of indirect comparisons for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003; 326:472–5. [PubMed: 12609941]

Sterne 2000 . Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. Journal of Clinical Epidemiology. 2000; 53:1119–29. [PubMed: 11106885]

Tang 2000 . Tang JL, Liu JLY. Misleading funnel plot for detection of bias in meta-analysis. Journal of Clinical Epidemiology. 2000; 53:477–84. [PubMed: 10812319]

Tramèr 1997 . Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. BMJ. 1997; 315:635–9. [PubMed: 9310564]

Warfield 1995 . Warfield CA, Kahn CH. Acute pain management. Programs in US hospitals and experiences and attitudes among US adults. Anaesthesiology. 1995; 83:1090–4.

References to other published versions of this review

Mason 2003 . Mason L, Edwards JE, Moore RA, McQuay HJ. Single-dose oral naproxen for acute postoperative pain: a quantitative systematic review. BMC Anesthesiology 2003. Sep 10.2003 3(4)

Europe PMC Funders Author Manuscripts

PLAIN LANGUAGE SUMMARY

Naproxen sodium is effective for pain relief in adults who have acute pain after surgery

Acute pain is a problem immediately after surgery and can be poorly managed. This review assessed the evidence from 996 patients in 10 randomised, double blind, placebo-controlled clinical trials of naproxen/naproxen sodium (a non-steroidal anti-inflammatory drug) in adults with acute postoperative pain. We found that naproxen sodium taken by mouth at doses of 550 mg and 440 mg is an effective pain killer for treating pain following surgery. The effects of one dose last, on average, up to seven hours. No conclusions can be drawn about the adverse effects of naproxen and naproxen sodium because reports of these events were inconsistent.