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Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults (Review)

Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B

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[Intervention Review]

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults

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ABSTRACT

Background

Pain is a common symptom with cancer, and 30% to 50% of all people with cancer will experience moderate to severe pain that can have a major negative impact on their quality of life. Non-opioid drugs are commonly used to treat cancer pain, and are recommended for this purpose in the World Health Organization (WHO) cancer pain treatment ladder, either alone or in combination with opioids.

A previous Cochrane review that examined the evidence for nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol, alone or combined with opioids, for cancer pain was withdrawn in 2015 because it was out of date; the date of the last search was 2005. This review, and another on paracetamol, updates the evidence.

Objectives

To assess the efficacy of oral NSAIDs for cancer pain in adults, and the adverse events reported during their use in clinical trials.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to April 2017, together with reference lists of retrieved papers and reviews, and two online study registries.

Selection criteria

We included randomised, double-blind, single-blind, or open-label studies of five days' duration or longer, comparing any oral NSAID alone with placebo or another NSAID, or a combination of NSAID plus opioid with the same dose of the opioid alone, for cancer pain of any pain intensity. The minimum study size was 25 participants per treatment arm at the initial randomisation.

Data collection and analysis

Two review authors independently searched for studies, extracted efficacy and adverse event data, and examined issues of study quality and potential bias. We did not carry out any pooled analyses. We assessed the quality of the evidence using GRADE and created a 'Summary of findings' table.

Main results

Eleven studies satisfied inclusion criteria, lasting one week or longer; 949 participants with mostly moderate or severe pain were randomised initially, but fewer completed treatment or had results of treatment. Eight studies were double-blind, two single-blind, and one open-label. None had a placebo only control; eight compared different NSAIDs, three an NSAID with opioid or opioid combination, and one both. None compared an NSAID plus opioid with the same dose of opioid alone. Most studies were at high risk of bias for blinding, incomplete outcome data, or small size; none was unequivocally at low risk of bias.

It was not possible to compare NSAIDs as a group with another treatment, or one NSAID with another NSAID. Results for all NSAIDs are reported as a randomised cohort. We judged results for all outcomes as very low-quality evidence.

None of the studies reported our primary outcomes of participants with pain reduction of at least 50%, and at least 30%, from baseline; participants with Patient Global Impression of Change (PGIC) of much improved or very much improved (or equivalent wording). With NSAID, initially moderate or severe pain was reduced to no worse than mild pain after one or two weeks in four studies (415 participants in total), with a range of estimates between 26% and 51% in individual studies.

Adverse event and withdrawal reporting was inconsistent. Two serious adverse events were reported with NSAIDs, and 22 deaths, but these were not clearly related to any pain treatment. Common adverse events were thirst/dry mouth (15%), loss of appetite (14%), somnolence (11%), and dyspepsia (11%). Withdrawals were common, mostly because of lack of efficacy (24%) or adverse events (5%).

Authors' conclusions

There is no high-quality evidence to support or refute the use of NSAIDs alone or in combination with opioids for the three steps of the three-step WHO cancer pain ladder. There is very low-quality evidence that some people with moderate or severe cancer pain can obtain substantial levels of benefit within one or two weeks.

PLAIN LANGUAGE SUMMARY

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults

Bottom line

There is no high-quality evidence to prove that NSAIDs are useful in treating people with cancer pain. Nor is there evidence to disprove that they are useful. Very low-quality evidence shows that some people with moderate or severe cancer pain have pain much reduced within one or two weeks.

Background

One person in two or three who gets cancer will suffer from pain that becomes moderate or severe in intensity. The pain tends to get worse as the cancer progresses. In 1986, the World Health Organization (WHO) recommended taking morphine-like drugs (opioids) for moderate to severe pain from cancer, and non-opioid drugs like NSAIDs, alone for mild to moderate pain, or alongside opioids in people with moderate to severe pain. There are many different types of NSAIDs. Common NSAIDs are ibuprofen and diclofenac.

Study characteristics

In this review we set out to examine the evidence on how well NSAIDs worked (alone or with morphine-like drugs) in adults with cancer pain. We also wanted to know how many people had side effects, and how severe they were.

In April 2017, we found 11 studies with 949 participants. They compared NSAID with NSAID, or NSAID with opioid drug (morphine or codeine). No studies looked at using NSAID together with an opioid-like morphine, which is how they are often used. The studies were small and of poor quality. They used different designs and different ways of showing their pain results. Outcomes important to people with cancer pain were often not reported. Many different NSAIDs were tested, and it was not possible to make sensible comparisons.

Key findings

With an NSAID, initially moderate or severe cancer pain was reduced to no worse than mild pain after one or two weeks in 1 in 4 (26%) to 1 in 2 (51%) people in four studies.

Side-effect reporting was poor. Two serious side effects were reported with NSAIDs, and 22 deaths, but these were not related to pain treatment. Common side effects were thirst/dry mouth (1 in 7; 15%), loss of appetite (1 in 7; 14%), sleepiness (1 in 10; 11%), and heartburn (1 in 10; 11%). One in four people stopped taking NSAIDs because the drug did not work, and 1 in 20 stopped because of side effects.

Quality of the evidence

The quality of the evidence was very low. Very low-quality evidence means that we are very uncertain about the impact of an NSAID alone for treating cancer pain. We do not know whether using NSAIDs together with an opioid such as codeine or morphine is worthwhile.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

NSAID for cancer pain - non-controlled data

Patient or population: people with cancer pain

Settings: inpatient or outpatient

Intervention: any NSAID, and dose

Comparison: no control - cohort of treated participants

Outcomes	Probable outcome with NSAID	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Participants with at least 30% or at least 50% reduction in pain	No data	No data	Very low	Limited data, several risks of bias
PGIC much or very much improved	No data	No data	Very low	Limited data, several risks of bias
Pain no worse than mild at one or two weeks (or equivalent)	Range of estimates from 260 in 1000 to 510 in 1000	4 studies 415 participants randomised	Very low	Limited data, several risks of bias
Serious adverse events	2 serious adverse events reported	11 studies 949 participants	Very low	Limited data, several risks of bias
Adverse events	Dry mouth 10% Loss of appetite 4% Somnolence 9% Dyspepsia 9%	Variously reported in studies	Very low	Limited data, several risks of bias
Withdrawals	All cause 23% Lack of efficacy 24% Adverse event 5%	Variously reported in studies	Very low	Limited data, several risks of bias
Death	22 deaths, not clearly related to treatment	11 studies 949 participants	Very low	Limited data, several risks of bias

Descriptors for levels of evidence (EPOC 2015):
High quality: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate quality: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low quality: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low quality: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

BACKGROUND

A previous Cochrane review that examined the evidence for nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol, alone or combined with opioids, for cancer pain was withdrawn in 2015 because it was out of date (McNicol 2015); the date of the last search was 2005.

This is one of three reviews on the efficacy and safety of oral non-opioid medicines to treat cancer pain, in this case focusing on oral NSAIDs in adults. A separate review will examine the efficacy of NSAIDs for cancer pain in children (Cooper 2017). The other review will examine oral paracetamol (acetaminophen) for cancer pain in both adults and children (Wiffen 2017a).

Description of the condition

Cancer is estimated to cause over eight million deaths per annum - approximately 13% of deaths worldwide (IARC 2012). Globally, 32 million people are living with cancer, and detailed information for individual countries is available on the WHO website for the International Agency for Research on Cancer (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). In the UK alone in 2014, there were around 350,000 new cases of cancer annually, with around 50% of people surviving for 10 years or more after diagnosis (Cancer Research UK 2016).

Cancer pain is perhaps one of the most feared symptoms associated with the disease. Pain may be the first symptom to cause someone to seek medical advice that leads to a diagnosis of cancer, and 30% to 50% of all people with cancer will experience moderate to severe pain (Portenoy 1999). Pain can occur at any time as the disease progresses, but the frequency and intensity of pain tends to increase as the cancer advances (Portenoy 1999; Van den Beuken-van Everdingen 2016). For people with advanced cancer, some 75% to 90% will experience pain having a major impact on daily living (Wiffen 2016). Pain had a significant negative correlation with quality of life in people with cancer in China, Japan, and Palestine, for example (Deng 2012; Dreidi 2016; Mikan 2016). A recent systematic review has shown that approximately 40% of patients suffered pain after curative treatment, 55% during cancer treatment, and 66% in advanced disease. Pain related to cancer is frequently described as distressing or intolerable by more than one-third of patients (Breivik 2009; Van den Beuken-van Everdingen 2016).

Cancer pain can be the result of the cancer itself, interventions to treat the cancer, and sometimes other underlying pains. Cancer-related pain is a mosaic of different types of pain generated through different mechanisms. The biology of pain from bone metastasis may well differ from pain due to obstruction of a viscus (an internal organ) or invasion of soft tissue, resulting in differences in responsiveness to analgesics that act via different mechanisms. Prevalence of pain is also linked to cancer type, with head and neck cancer showing the highest prevalence. Age also has an impact, with younger patients experiencing more pain (Prommer 2015). For this review, we will not consider postsurgical pain or specific neuropathic pain conditions.

The current World Health Organization (WHO) cancer pain ladder for adults recommends the use of oral non-opioid analgesics, including NSAIDs, as the first step on the ladder, with or without an adjuvant (WHO 2017). Non-opioid analgesics are also to be used on the second and third steps, together with weak or strong opioids. The current National Institute for Health and Care Excellence (NICE) guidelines in the UK advises that non-opioid analgesics alone be used for treating mild pain (0 to 3 on a 0 to 10 pain scale), together with a weak opioid such as codeine or tramadol for mild to moderate pain (3 to 6), and with a strong opioid such as morphine for severe pain (6 to 10) (NICE 2016). Some authorities have suggested that the second step on the ladder could be removed, and replaced with low doses of strong opioids such as morphine (Twycross 2014).

Description of the intervention

NSAIDs have been prescribed for pain and inflammation for more than 100 years. Salicylic acid and phenazone were produced in a synthetic process in the late 1870s, and salicylic acid, phenazone, and phenacetin were available for the treatment of pain, fever, and inflammation by the turn of the 20th century. The past 60 years has seen the introduction of paracetamol (which is probably a weak NSAID (Hinz 2008)) followed by ibuprofen, diclofenac, and many others (Brune 2004). NSAIDs are used with the aim of providing anti-inflammatory, antipyretic, and analgesic effects in acute and chronic conditions of pain and inflammation (Dwivedi 2015).

NSAIDs are among the most commonly used analgesics, mostly by prescription for musculoskeletal problems (Laine 2001) or fibromyalgia (Häuser 2012; Wolfe 2014), but also widely used without prescription (Sheen 2002). NSAIDs act by inhibiting the cyclooxygenases (COXs), which are catalysts in the synthesis of prostaglandin. The analgesic and anti-inflammatory actions of NSAIDs are attributed to the inhibition of cyclooxygenase-2 (COX-2), while any anti-platelet and adverse gastrointestinal effects are attributed to the inhibition of cyclooxygenase-1 (COX-1). Many traditional NSAIDs such as ibuprofen are non-selective.

COX-2-selective NSAIDs were therefore developed to reduce adverse gastrointestinal effects, but were later considered to increase the risk of myocardial infarction and stroke (CNT 2014), and some drugs were withdrawn (EMEA 2005; FDA 2004). Whether available drugs increase the risk of cardiovascular effects is a matter of dispute, with the randomised trial evidence pointing to some increased risk for many (CNT 2014), while large-scale observational studies can point to no increased risk or even a reduced risk of serious harm (Mangoni 2010). There is a fine balance of benefits and risks (Moore 2014b).

How the intervention might work

Anti-inflammatory, antipyretic, and analgesic effects of NSAIDs are based on the suppression of the COX-1 and COX-2 enzymes. By blocking the COX enzymes, vasodilation is reduced and inflammation relieved. Further, the synthesis of prostaglandins is blocked, leading to reduced pain (Dwivedi 2015). NSAIDs block the prostaglandin synthesis as do steroids, but have a different side-effect profile to steroids. Conventional NSAIDs (aspirin, ibuprofen, diclofenac, indomethacin, naproxen, and piroxicam) block COX-1 and COX-2 enzymes to various degrees. Selective COX-2 inhibiting NSAIDs (celecoxib, etoricoxib) inhibit the COX-2 enzyme with a 5 to 50 fold selectivity (Brune 2004), and some conventional NSAIDs are selective for COX-1 (aspirin, for instance).

NSAIDs are responsible for anti-platelet, gastrointestinal, cardiovascular, renal, and hepatotoxic side effects (Brune 2015).

Gastrointestinal adverse events with NSAIDs are the result of blocking of the COX-1 enzyme, leading to a reduction in mucosal prostaglandin synthesis and its protective effects.

Because there is strong evidence for an important role for increased COX-2 expression and prostaglandin-E2 production in colorectal tumorigenesis, drugs that inhibit COX-2 have been of interest in the potential chemoprevention and therapy of colorectal cancer (Chell 2005; Wender 2015).

Why it is important to do this review

A previous Cochrane review examined the evidence for NSAIDs or paracetamol, alone or combined with opioids, for cancer pain (McNicol 2015), with the last search date in 2005. There have been few subsequent systematic reviews of the evidence. Nabal and colleagues (Nabal 2012) examined the evidence for combinations with opioids, finding little evidence. A review of paracetamol and NSAIDs concluded that the role of these non-opioid drugs remains controversial (Mercadante 2013).

The evidence of effectiveness of the WHO pain ladder for cancer has been examined several times in the past two decades. These studies report varying degrees of success, typically between 20% and 100% of people with cancer pain achieving good relief (Azevedo São Leão Ferreira 2006; Carlson 2016; Jadad 1995), with some suggesting that as many as 50% of people with cancer pain are undertreated (Deandrea 2008).

In many countries, opioids are severely restricted, if available at all. This means that many people with cancer will have considerable pain and suffering unless non-opioid analgesics can be used. This review was designed with the intention of informing policy makers such as the WHO on the possible utility of NSAIDs to treat cancer-related pain. It is hoped that the review will inform patients and carers on the value or otherwise of NSAIDs in this context.

Other relevant Cochrane reviews include an assessment of codeine alone and with paracetamol (Straube 2014), and an evaluation of tramadol alone and with paracetamol (Wiffen 2017b). A number of other reviews have evaluated the evidence for opioids, including buprenorphine (Schmidt-Hansen 2015a), transdermal fentanyl (Hadley 2013), hydromorphone (Bao 2016), morphine (Wiffen 2016), oxycodone (Schmidt-Hansen 2015b), and tapentadol (Wiffen 2015).

The standards used to assess evidence in pain trials have changed substantially in recent years, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy (Moore 2013b). The most important change is the move away from using mean pain scores, or mean change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) (Dworkin 2008; Moore 2013a). Pain intensity reduction of 50% or more correlates with improvements in comorbid symptoms, function, and quality of life generally (Moore 2014a). These standards are set out in the PaPaS author and referee guidance for pain studies of the Cochrane Pain, Palliative and Supportive Care Group (PaPaS 2012).

Three additional issues potentially affect how evidence is evaluated.

The first issue is study size and the overall amount of information available for analysis. There are issues over both random chance effects with small amounts of data, and potential bias in small studies, especially in pain (Dechartes 2013; Dechartres 2014; Fanelli 2017; Moore 1998; Nguyen 2017; Nüesch 2010; Thorlund 2011). Cochrane reviews have been criticised for perhaps over-emphasising results of underpowered studies or analyses (AlBalawi 2013; Turner 2013). On the other hand, it may be unethical to ignore potentially important information from small studies or to randomise more participants if a meta-analysis including small, existing studies provided conclusive evidence. In this review, we have therefore chosen to limit analyses to studies with a minimum of 25 participants per treatment group, which we believe has not been done previously.

The second issue is that of study duration. Previous reviews have examined studies of any duration, even in some cases single-dose studies, or studies lasting one day or less, often with intravenous or intramuscular formulations (McNicol 2015; Mercadante 2013). While short-term studies and non-oral formulations may have some relevance in some circumstances, they have little relevance to the vast majority of people with cancer pain who will be treated with oral NSAIDs over weeks, months, or even years. We have therefore chosen to include only studies with five days' duration or longer.

The third issue is that of comparators. Many cancer pain studies involve direct comparisons of one or more formulations of the same drug, as particularly noted for oral morphine (Wiffen 2016). This type of design has limited importance in evaluating the analgesic contribution of a drug, if that is not already well established (McQuay 2005). For that reason, we have limited this review to the two comparators that speak to the efficacy of NSAIDs in cancer pain, namely the comparison of an NSAID versus placebo, and NSAID plus opioid versus the same dose of opioid alone. The latter comparison would be similar to methods used for determining dose-response of analgesics in acute pain (McQuay 2007), or caffeine as an analgesic adjuvant in acute pain (Derry 2014).

OBJECTIVES

To assess the efficacy of oral NSAIDs for cancer pain in adults, and the adverse events reported during their use in clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

To be included, studies had to:

- be randomised (described as 'randomised' anywhere in the manuscript);
- ideally be double-blind, but we included single-blind or open studies because we expected there to be a limited literature on this important topic, and we wanted to be as inclusive as possible;
- include a minimum of 25 participants per treatment arm; for cross-over studies this meant a minimum of 25 participants at the initial randomisation.
- have a study duration of at least five days of continuous treatment, with outcomes reported at the end of that period.

We excluded non-randomised studies, studies of experimental pain, case reports and clinical observations. Studies had to be fully published or available as extended abstracts (e.g. from clinical trial websites); we excluded short (usually conference) abstracts as these are often unreliable (PaPaS 2012).

Because dipyrone is known to produce substantial (90% or greater) inhibition of COX-1 and COX-2 through its 4-methyl-amino-antipyrine metabolite (Hinz 2007), we have included it in the list of NSAIDs.

Types of participants

We included studies of adults (18 years or older) with cancer pain of any intensity. We did not consider postsurgical pain or specific neuropathic pain conditions.

Types of interventions

Orally administered NSAID for cancer pain where the NSAID alone was compared with placebo or another analgesic (e.g. a different NSAID, paracetamol, or an opioid), or orally administered NSAID combined with an opioid compared with the same dose of opioid alone.

Types of outcome measures

Pain had to be measured using a validated assessment tool. For pain intensity, for example, this could be a 100 mm visual analogue scale (VAS) or 11-point numerical rating scale (no pain to worst pain imaginable), or a four-point categorical scale (none, mild, moderate, severe); for pain relief, for example, it could be a 100 mm VAS (no relief to complete relief), or five-point categorical scale (none, a little, some, a lot, complete or words to that effect). Measures of 30% or greater (moderate) and 50% or greater (substantial) reduction of pain over baseline are recommended outcomes for chronic pain studies from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008).

A 30% or greater reduction of pain from baseline corresponds to much or very much improved on Patient Global Impression of Change (PGIC), and 50% or greater reduction corresponds to very much or completely improved. We would also use results equivalent to no pain or mild pain, because these are also outcomes acceptable to people with various types of pain (Moore 2013a).

Primary outcomes

- Number of participants with pain reduction of 50% or greater from baseline.
- Number of participants with pain reduction of 30% or greater from baseline.
- Number of participants with pain no worse than mild (Moore 2013a).
- Number of participants with PGIC of much improved or very much improved (or equivalent wording).

Secondary outcomes

- Quality of life.
- Use of rescue medication.
- Participant satisfaction or preference.
- Serious adverse events, including death.
- Other adverse events, particularly reports of effects of treatment on somnolence, appetite, or thirst, because these are of particular interest (Wiffen 2014).
- Withdrawals due to lack of efficacy, adverse events, or any cause.

Search methods for identification of studies

Electronic searches

We searched the following databases, without language or date restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) on 4 April 2017.
- MEDLINE (via Ovid) from 1946 to 4 April 2017.
- Embase (via Ovid) from 1974 to 4 April 2017.

We used a combination of MeSH (or equivalent) and text word terms and tailored search strategies to individual databases. The search strategy for CENTRAL, MEDLINE, and Embase are in Appendix 1, Appendix 2, and Appendix 3, respectively.

Searching other resources

We searched the metaRegister of controlled trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing and unpublished trials. In addition, we checked reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles. We did not contact authors for additional information.

Data collection and analysis

Selection of studies

Two review authors (RAM, SD) independently read the abstract of each study identified by the search, eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. Two review authors (RAM, SD) read these studies independently to select relevant studies for inclusion. In the event of disagreement, a third review author (PW) was available to adjudicate. We did not anonymise the studies before assessment. We have included a PRISMA flow chart in the review to show the status of identified studies as recommended in Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included studies in the review, irrespective of whether measured outcome data were reported in a 'usable' way.

Data extraction and management

Two review authors (RAM, SD) independently extracted data using a standard form and checked for agreement before entry into Review Manager (RevMan) (RevMan 2014). We included information about the number of participants treated and demographic details, type of cancer, drug and dosing regimen, study design (placebo or active control) and methods, study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events. We collated multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We collected characteristics of the included studies in sufficient detail to complete a Characteristics of included studies table.

Assessment of risk of bias in included studies

Two review authors (RAM, SD) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We completed a 'Risk of bias' table for each included study, using the 'Risk of bias' tool in RevMan (RevMan 2014).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated); high risk of bias where study did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved); high risk of bias (study participants or personnel, or both, not blinded).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how it was achieved); high risk of bias (outcome assessment not blinded).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (fewer than 10% of participants did not complete the study or used ‘baseline observation carried forward’ analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Reporting bias due to selective outcome reporting (reporting bias). We checked if an a priori study protocol was available and if all outcomes of the study protocol were reported in the publications of the study. We assessed the methods used to deal with incomplete data as: low risk of reporting bias if the study protocol was available and all of the study’s prespecified (primary and secondary) outcomes that were of interest in the review were reported in the pre-specified way, or if the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon); high risk of reporting bias if not all of the study’s pre-specified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study; and unclear risk of bias risk’ of bias if insufficient information is available to permit judgement of ‘Low risk’ or ‘High risk’.
- Size of study (checking for possible biases confounded by small size (Dechartes 2013; Dechartres 2014; Moore 1998; Nüesch 2010; Thorlund 2011)). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We planned to use dichotomous data to calculate risk difference (RD) or risk ratio (RR) with 95% confidence intervals (CIs) using a fixed-effect model, and calculate numbers needed to treat for one additional beneficial outcome (NNT) as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the number needed to treat (NNT) becomes the number needed to treat for one additional harmful outcome (NNH), and is calculated similarly.

We planned to use the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with NSAIDs than with control (placebo or active control), we used the term number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with NSAIDs compared with control (placebo or active control) we used the term number needed to treat for an additional harmful outcome or cause one event (NNH).

We did not plan to use continuous data for the primary outcome because it is inappropriate where there is an underlying skewed distribution, as is usually the case with analgesic response.

Unit of analysis issues

The unit of randomisation was the individual participant.

Dealing with missing data

We planned to use intention-to-treat (ITT) analyses: participants who were randomised, took the study medication, and gave a minimum of one post-baseline assessment. We have reported per-protocol data in the absence of ITT data.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using L'Abbé plots, a visual method for assessing differences in results of individual studies (L'Abbé 1987), and by use of the I^2 statistic. We anticipated that there could be an effect of differences between participants, environment (inpatient versus outpatient), and outcome measures. We planned to explore these with subgroup and sensitivity analyses where there were sufficient data, recognising the difficulties of assessing heterogeneity with small numbers of small studies (Gavaghan 2000; IntHout 2015). In the event, there were insufficient data to assess heterogeneity.

Assessment of reporting biases

We planned to use dichotomous data of known utility (Moore 2010a; Moore 2013a). The review would not depend on what authors of the original studies chose to report or not.

We planned to undertake an assessment of publication bias if there were sufficient data for meta-analysis, using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher) (Moore 2008). In the event, there were insufficient data to assess publication bias.

Data synthesis

We planned to undertake a quantitative synthesis and present data in forest plots if there were sufficient data. In the event of substantial clinical heterogeneity, we would switch off the totals in the forest plots.

- We would undertake a meta-analysis only if participants, interventions, comparisons, and outcomes were judged to be sufficiently similar to ensure an answer that is clinically meaningful.
- We would undertake a meta-analysis only where there were data from at least two studies and 200 participants for analysis.
- We planned to use RevMan for meta-analysis (RevMan 2014) and Excel for NNT and NNH.

In the event, there were insufficient data for pooling of data for any outcome.

Quality of the evidence

We used the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 4). Two review authors (RAM, SD) independently rated the quality of each outcome.

We paid particular attention to inconsistency, where point estimates vary widely across studies or confidence intervals (CIs) of studies show minimal or no overlap (Guyatt 2011), and to the potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if a study uses last observation carried forward (LOCF) imputation in circumstances where there are substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels, to very low quality. In circumstances where there were no data reported for an outcome, we have reported the level of evidence as very low quality (Guyatt 2013b).

In addition, we are aware that many Cochrane reviews are based largely or wholly on small underpowered studies, and that there is a danger of making conclusive assessments of evidence based on inadequate information (AlBalawi 2013; Brok 2009; Roberts 2015; Turner 2013).

'Summary of findings' table

We have included a 'Summary of findings' table as set out in the Pain, Palliative and Supportive Care Review Group author guide (PaPaS 2012) and recommended in Chapter 4.6.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We present the main findings in a simple tabular format, to include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, the sum of available data on the outcomes of at least 30% and at least 50% pain relief, PGIC much or very much improved, adverse events, and serious adverse events. In addition, we have also included other measures of efficacy or harm (quality of life or well-being at end of treatment, use of rescue medication, patient satisfaction or preference, withdrawals, and death).

For the 'Summary of findings' table we used the following descriptors for levels of evidence (EPOC 2015).

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

Subgroup analysis and investigation of heterogeneity

We planned several possible subgroup analyses, depending on the availability of data.

- Because we expected that many studies would have a cross-over design that could impede meta-analysis (Elbourne 2002), we planned to examine cross-over and parallel-group designs separately.
- We planned to investigate whether subgroup analysis by individual drug or dose was possible.
- We planned to analyse separately studies with NSAID alone, and NSAID combined with opioid. We anticipated that these studies might also reflect different levels of initial pain intensity.

We planned no other subgroup analyses because the data were expected to be sparse, with small numbers of small trials. In the event, there were insufficient data for any subgroup analysis.

Sensitivity analysis

We did not plan any sensitivity analyses because the data were expected to be sparse, with small numbers of small trials.

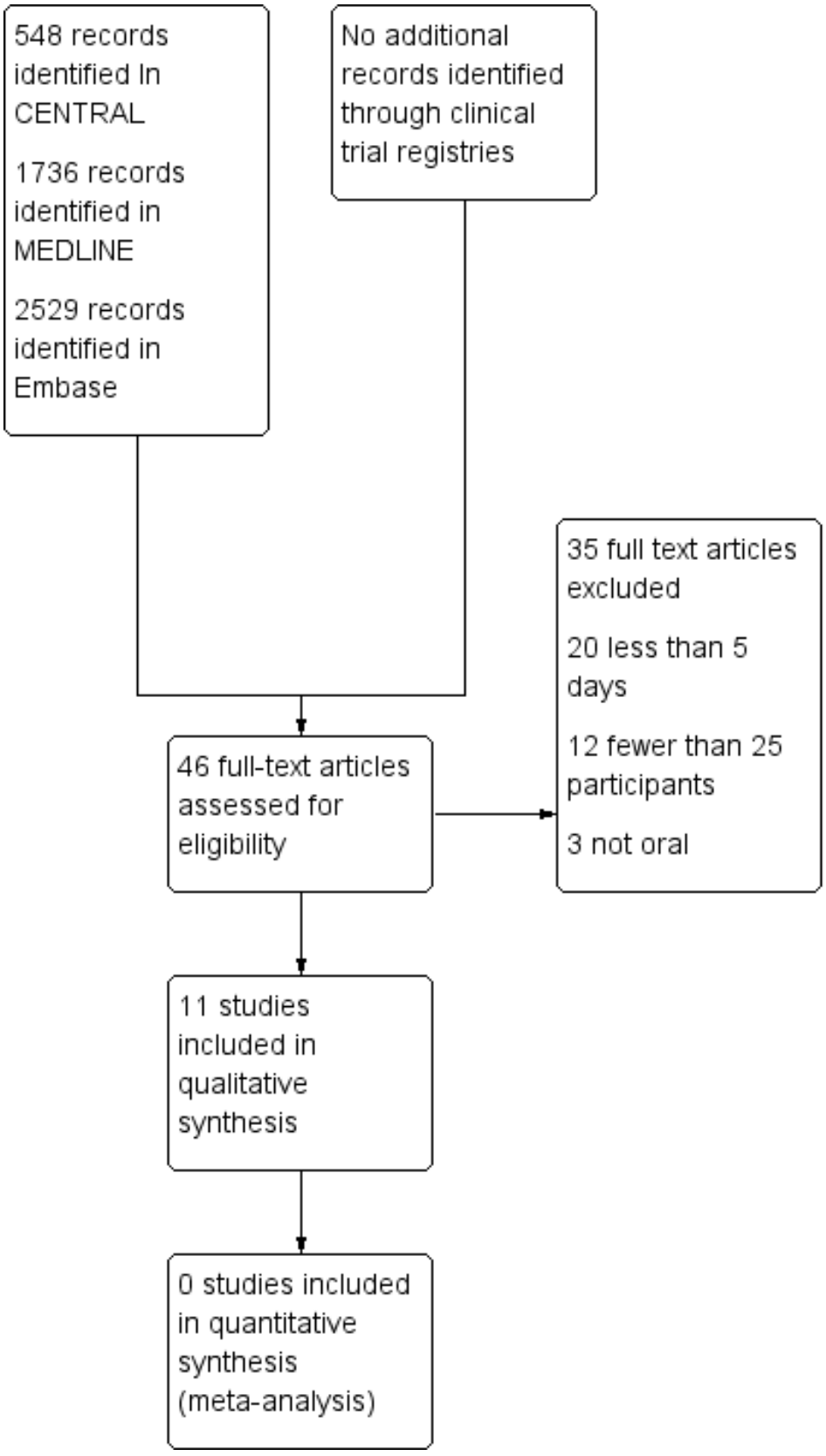
RESULTS

Description of studies

Results of the search

Searches identified 548 articles in CENTRAL, 1736 articles in MEDLINE, 2529 articles in Embase, and no additional relevant reports in clinical trial registries. We reassessed all studies included in the earlier review (McNicol 2015). After screening and assessment of relevant full texts, we included 11 studies and excluded 35 studies (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 11 studies, all of which were randomised Carlson 1990; Gallucci 1992; Minotti 1989; Mohammadinejad 2015; Pannuti 1999; Rodriguez 2003; Rodriguez 1994; Toscani 1994; Turnbull 1986; Ventafrida 1990a; Yalçin 1998). Two were not in the earlier review (Mohammadinejad 2015; Rodriguez 2003). Eight studies were double-blind, two were single-blind, and one was open-label. None had a placebo only control. They initially randomised 949 participants, although not all contributed to outcomes.

Three studies used a cross-over design with treatment periods of seven days (Pannuti 1999; Turnbull 1986; Yalçin 1998). Yalçin 1998 specified a 12-hour washout between treatment phases, but there was no washout reported in the other two studies. Eight studies used a parallel-group design, with treatment periods mostly between seven and 14 days, and one study (primarily investigating depression) lasting six weeks.

No included study compared an NSAID with placebo, or compared an NSAID plus opioid with the same dose of opioid alone.

Nine studies included treatment arms comparing one NSAID with a different NSAID (Gallucci 1992; Minotti 1989; Mohammadinejad 2015; Pannuti 1999; Rodriguez 2003; Toscani 1994; Turnbull 1986; Ventafrida 1990a; Yalçin 1998), one of which was reported in three articles (Gallucci 1992). Three studies compared an NSAID with an opioid (morphine; Rodriguez 1994), or an oral opioid combination (paracetamol plus codeine; Carlson 1990, and aspirin plus codeine; Minotti 1989).

Ten studies included both men and women, with a slight preponderance of men (60% overall). These studies each included participants with various types of cancer, except one that exclusively enrolled participants with bone cancer (Rodriguez 2003). The other study included women with breast cancer (Mohammadinejad 2015). Where reported, the mean age was 52 to 70 years (age range 30 to 89 years).

Most studies required participants to have moderate or severe pain levels at study entry, or reported baseline pain levels of at least moderate intensity. Mohammadinejad 2015 required mild to moderate pain as an entry criterion, and reported mean baseline levels of 60 (± 7)/100. Gallucci 1992 recruited participants who "needed analgesic treatment according to the first step of WHO scale" and reported a mean baseline Integrated Pain Score of 40 to 50, which equates to at least moderate pain (De Conno 1994). Turnbull 1986 reported only changes in pain levels, not absolute values.

Doses of NSAIDs used were within recommended dosing schedules, and doses of oral morphine were 60 mg to 180 mg daily (Rodriguez 1994), and of oral codeine in combination with a non-opioid were 160 mg or 240 mg daily (Carlson 1990; Minotti 1989).

Further details are in the Characteristics of included studies table.

Excluded studies

We excluded 35 studies, 31 of which were included in the earlier review (Bjorkman 1993; Bosek 1994; Chary 1994; Corli 1993; Dellemijn 1994; Estapé 1990; Ferrer-Brechner 1984; Frankendal 1973; Johnson 1994; Lauretti 1999; Levick 1988; Lomen 1986; Martino 1976; Minotti 1998a; Minotti 1998b; Moertel 1971; Moertel 1974; Sacchetti 1984; Saxena 1994; Stambaugh 1988a; Stambaugh 1988b; Staquet 1989; Staquet 1993; Strobel 1992; Sunshine 1988; Tonachella 1985; Ventafridda 1975; Ventafridda 1990b; Weingart 1985; Wool 1991; Yalcin 1997), and four were newly identified (Chen 2003; Dutre Souza 2007; Mercadante 2002; Shen 2003).

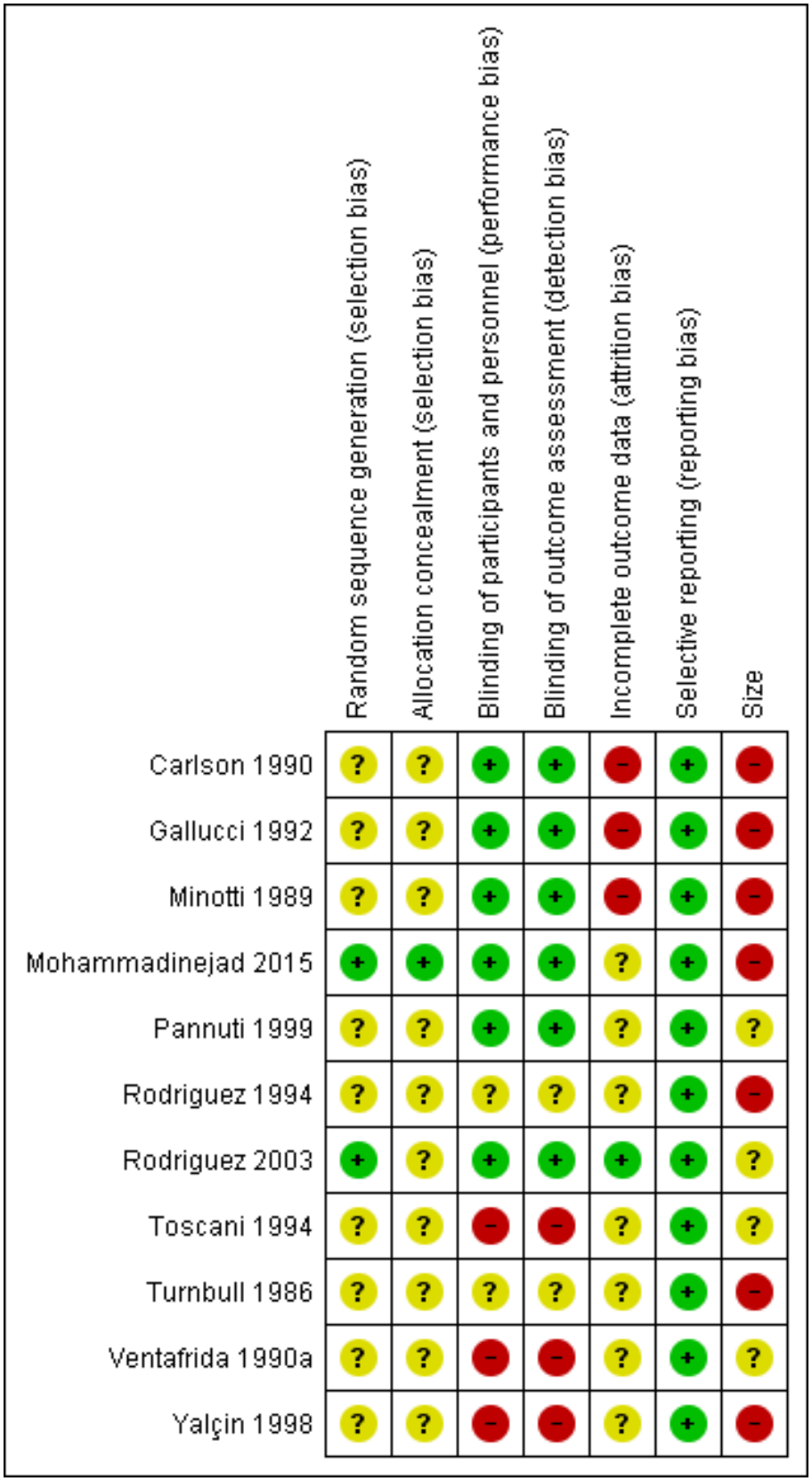
We excluded studies because the treatment duration was less than five days (20), they had fewer than 25 participants per treatment arm (12), or used a non-oral route of administration (3).

Other studies had been excluded from the earlier review because the drug had been discontinued due to serious adverse events, and we did not consider these for inclusion.

Risk of bias in included studies

Only two studies were without at least one high risk of bias (Pannuti 1999; Rodriguez 2003; Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

All studies were described as randomised, but only two adequately described the method used to generate the random sequence (Mohammadinejad 2015; Rodriguez 2003; low risk of bias). One study adequately described how the allocation of the sequence was concealed (Mohammadinejad 2015; low risk of bias).

Blinding

We judged three studies at high risk of bias for blinding because one was open-label (Yalçin 1998), and two were single-blind (Toscani 1994; Ventafrida 1990a). Two studies did not adequately describe the methods of blinding (Rodriguez 1994; Turnbull 1986; unclear risk of bias), and the remainder we judged at low risk.

Incomplete outcome data

We judged three studies at high risk of bias for incomplete outcome data because they did not report how withdrawals were handled in a situation where there were very high levels of attrition (Carlson 1990; Gallucci 1992; Minotti 1989). We judged Rodriguez 2003 at low risk because it used and described an appropriate method of imputation. We judged the remaining studies at unclear risk because they did not adequately report on how withdrawals were handled in analyses.

Selective reporting

Although protocols were not available for any of the included studies, we judged all of the studies to be at low risk of bias because they reported the outcomes stated in their Methods sections. Outcomes reported frequently did not include the efficacy outcomes of interest to this review.

Other potential sources of bias

We judged seven studies at high risk of bias because they had fewer than 50 participants in each treatment arm. The remaining four studies had between 50 and 200 participants per treatment arm, but most groups included fewer than 60 participants and the largest included 72; not all of the participants contributed to outcomes.

Effects of interventions

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

A summary of results for efficacy outcomes in individual studies is available in Appendix 5, and for rescue medication, adverse events and withdrawals in Appendix 6. Summary of findings for the main comparison includes several of the main outcomes.

Efficacy

No included study compared an NSAID with placebo, or compared an NSAID plus opioid with the same dose of opioid alone.

Primary outcomes

Few studies reported any of our primary outcomes: participants with pain reduction of at least 50%, and at least 30%, from baseline; participants with pain no worse than mild at the end of the treatment period; participants with PGIC of much improved or very much improved (or equivalent wording).

NSAID versus NSAID

Minotti 1989 defined a "responder" as a participant who experienced ≥ 50% reduction in pain intensity or had pain of < 40/100 at the end of the study, but did not report this or any pain outcome for the intended 10 days of treatment. Non-responders at two days were withdrawn from the study (pain intensity > 40/100 at two days: 16/33 diclofenac and 14/33 nefopam), and withdrawal rates were typically above 60%.

Pannuti 1999 reported a Patient Global Evaluation of "moderate, good or complete" in 83/128 participants with ketorolac 30 mg daily and 74/129 with diclofenac 150 mg daily after seven days. We judged this equivalent to PGIC of much improved or very much improved (≥ moderate benefit). A Patient Global Evaluation of "good or complete" (≥ substantial benefit) was reported in 34/128 participants with ketorolac 30 mg daily and 33/129 with diclofenac 150 mg daily (26% response rate at seven days with NSAID).

Rodriguez 2003 reported the number of participants with pain intensity < 30/100 at the end of the study; 31/56 with dexketoprofen trometamol 100 mg daily, and 27/57 with ketorolac 40 mg daily. With NSAID, therefore, 58/113 (51%) participants had a pain intensity below 30/100 after seven days.

There were insufficient data to compare one NSAID with another. We assessed this as very low-quality evidence.

NSAID versus opioid

Minotti 1989 defined a "responder" as a participant who experienced ≥ 50% reduction in pain intensity or had pain of < 40/100 at the end of the study, but did not report this or any pain outcome for the intended 10 days of treatment. Non-responders at two days were withdrawn from the study (pain intensity > 40/100 at two days: 16/33 diclofenac, 14/33 nefopam, 10/33 aspirin plus codeine), and withdrawal rates were typically above 60%.

Rodriguez 1994 reported the number of participants experiencing at least 50% improvement in pain at five days as 5/41 with dipyrone 3000 mg daily, 15/38 with dipyrone 6000 mg daily, and 10/42 with morphine 60 mg daily. In an overall rating of efficacy, the numbers reporting "good or excellent" (judged equivalent to PGIC of much improved or very much improved) were 16/41 with dipyrone 3000 mg daily, 17/38 with dipyrone 6000 mg daily, and 19/42 with morphine 60 mg daily (42% response rate at seven days with NSAID). The evaluation of pain improvement appeared to show a difference between the two doses of dipyrone (higher was better), but not between the higher dose of dipyrone and morphine. The evaluation of overall efficacy did not replicate this difference.

There were insufficient data to compare one NSAID with an opioid. We assessed this as very low-quality evidence.

Other pain outcomes

NSAID versus NSAID

Gallucci 1992 reported that in participants who completed two weeks of treatment (43/68), the mean Integrated Pain Score was reduced by 65% with nimesulide 400 mg daily and by 70% with naproxen 1000 mg daily. We estimate that the mean baseline Integrated Pain Score of 40 to 50 was equivalent to moderate pain, and the mean 14-day score of approximately 15 was equivalent to mild pain (De Conno 1994). It seems likely that most participants

who could tolerate treatment had no worse than mild pain at 14 days.

Minotti 1989 reported a physician assessment of therapeutic efficacy of very good in 1/33 (3%) participants with diclofenac and 3/33 (10%) with nefopam.

Mohammadinejad 2015 reported that mean pain was reduced from about 60/100 to about 45/100 after six weeks with both celecoxib 400 mg daily and diclofenac 100 mg daily. It is likely that most participants still had moderate pain levels.

Turnbull 1986 did not report baseline pain levels, but results suggest that pain was reduced by an average of about 15/100 with both naproxen 1000 mg daily and aspirin 3600 mg daily, with very large standard deviations.

Ventafrida 1990a reported that the mean Integrated Pain Score decreased by about 25 points (> halved) in both groups, to 16 with naproxen sodium 1100 mg daily and 17 with diclofenac sodium 200 mg daily. This probably equates to moderate pain reduced to mild pain for most participants as the mean integrated pain score for weeks one and two was equivalent to all-day slight pain or below (score of 1 for 24 hours = 24).

Yalçin 1998 reported a mean reduction in pain intensity of 4.7/10 with diflunisal 1000 mg daily and 3.3/10 with dipyrone 1500 mg daily, but with large standard deviations.

These results using mean data for the most part indicate that NSAIDs reduce pain to an acceptable level (≤ mild) in a proportion of participants, but the large standard deviations show that the response is variable, and some participants will not achieve good pain relief.

We assessed this as very low-quality evidence because of high risk of bias and small size.

NSAID versus opioid

Carlson 1990 reported that mean daily pain relief was greater for the combination of paracetamol and codeine than ketorolac over seven days, with statistical significance on the second and fourth days of treatment.

Minotti 1989 reported a physician assessment of therapeutic efficacy of very good occurred in 1/33 participants with diclofenac, 3/33 with nefopam, and 1/33 with codeine plus aspirin.

We assessed this as very low-quality evidence because of high risk of bias and small size.

Secondary outcomes

None of the studies reported on quality of life or participant satisfaction or preference in cross-over studies.

Use of rescue medication

Two studies reported on the number of participants who used rescue medication during treatment periods.

In Rodriguez 2003, 40/57 participants taking dexketoprofen trometamol 100 mg daily and 42/58 taking ketorolac 40 mg daily used rescue medication; the median number of tablets (paracetamol + codeine 500 mg/30 mg) taken over the whole study period was three with dexketoprofen and six with ketorolac.

In Rodriguez 1994, 17/41 participants taking dipyrone 3000 mg daily, 11/38 taking dipyrone 6000 mg daily, and 12/42 taking morphine 60 mg daily used rescue medication.

We assessed this as very low-quality evidence because of high risk of bias and small size.

Harm

Serious adverse events and deaths

Nine studies did not report specifically on serious adverse events.

Rodriguez 2003 reported two serious adverse events, each with dexketoprofen trometamol 100 mg daily and ketorolac 40 mg daily. One event, gastrointestinal haemorrhage with ketorolac was considered treatment-related.

Turnbull 1986 reported that there were no adverse events during the study.

Deaths were reported separately from adverse events in these studies, probably because most were due to progression of the cancer and not considered relevant to the study drugs.

Twenty-two deaths were reported in the 11 studies. Gallucci 1992 reported 5/34 deaths with nimesulide and 9/58 with naproxen, Ventafrida 1990a reported 2/50 deaths with naproxen and 2/50 with diclofenac, and Turnbull 1986 reported two deaths, judged unrelated to treatment (group not given). These studies enrolled participants with advanced cancers. Rodriguez 2003 reported one death with dexketoprofen, and Yalçin 1998 reported one death (group not given) due to progression of the disease.

We assessed this as very low-quality evidence because of high risk of bias and small size.

Specific adverse events

For cancer patients we were particularly interested in somnolence, loss of appetite (or anorexia), and thirst (or dry mouth), which have been highlighted as of concern (Wiffen 2014). Where results were reported at one week and two weeks, we have used the one week data for consistency with other studies.

Turnbull 1986 reported that there were no adverse events with either treatment in 28 participants. While all the remaining studies reported some information on specific adverse events, the categories that were reported (e.g. the most common, those that were of "high intensity") differed, as did the descriptions of the events. It was often difficult to determine which events could be counted together (e.g. somnolence, tiredness, sleepiness, fatigue; or dyspepsia, stomach pain, gastralgia). There were no obvious differences between treatment groups within a study.

There were 47 somnolence events reported in 543 participants (9%) in seven comparisons of NSAID versus NSAID, and 22 amongst 115 participants (19%) taking an opioid (or opioid combination) in three comparisons with NSAIDs.

There were 11 anorexia events reported in 313 participants (4%) in four comparisons of NSAID versus NSAID, and two amongst 82

participants (2%) taking an opioid (or opioid combination) in two comparisons with NSAIDs.

There were 23 dry mouth events reported in 234 participants (10%) in three comparisons of NSAID versus NSAID, and two amongst 40 participants (5%) taking an opioid (or opioid combination) in one comparison with an NSAID.

Since gastrointestinal events are of concern with NSAIDs, we looked for evidence of a difference in frequency between NSAIDs and between NSAIDs and opioids (or opioid combinations). There were no obvious differences between treatment groups within a study.

Dyspepsia or epigastric pain was one of the more common specific gastrointestinal events reported. There were 83 events in 971 participants (9%) in 10 comparisons of NSAID versus NSAID, and nine amongst 115 participants (8%) taking an opioid (or opioid combination) in three comparisons with NSAIDs.

We assessed all evidence on specific adverse events as very low quality because of high risk of bias and small size.

Withdrawals

All-cause

There were 204 withdrawals for any reason reported amongst 874 participants (23%) in 10 comparisons of NSAID versus NSAID, and 48 amongst 73 participants (66%) taking an opioid (or opioid combination) in two comparisons with NSAIDs. It was not always clear whether reported withdrawals included participants who progressed to step II analgesics. There were no obvious differences between treatment groups.

Lack of efficacy

There were 136 withdrawals due to lack of efficacy reported amongst 567 participants (24%) in 14 comparisons of NSAID versus NSAID, and 17 amongst 73 participants (23%) taking an opioid (or opioid combination) in two comparisons with NSAIDs. There were no obvious differences between treatment groups. Some studies reported lack of efficacy withdrawals, some reported participants progressing to step II (we judged probably due to lack of efficacy), some reported neither, and others reported both. It is difficult to interpret these numbers in a situation where the natural course of the disease is likely to require progression to step II.

Adverse events

Withdrawals due to adverse events were not common; 39 events were reported for 718 participants (5%) in 17 comparisons of NSAID versus NSAID, and 10 events reported for 115 participants taking an opioid (9%) or opioid combination) in three comparisons with NSAIDs. There were no obvious differences between treatment groups, and too few events for analysis.

We assessed all evidence on withdrawals as very low quality because of high risk of bias and small size..

DISCUSSION

Summary of main results

Few studies met the criteria for inclusion, and together with the nature of the efficacy results presented, the results of the available studies for NSAIDs for cancer pain are insufficient to allow any conclusions to be drawn about efficacy or harm. The evidence is insufficient to support or refute their use.

No studies were found for the use of NSAIDs alone in mild or moderate cancer pain, as suggested for the first step of the WHO analgesic ladder (WHO 2017). Included studies typically had initial pain that was moderate or severe in intensity. No studies were found examining the additional analgesic efficacy of NSAIDs combined with strong opioids.

The 11 included studies randomised 949 participants with cancer pain, predominantly of moderate or severe intensity. Studies typically compared one NSAID with another, though a few compared an NSAID with an opioid or opioid combination. In this circumstance no comparative analyses were possible. What was possible was an assessment of the proportion of participants who had a pain score of no or mild pain (or some equivalent measure) around one or two weeks following the start of NSAID treatment. This was highly variable, with assessments of 3% for a physician assessment of very good efficacy (Minotti 1989) or 7% for participant evaluation of complete relief (Pannuti 1999), to 26% for complete or good relief (Pannuti 1999), 52% for overall analgesic efficacy good or excellent (Rodriguez 1994), and 51% for pain intensity of below 30/100 mm on the final day of treatment (Rodriguez 2003). One other study, while providing no comparable results, also reported a mean integrated pain score equivalent to all-day slight pain or below at one and two weeks (Ventafrida 1990a). This impression of efficacy was also seen in a study excluded for its small size for individual NSAIDs, but which was essentially a randomised cohort study of NSAIDs given to 65 participants with moderate or severe cancer pain (Ventafridda 1990b); pain scores were below 30/100 at one and two weeks for seven of eight NSAIDs tested.

Reporting of harms provided no useful information, and could not be expected to do so given the small size of the studies, individually and together. There are limits on how comparable adverse event information can be, but for particular adverse events, such as somnolence (11%), loss of appetite (14%), or thirst or dry mouth (15%), rates with NSAIDs were similar to those found with opioids (somnolence 23%, anorexia 17%, dry mouth 17%) (Wiffen 2014).

A large number of studies were excluded, mainly because of short treatment duration or their very small size limiting applicability.

Where there are small numbers of small studies, there is a situation where a positive bias in favour of a therapy might be found (Dechartes 2013; Dechartres 2014; Fanelli 2017; Nguyen 2017; Nüesch 2010) even by the random play of chance (Brok 2009; Moore 1998; Thorlund 2011), and overemphasising results of underpowered studies or analyses has been criticised (AlBalawi 2013; Roberts 2015; Turner 2013). Because of the small number of studies and participants in this review, any reported positive effect of NSAIDs in cancer pain should be treated with caution.

NSAIDs are known to have good efficacy in acute postoperative pain (Moore 2015a), migraine (Rabbie 2013), and dysmenorrhoea (Edwards 2004). In chronic pain, they have efficacy in musculoskeletal conditions like arthritis (van Walsem 2015), but not in neuropathic pain (Moore 2015b) or fibromyalgia (Derry 2017).

Overall completeness and applicability of evidence

This review highlights our lack of knowledge about the effectiveness of NSAIDs for cancer pain. The WHO ladder recommends non-opioid analgesics for all three steps of the WHO ladder (WHO 2017), and NSAIDs in many countries are the mainstay of the first two steps.

Not all of the studies reported on primary outcomes of efficacy known to be important to people with pain (Moore 2013a).

Quality of the evidence

Our GRADE judgement was very low quality for all outcomes. Very low quality means that this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

A number of individual studies had high risk of bias for issues such as incomplete outcome data and small size, and none of the trials was unequivocally at low risk of bias for all criteria.

Potential biases in the review process

We are unaware of any biases in the review process. A number of the authors prescribe or have prescribed NSAIDs for cancer pain, or have been involved with its use in people with cancer pain.

Agreements and disagreements with other studies or reviews

Our findings are in broad agreement with a previous Cochrane review (McNicol 2015) and other reviews in adults (Mercadante 2013; Nabal 2012). In this review we included only studies with a minimum treatment period of five days, excluding some studies of short duration in these earlier reviews, but allowing any pain-relieving effects of NSAIDs that might be seen in clinical practice to emerge. We also excluded very small studies. That meant that we excluded some studies in these previous reviews.

AUTHORS' CONCLUSIONS

Implications for practice

For people with cancer pain

The amount and quality of evidence around the use of NSAIDs for treating cancer pain is very low. The amount of evidence we have indicates that oral NSAIDs may have pain-relieving effects in some people with cancer pain, but we are very unsure of this. No judgement can be made about adverse events or withdrawals.

For clinicians

The amount and quality of evidence around the use of NSAIDs for treating cancer pain is very low. There is very limited evidence supporting the use of NSAIDs as part of the WHO ladder, and none on any additional pain-relieving effects when combined with strong opioids. The small amount of evidence we have indicates that NSAIDs may have pain-relieving effects in some people with cancer pain, but we are very unsure of this. No judgement can be made about adverse events or withdrawals. We have no evidence about which drug at which dose may be more or less effective.

For policy makers

The amount and quality of evidence around the use of NSAIDs for treating cancer pain is very low. There is very limited evidence supporting the use of NSAIDs as part of the WHO ladder, and none on any additional pain-relieving effects when combined with oral strong opioids. The small amount of evidence we have indicates that NSAIDs may have pain-relieving effects in some people with cancer pain, but we are very unsure of this. No judgement can be made about adverse events or withdrawals. We have no evidence about which drug at which dose may be more or less effective.

For funders

The amount and quality of evidence around the use of NSAIDs for treating cancer pain is very low. There is very limited evidence supporting or refuting the use of NSAIDs as part of the WHO ladder, and none on any additional pain-relieving effects when combined with oral strong opioids. The small amount of evidence we have indicates that NSAIDs may have pain-relieving effects in some people with cancer pain, but we are very unsure of this. No judgement can be made about adverse events or withdrawals. We have no evidence about which drug at which dose may be more or less effective.

Implications for research

General

This review on NSAIDs for cancer pain reveals major problems with the evidence available. The WHO pain ladder is now over 30 years old, and remains probably the most-used and best-understood pain guidance worldwide. Despite its obvious importance there are few exemplars for how best to perform cancer pain studies with non-opoid drugs like NSAIDs, alone or in combination with opioids. We know of no ongoing studies.

Design

Several methodological issues stand out.

The first is the use of outcomes of value to people with cancer pain. Existing trials are designed more for purposes of registration and marketing than informing and improving clinical practice, often because the outcomes chosen are average pain scores, or statistical differences, rather than how many individuals achieve satisfactory pain relief. In the situation where initial pain is mild or moderate initially, some consideration needs to be given to what constitutes a satisfactory outcome. The situation is somewhat different to that of strong opioids in cancer pain that are used for moderate to severe pain.

The second is the time taken to achieve good pain relief. We have no information about what constitutes a reasonable time to achieve a satisfactory result. Initially this may best be approached with a Delphi methodology.

The third is design. Studies with cross-over design often have significant attrition. Parallel group designs may be preferable, and while this is a matter of debate (Bell 2006), considerable thinking has already gone into study design.

The fourth is size. The studies were small, and, combined with cross-over design and consequent attrition, ended up reporting

on very few participants. Much larger studies of several hundred participants or more are needed.

The fifth is the dose of opioid allowable in add-on studies to test the analgesic efficacy or effectiveness of oral NSAIDs. In the circumstance of high oral opioid doses, additional benefit is unlikely to be measurable, and some upper limit of opioid dose may be needed.

The sixth is that in the current era of precision medicine investigator may have an opportunity to conduct clinical trials involving specific aetiologies of cancer pain, or accrue sufficient numbers of participants to conduct well-powered subgroup analyses.

There are some other design issues that might be addressed. Most important might be a clear decision concerning the gold-standard treatment comparator. Placebo-controlled studies in cancer pain are unlikely to be ethically feasible unless rescue morphine is freely available (Bell 2006). It may be that low-dose oral morphine is a suitable comparator, as a suggested alternative treatment for mild to moderate pain (Twycross 2014).

Measurement (endpoints)

Trials need to consider the additional endpoints of no worse than mild pain and the impact of morphine on symptoms that raise serious concerns such as consciousness, appetite, and thirst. The choice of measures to be used in cancer pain studies is not necessarily straightforward.

Other

Prospective randomised trials are the obvious design of choice, but other pragmatic designs may be worth considering. Studies could incorporate initial randomisation but a pragmatic design in order to provide immediately-relevant information on effectiveness and costs. Such designs in pain conditions have been published (Moore 2010b).

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CHARACTERISTICS OF STUDIES

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

Wiffen 2014

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Wiffen 2015

Wiffen PJ, Derry S, Naessens K, Bell RF. Oral tapentadol for cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD011460.pub2]

Wiffen 2016

Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD003868.pub4]

Wiffen 2017a

Wiffen PJ, Derry S, Moore RA, McNicol ED, Bell RF, Carr DB, et al. Oral paracetamol (acetaminophen) for cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 4. [DOI: 10.1002/14651858.CD012637]

Wiffen 2017b

Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 5. [DOI: 10.1002/14651858.CD012508.pub2]

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Derry 2017a

Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, et al. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 4. [DOI: 10.1002/14651858.CD012638]

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McNicol ED, Strassels S, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD005180.pub2]

* Indicates the major publication for the study

Carlson 1990

Methods	Multicentre, randomised, double-blind, parallel groups Duration: 7 days (multiple-dose phase)
Participants	Cancer (mostly genitourinary, lung, breast, GI); pain > 1 week, moderate/severe intensity Excluded: known coagulopathy, recent (4 h or 6 h) treatment with opioids, contraindication to NSAIDs, unable to abstain from narcotics N = 75 (randomised), 74 (safety), 70 (efficacy) M 43, F 32 Mean age 63 years (range 30 to 88)
Interventions	Initial single-dose phase compared placebo, ketorolac tromethamine, paracetamol + codeine Multiple-dose period (all oral): Ketorolac tromethamine 4 x 10 mg daily, n = 34 Paracetamol + codeine 4 x 600 mg/60 mg daily, n = 40
Outcomes	Daily overall evaluation of medication: 1 to 5 (poor to excellent) PR: 0 to 4 (complete) AEs reported in response to global questions about adverse symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical-appearing capsules"; each dose consisted of two capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical-appearing capsules"; each dose consisted of two capsules
Incomplete outcome data (attrition bias) All outcomes	High risk	50% (ketorolac) and 32% (paracetamol + codeine) attrition, imputation method not mentioned for multiple dose phase
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Gallucci 1992

Methods	Randomised, double-blind (double-dummy), parallel groups

Gallucci 1992 *(Continued)*

	Duration: 2 weeks
Participants	Advanced cancer (mainly digestive, lung, breast, male genitourinary tract), requiring step 1 analgesia Excluded: severe hepatic or renal dysfunction, hypersensitivity to NSAID N = 68 (43 evaluated at 2 weeks) M 40, F 28 Mean age 65 years (range 32 to 82)
Interventions	Nimesulide 2 x 200 mg daily, n = 34 Naproxen 2 x 500 mg daily, n = 34 Other NSAIDs and opioids not used
Outcomes	Daily: PI: integrated score AEs: checklist Severity of symptoms: 4-point scale (0 to 3) Average of scores for first 2 weeks used for analysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"indistinguishable (hydrosoluble granulated)"; double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"indistinguishable (hydrosoluble granulated)"; double-dummy method
Incomplete outcome data (attrition bias) All outcomes	High risk	Imputation not mentioned. Pain reduction reported (as average) for participants remaining in treatment (34/68)
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Minotti 1989

Methods	Randomised, double-blind (double-dummy), parallel groups Duration: 10 days

Minotti 1989 *(Continued)*

Participants	Cancer pain > 40/100, (mainly lung, breast, GI, with metastases) not receiving opioids Excluded: impaired renal, liver, or cerebral function, Hx peptic ulcer or GI bleeding. No chemo or radiotherapy, antidepressants, anti-inflammatory drugs N = 99 M 63, F 36 Mean age 60 years Baseline PI 62/100 (SD 16)
Interventions	All oral Diclofenac Na (Voltaren) 4 x 50 mg daily, n = 33 Nefopam 4 x 60 mg daily, n = 33 Aspirin + codeine 4 x 640 + 40 mg daily, n = 33
Outcomes	Daily: PI: VAS and 4-point scale Time to drug failure "Responder" at 2 days: ≥ 50% PI reduction or PI < 40/100 Investigator global at end of treatment: 4-point scale AEs - spontaneous report
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"diclofenac, nefopam and ASA tablets were put into identical dragees, while codeine phosphate powder or lactose (placebo) powder was put into sachets"; double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"diclofenac, nefopam and ASA tablets were put into identical dragees, while codeine phosphate powder or lactose (placebo) powder was put into sachets"; double-dummy method
Incomplete outcome data (attrition bias) All outcomes	High risk	High levels of withdrawal early in the study, and unclearly defined responder analysis after only one or two days of a 10-day study
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Mohammadinejad 2015

Methods	Single-centre, randomised, double-blind, parallel groups

Mohammadinejad 2015 *(Continued)*

	Duration: 6 weeks
Participants	Breast cancer (diagnosis > 100 days) and major depression (DSM-IV-TR), with score ≤ 18 (17-item HDRS) to have mild to mod depression, mild to mod pain, needing analgesic Excluded: antidepressant within 1 month, electroconvulsive within 2 months, Hx mental disorder on DSM-IV axis I, alcohol or substance dependence, medication with risk of GI bleeding, opioid analgesics, Hx cardiovascular, thyroid disease N = 56 (52 completed) All F Mean age 58 years (SD 7) Baseline PI 60/100 (SD 6.5)
Interventions	Celecoxib 2 x 200 mg daily, n = 28 (26) Diclofenac 2 x 50 mg daily, n = 28 (26) All received "standard breast cancer treatment". No other psychotropic medication or behavioural intervention
Outcomes	PI: 100 mm VAS HDRS at baseline, 3, 6 weeks Reduction in HDRS and difference between groups Change in HDRS from baseline to each time point Response: ≥ 50% red in HDRS Severity of pain between groups "Unexpected" symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerized random number generator"; carried out by independent group
Allocation concealment (selection bias)	Low risk	"Sequentially numbered and sealed packages were used to conceal allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The participants, the physician who referred the patients, the physician who prescribed the medications, the rater, and the statistician were all blinded to the allocated treatment. Celecoxib and diclofenac capsules were completely identical in their size, shape, color, texture, and odor"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The participants, the physician who referred the patients, the physician who prescribed the medications, the rater, and the statistician were all blinded to the allocated treatment. Celecoxib and diclofenac capsules were completely identical in their size, shape, color, texture, and odor"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned, but few withdrawals; mean data for pain
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Pannuti 1999

Methods	Multicentre, randomised, double-blind, cross-over study Duration: 2 x 7 days (single- and multiple-dose phases)
Participants	Cancer pain, moderate or severe Excluded: abnormal hepatic or renal function, Hx thrombosis, hypertension, diabetes, cardiovascular disease N = 137 M 65, F 72 Median age 63 years (range 30 to 71) Baseline PI: 5.3 (SD 2.2); 3 participants had mild pain
Interventions	Ketorolac 10 mg (single dose phase, 8 h), then 3 x 10 mg daily Diclofenac 50 mg (single dose phase, 8 h), then 3 x 50 mg daily No washout mentioned. If inadequate pain control with first drug, participants crossed over early
Outcomes	Daily PI: 0 to 4 scale (none to extreme) and 10 cm VAS QoL (Spitzer test) at baseline and end of treatment Overall drug efficacy at end of treatment (PGE): 0 to 4 scale (no relief to complete relief) AEs at each monitoring time
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical-looking tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical-looking tablets"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned; approximately 10% withdrew < 7 days, mainly for lack of efficacy
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	Unclear risk	50 to 200 participants per treatment arm

Rodriguez 1994

Methods	Multicentre, randomised, double-blind (double-dummy), parallel groups Duration: 7 days
Participants	Cancer (mainly lung, breast, bowel, mouth), PI ≥ 70/100 Excluded: radiotherapy or chemotherapy within 15 days, adjuvant therapy at entry, contraindications to study drugs, severe underlying disease, brain or liver metastases N = 121 M 84, F 37 Mean age ~ 60 years (SD 10) Baseline PI ~ 83/100
Interventions	All oral Dipyrone 3 x 1000 mg daily, n = 41 Dipyrone 3 x 2000 mg daily, n = 38 Morphine 6 x 10 mg daily, n = 42 Dose could be increased on day 4: up to 3 x 2000 mg dipyrone in group 1, and 6 x 30 mg morphine in group 2 Rescue medication: paracetamol + codeine (300 mg/15 mg)
Outcomes	Daily PI: 100 mm VAS Pts with ≥ 50% improvement AEs: self-reported, checklist - investigator assessed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Interventions not described, but different dosing schedules accounted for: "In order to keep the double-blind design of the study, patients in the dipyrone groups were given placebo at 4 a.m., noon and midnight"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Interventions not described, but different dosing schedules accounted for: "In order to keep the double-blind design of the study, patients in the dipyrone groups were given placebo at 4 a.m., noon and midnight"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Rodriguez 2003

Methods	Multicentre, randomised, double-blind, parallel groups Duration: 7 days
Participants	Bone cancer pain ≥ 40/100, lasting ≥ 10 days, and pain rating index ≥ 10/20 Excluded: mainly visceral or neuropathic pain, adjuvant therapy at entry, radiotherapy or chemotherapy within 15 days, contraindications to study drugs, severe underlying disease, brain or liver metastases, current schedule of opioids or NSAIDs (not aspirin or paracetamol), other significant medical conditions N = 115 (113 for efficacy) M 86, F 27 Mean age 70 (range 39 to 89) Baseline PI ~ 72/100 Baseline pain rating index 12.5/20
Interventions	Dexketoprofen trometamol 4 x 25 mg daily, n = 57 Ketorolac 4 x 10 mg daily, n = 58 Rescue medication: paracetamol/codeine 500 mg/30 mg. If > 2 doses taken per day, withdrawn due to LoE
Outcomes	At 3 and 7 days: PI: 100 mm VAS Pain rating index: 0 to 20 Participants with PID ≥ 20/100 and pain < 30/100 at end of study Karnovsky performance (QoL) Analgisic efficacy after 3 and 7 days Rescue medication AEs, withdrawals
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"predetermined computer-generated randomization schedule"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All the medications were identical-looking tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All the medications were identical-looking tablets"
Incomplete outcome data (attrition bias)	Low risk	WOCF for withdrawals due to AE or LoE, otherwise LOCF for missing values

Rodriguez 2003 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	Unclear risk	50 to 200 participants per treatment arm

Toscani 1994

Methods	Multicentre, randomised, single-blind, parallel groups Duration: 14 days
Participants	Somatic or visceral pain due to advanced cancer (mostly lung, head and neck, colorectal), not treated according to WHO guidelines Excluded: neuropathic pain, active or chronic gastroduodenal ulcer, severe coagulation problems, asthma, renal or liver diseases, known hypersensitivity to NSAIDs, Hx addiction, psychiatric patients, treatment of cancer within 15 days, opioids, NSAIDS according to WHO guidelines N = 100 M 61, F 39 Mean age 63 year Mean baseline PI moderate
Interventions	Ketorolac 4 x 10 mg daily, n = 50 Diclofenac Na 3 x 50 mg daily, n = 50
Outcomes	Daily Integrated Score (0 to 240) Days before moving to WHO step II AEs
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel not blinded to treatment. Each week participants self-assessed pain intensity; total hours asleep, without pain and in pain (= 24); and concomitant symptoms
Blinding of outcome assessment (detection bias) All outcomes	High risk	Personnel not blinded to treatment. Decision to move to step II was "according to the opinion of the experimenting physician"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned

Toscani 1994 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	Unclear risk	50 participants per treatment arm

Turnbull 1986

Methods	Randomised, double-blind (double-dummy), cross-over study Duration: 2 x 1 week
Participants	Advanced cancer (mainly rectum/colon, lung) with pain Excluded: receiving drugs that were highly protein-bound, steroids or NSAIDs within 6 weeks N = 28 Mean age 65 years M 15, F 13 Baseline PI not reported; only reported change in PI with treatment
Interventions	Naproxen 2 x 500 mg daily, n = 28 Aspirin 6 x 600 mg daily, n = 28
Outcomes	PI: VAS (0 to 100) and McGill AEs
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Interventions not described; double-dummy method used but not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Interventions not described; double-dummy method used but not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm

Ventafrida 1990a

Methods	Randomised, single-blind, parallel groups Duration: 14 days, or progression to Step II
Participants	Advanced somatic and/or visceral neoplastic pain (mainly digestive tract) Excluded: deafferentation-related pain, active or chronic gastroduodenal ulcerative disease, serious clotting disorders, undergoing treatment for cancer with 15 days N = 100 M 51, F 49 Mean age 65 years Baseline Integrated Pain Score 42/240
Interventions	Naproxen Na 2 x 550 mg daily, n = 50 Diclofenac Na 2 x 100 mg daily n = 50
Outcomes	Daily Integrated Score (0 to 240) Days before moving to step II AEs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind; participant-reported pain and AEs, but personnel aware of allocation and decision to switch to next step made "at experimenter's discretion"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind; participant-reported pain and AEs, but personnel aware of allocation and decision to switch to next step made "at experimenter's discretion"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	Unclear risk	50 to 200 participants per treatment arm

Yalçin 1998

Methods	Randomised, open, cross-over, 2 x 7 days with 12-h washout between

Yalçin 1998 *(Continued)*

Participants	Cancer (mostly breast, lung, colorectal, stomach) pain > 5/10 Excluded: significant renal or liver performance, GI malabsorption, active peptic ulcer, haemorrhagic diathesis, brain metastasis, Hx long-term analgesic use N = 50 (47 evaluated) M 26, F 21 median age 52 (range 18 to 69) Baseline PI: 8.6/10 (SD 1.3)
Interventions	Diflunisal 2 x 500 mg daily Dipyrone 3 x 500 mg daily No other therapy allowed
Outcomes	PI: VAS (0 to 10) worst pain over last 24 h at baseline and end of study
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not mentioned
Selective reporting (reporting bias)	Low risk	Protocol not available, but no obvious omissions
Size	High risk	< 50 participants per treatment arm (evaluated)

AE: adverse event; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders- fourth edition- text revisions; F: female; GI: gastrointestinal; HDRS: Hamilton Depression Rating Scale; Hx: history; LOCF: last observation carried forward; LoE: lack of efficacy; M: male; N: number of participants in study; n: number of participants in treatment arm; NSAID: nonsteroidal anti-inflammatory drug; PGE: Patient Global Evaluation; PI: pain intensity; PR: pain relief; QoL: quality of life; SD: standard deviation; VAS: visual analogue scale; WOCF: worst observation carried forward.

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

Study	Reason for exclusion
Bjorkman 1993	Each treatment period only 2 days
Bosek 1994	Intravenous route of administration, postoperative pain. Treatment period only 2 days
Chary 1994	Treatment period only 4 days
Chen 2003	Only 18 cancer patients in cross-over study
Corli 1993	Fewer than 25 participants per treatment group
Dellemijn 1994	Fewer than 25 participants per treatment group
Dutre Souza 2007	Fewer than 25 participants per treatment group
Estapé 1990	Fewer than 25 participants per treatment group
Ferrer-Brechner 1984	Each treatment period only 1 day
Frankendal 1973	Treatment duration only 3 hours
Johnson 1994	Each treatment period only 1 day. Each participant took 2 active and 1 placebo, or 1 active and 2 placebo single doses over 3 days
Lauretti 1999	Fewer than 25 participants per treatment group
Levick 1988	Treatment period only 3 days. Compares two doses of naproxen
Lomen 1986	Small number of participants (26) with high attrition rates and completer analysis, variable opioid dosing
Martino 1976	Single-dose study
Mercadante 2002	Fewer than 25 participants in control arm (morphine)
Minotti 1998a	Single-dose study
Minotti 1998b	Treatment period only 2 days
Moertel 1971	Only 13 participants in the treatment arm. Treatment duration not stated
Moertel 1974	Single-dose study
Sacchetti 1984	Single-dose study
Saxena 1994	Treatment period only 2 days
Shen 2003	Fewer than 25 participants in control arm (morphine only)
Stambaugh 1988a	Single-dose study
Stambaugh 1988b	Fewer than 25 participants per treatment group
Staquet 1989	Intramuscular route of administration. Single-dose study
Staquet 1993	Single-dose study

Study	Reason for exclusion
Strobel 1992	Treatment duration only 6 hours
Sunshine 1988	Single-dose study
Tonachella 1985	Intramuscular route of administration, each treatment period only 3 days
Ventafridda 1975	Single-dose study
Ventafridda 1990b	Fewer than 25 participants in control arm (morphine)
Weingart 1985	Each treatment period only 3 days. Each participant had 2 active and 1 placebo, or 1 active and 2 placebo periods in addition to constant opioid regimen
Wool 1991	Single-dose study
Yalcin 1997	Each treatment period only 2 days

APPENDICES

Appendix 1. Search strategy for CENTRAL (via CRSO)

1. MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES (15201)
2. (NSAID* or "non-steroidal anti-inflammatory drug*"):TI,AB,KY (3754)
3. ((aceclofenac or acemetacin or azapropazone or celecoxib or ketoprofen or dexketoprofen or diclofenac or dipyrone or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or Indomet?acin or “mefenamic acid” or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid)):TI,AB,KY (14109)
4. (Apazone or Ketoprofen or Diclofenac or Etodolac or Fenoprofen or Flurbiprofen or Ibuprofen or Indomethacin or Mefenamic Acid or Naproxen or Piroxicam or Sulindac):MH (5867)
5. #1 OR #2 OR #3 OR #4 (23883)
6. MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES (48784)
7. (neoplasm* or malignan* or tumour* or tumor* or cancer* or carcinoma*):TI,AB,KY (112035)
8. #6 OR #7 (117073)
9. MESH DESCRIPTOR Pain EXPLODE ALL TREES (34252)
10. (pain* or nocicept* or neuropath*):TI,AB,KY (99145)
11. #9 OR #10 (104045)
12. #5 AND #8 AND #11 (548)

Appendix 2. Search strategy for MEDLINE (via Ovid)

1. exp Anti-Inflammatory Agents, Non-Steroidal/ (181078)
2. (NSAID* or "non-steroidal anti-inflammatory drug*".tw. (24689)
3. Apazone/ or Ketoprofen/ or Diclofenac/ or Etodolac/ or Fenoprofen/ or Flurbiprofen/ or Ibuprofen/ or Indomethacin/ or Mefenamic Acid/ or Naproxen/ or Piroxicam/ or Sulindac/ (51468)
4. (aceclofenac or acemetacin or azapropazone or celecoxib or ketoprofen or dexketoprofen or diclofenac or dipyrone or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or Indomet?acin or “mefenamic acid” or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid).tw (66755)
5. 1 or 2 or 3 or 4 (202029)
6. exp Neoplasms/ (2963191)
7. (neoplasm* or malignan* or tumour* or tumor* or cancer* or carcinoma*).mp. (3245993)
8. 5 or 6 (3579379)
9. exp Pain/ (349136)
10. (pain* or nocicept* or neuropath*).mp. (682211)

11.8 or 9 (756162)
12.randomized controlled trial.pt. (456758)
13.controlled clinical trial.pt. (93340)
14.randomized.ab. (348554)
15.placebo.ab. (171262)
16.drug therapy.fs. (1967607)
17.randomly.ab. (239695)
18.trial.ab (363855)
19.12 or 13 or 14 or 15 or 16 or 17 or 18 (2663271)
20.5 and 8 and 11 and 19 (1736)

Appendix 3. Search strategy for Embase (via Ovid)

1. exp Anti-Inflammatory Agents, Non-Steroidal/ (533081)
2. (NSAID* or "non-steroidal anti-inflammatory drug*").tw. (42811)
3. (aceclofenac or acemetacin or azapropazone or celecoxib or ketoprofen or dexketoprofen or diclofenac or dipyrone or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or ibuprofen or Indomet?acin or mefenamic or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid).tw. (94288)
4. Apazone/ or Ketoprofen/ or Diclofenac/ or Etodolac/ or Fenoprofen/ or Flurbiprofen/ or Ibuprofen/ or Indomethacin/ or Mefenamic Acid/ or Naproxen/ or Piroxicam/ or Sulindac/
5. 1 or 2 or 4 (545302)
6. exp Neoplasms/ (4021384)
7. (neoplasm* or malignan* or tumour* or tumor* or cancer* or carcinoma*).mp. (4471451)
8. 6 or 7 (4961554)
9. exp Pain/ (1138211)
10. (pain* or nocicept* or neuropath*).mp. (1310694)
11. 9 or 10 (1578116)
12. (random* or factorial* or crossover or "cross-over" or cross-over).tw. (1253752)
13. (placebo* or (doubl* adj blind*) or (singl* adj blind*)).tw. (331489)
14. (assign* or allocat*).tw. (420484)
15. crossover procedure/ (55966)
16. double-blind procedure/ (142603)
17. Randomized Controlled Trial/ (488123)
18. 12 or 13 or 14 or 15 or 16 or 17 (1675367)
19. 5 and 8 and 11 and 18 (2529)

Appendix 4. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

1. **High**: randomised trials; or double-upgraded observational studies.
2. **Moderate**: downgraded randomised trials; or upgraded observational studies.
3. **Low**: double-downgraded randomised trials; or observational studies.
4. **Very low**: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

1. limitations in the design and implementation of available studies suggesting high likelihood of bias;
2. indirectness of evidence (indirect population, intervention, control, outcomes);
3. unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
4. imprecision of results (wide confidence intervals);
5. high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

1. large magnitude of effect;
2. all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;

3. dose-response gradient.

Appendix 5. Summary of results in individual studies: efficacy

Study	Intervention	Participants with at least 50% and at least 30% reduction in pain	Participants with pain no worse than mild	Participants with PGIC of much improved or very much improved	Other measures of pain intensity or pain relief
NSAID versus NSAID					
Gallucci 1992	Nimesulide 2 x 200 mg daily, n = 34 Naproxen 2 x 500 mg daily, n = 34	No data	No data	No data	In participants completing 2 weeks (43) Integrated Score reduced by 65% with nimesulide and 70% with naproxen. No significant difference between groups
Minotti 1989	Diclofenac Na (Voltaren) 4 x 50 mg daily, n = 33 Nefopam 4 x 60 mg daily, n = 33 Aspirin + codeine 4 x 640 mg + 40 mg daily, n = 33	Responder defined as ≥ 50% PI reduction or PI ≤ 40/100 But individual data given only for pain ≥40/100 mm on day 2		No data	Mean PR: Diclofenac 20/100 Nefopam 18/100 Codeine + aspirin 19/100
Mohammadinejad 2015	Celecoxib 2 x 200 mg daily, n = 28 (26) Diclofenac 2 x 50 mg daily, n = 28 (26)	No data	No data	No data	No difference between groups at baseline or end of study Mean PI reduced from about 60/100 to about 45/100
Pannuti 1999	Ketorolac 3 x 10 mg daily Diclofenac 50 mg 3 x 50 mg daily Cross-over, n = 137	No data	No data	PGE "good or complete": Ketorolac 34/128 Diclofenac 33/129 PGE "moderate, good or complete": Ketorolac 83/128 Diclofenac 74/129	15 participants had relief with ketorolac but not diclofenac; 14 participants had relief with diclofenac but not ketorolac
Rodriguez 2003	Dexketoprofen trometamol 4 x 25 mg daily, n = 57 Ketorolac 4 x 10 mg daily, n = 58	No data	PI < 30/100 at end of study: Dexketoprofen 31/56 Ketorolac 27/57	Overall efficacy of medication quite or very effective: Dexketoprofen 76% Ketorolac 67%	PID ≥ 20/100 at end of study: Dexketoprofen 42/56 Ketorolac 37/57

(Continued)

Toscani 1994	Ketorolac 4 x 10 mg daily, n = 50 Diclofenac Na 3 x 50 mg daily, n = 50		No data	No data	Pain Integrated Score halved in first week (mostly by 1 day) from about 40 to 20 Patients remaining on treatment > 14 days: Ketorolac 20/50 Diclofenac 15/50 Mean time to step II: Ketorolac 58 (SD 46, median 41) days Diclofenac 33 (SD 15, median 27) days NSD
Turnbull 1986	Naproxen 2 x 500 mg daily, n = 28 Aspirin 6 x 600 mg daily, n = 28	No data	No data	No data	PI reduced by about 15/100 in both groups, with large SDs
Ventafrida 1990a	Naproxen Na 2 x 550 mg daily, n = 50 Diclofenac Na 2 x 100 mg daily n = 50	No data	No data	No data	Mean Integrated Pain Score decreased by ˜25 points in both groups (> halved) to 15.7 with naproxen and 17 with diclofenac [judged equivalent to < 35/100 on VAS] In participants who switched to step II Treatment for ≥ 14 days: Naproxen 14/33 Diclofenac 8/32
Yalçin 1998	Diflunisal 2 x 500 mg daily Dipyrone 3 x 500 mg daily Cross-over, n = 50	No data	No data	No data	Mean reduction in PI (scale 0 - 10): Diflunisal 4.7 (SD 3.1) Dipyrone 3.3 (SD 2.9)
NSAID versus opioid					
Carlson 1990	Ketorolac tromethamine 4 x 10 mg daily, n = 34 Paracetamol + codeine 4 x 600 mg/60 mg daily, n = 40	No data	No data	No data	Mean daily PR greater for combination than ketorolac over 7 days; statistically significant for days 2 and 4 Mean daily medication ratings similar - no difference between treatments
Minotti 1989	See above				
Rodriguez 1994	Dipyrone 3 x 1000 mg daily, n = 41 Dipyrone 3 x 2000 mg daily, n = 38	≥ 50% pain improvement: Day 3	No data	No data	Decrease in mean PI on day 7: Dipyrone 3000 mg 30.9 (SD 32.6) Dipyrone 6000 mg 39.8 (SD 28.6) Morphine 60 mg 42.6 (SD 32.9)

(Continued)

	Morphine 6 x 10 mg daily, n = 42 Dose could be increased on day 4: up to 3 x 2000 mg dipyrone, and 6 x 30 mg morphine	Dipyrone 3000 mg 5% (2/41) Dipyrone 6000 mg 8% (3/38) Morphine 60 mg 25% (10/42) Day 5 Dipyrone 3000 mg 12% (5/41) Dipyrone 6000 mg 48% (15/38) Morphine 60 mg 39% (20/42)

n: number of participants in treatment arm; Na: sodium; PGE: Patient Global Evaluation; PGIC: Patient Global Impression of Change; PI: pain intensity; PID: pain intensity difference; PR: pain relief; SD: standard deviation

Appendix 6. Summary of results in individual studies: rescue medication, adverse events, withdrawals

Study	Intervention	Use of rescue or breakthrough medication	Participants with any adverse event and serious adverse events	Participants with specific adverse events	Withdrawals
NSAID versus NSAID					
Gallucci 1992	Nimesulide 2 x 200 mg daily, n = 34 Naproxen 2 x 500 mg daily, n = 34	No data	Any AE: no data SAE: none specifically reported Deaths: Nimesulide 5/34 Naproxen 9/34	Somnolence: Nimesulide 6/34 Naproxen 6/34 Dyspepsia: Nimesulide 18/34 Naproxen 12/34	AE: Nimesulide 4/34 Naproxen 6/34 (gastric pain, haemorrhage, vomiting) Participant refusal or lost to follow-up: Nimesulide 3/34 Naproxen 1/34 Shift to step II: Nimesulide 22/34 Naproxen 18/34
Minotti 1989	Diclofenac Na (Voltaren) 4 x 50 mg daily, n = 33 Nefopam 4 x 60 mg daily, n = 33 Aspirin + codeine 4 x 640 mg + 40 mg daily, n = 33	No data	Any AE: no data SAE: none reported	Somnolence: Diclofenac 0/33 Nefopam 2/33 Aspirin + codeine 4/33 Dyspepsia:	All cause: Diclofenac 23/33 Nefopam 29/33 Codeine + aspirin 21/33 AE: Diclofenac 1/33 Nefopam 5/33 Codeine aspirin 6/33

(Continued)

				Diclofenac 0/33 Nefopam 3/33 Aspirin + codeine 1/33	LoE: Diclofenac 16/33 Nefopam 14/33 Codeine + aspirin 10/33 LoE + AE: Nefopam 1/33 Participant refusal: Nefopam 2/33 Exclusion criteria occurred during trial: Diclofenac 4/33 Nefopam 4/33 Codeine + aspirin 1/33 Other: Diclofenac 2/33 Nefopam 3/33 Codeine + aspirin 4/33
Mohammadinejad 2015	Celecoxib 2 x 200 mg daily, n = 28 (26) Diclofenac 2 x 50 mg daily, n = 28 (26)	No data	Any AE: no data SAE: none	Dyspepsia: Celecoxib 2/28 Diclofenac 5/28	AE: none 2 participants in each group withdrew before 3 weeks because depression worsened from moderate to severe
Pannuti 1999	Ketorolac 3 x 10 mg daily Diclofenac 50 mg 3 x 50 mg daily Cross-over, n = 137	No data	Any AE: Ketorolac 10/128 (8%) Diclofenac 7/129 (5%) Most mild or moderate SAE: none reported	Dyspepsia: Ketorolac 6/128 Diclofenac 5/129	All cause: Ketorolac 10/128 Diclofenac 15/129 (due to intolerance [AE] 2, LoE 23 - group not given)
Rodriguez 2003	Dexketoprofen trometamol 4 x 25 mg daily, n = 57 Ketorolac 4 x 10 mg daily, n = 58	Dexketoprofen 71% Ketorolac 72% Median number of tablets (25 - 75 percentile) Dexketo 3 (0 - 10) Ketorolac 6 (0 - 12)	Any AE: Dexketoprofen 19/57 Ketorolac 20/58 [Note, these data from text. Data in table 6 indicated dexketoprofen 12 and ketorolac 19 - but 'treatment-related'. Unable to reconcile] Most of mild to moderate intensity SAE: Dexketoprofen 2/57 Ketorolac 2/58	Dyspepsia: Dexketoprofen 3/57 Ketorolac 3/58	1 participant in each group had missing post-baseline efficacy data AE: Dexketoprofen 1/57 (death due to progression of disease) Ketorolac 5/58 LoE: Dexketoprofen 1/57 Ketorolac 6/58 Concomitant disease/other treatments: Dexketoprofen 3/57 Ketorolac 2/58
Toscani 1994	Ketorolac 4 x 10 mg daily, n = 50	No data	Any "symptoms" of high intensity	Somnolence:	AE: "none due to drug treatment"

(Continued)

	Diclofenac Na 3 x 50 mg daily, n = 50		1st week: Ketorolac 20/50 Diclofenac 26/50 2nd week: Ketorolac 15/50 Diclofenac 21/50	Ketorolac 2/50 Diclofenac 4/50 Anorexia: Ketorolac 1/50 Diclofenac 6/50 Dry mouth: Ketorolac 4/50 Diclofenac 5/50 Dyspepsia: Ketorolac 2/50 Diclofenac 2/50	Compliance issues: Ketorolac 4/50 Dicofenac 7/50 Participant request/lost to follow-up: Ketorolac 3/50 Dicofenac 3/50
Turnbull 1986	Naproxen 2 x 500 mg daily, n = 28 Aspirin 6 x 600 mg daily, n = 28	No data	"No side effects were reported and haematological and biochemical parameters did not significantly alter during the study" SAE: 2 deaths not related to study drugs	None	All cause: 5/28 LoE: 1 with naproxen Particiapnt decision: 2 due to number of tablets to be taken
Ventafrida 1990a	Naproxen Na 2 x 550 mg daily, n = 50 Diclofenac Na 2 x 100 mg daily n = 50	No data	Any AE: no data Deaths: Naproxen 2/50 Diclofenac 2/50	Somnolence: Naproxen 4/50 Diclofenac 10/50 Dry mouth: Naproxen 6/50 Diclofenac 8/50 Dyspepsia: Naproxen 6/50 Diclofenac 8/50	All cause: Naproxen 17/50 Diclofenac 18/50 AE: Naproxen 1/50 (GIH) Diclofenac 0/50 Start of other treatment: Naproxen 11/50 Diclofenac 12/50 Lost to follow-up Naproxen 2/50 Diclofenac 3/50 Participant decision: Naproxen 1/50 Pain resolved: Diclofenac 1/50 Move to step II LoE: Naproxen 25/50 Diclofenac 25/50 AEs: Naproxen 4/50 Diclofenac 5/50 Both:

(Continued)

					Naproxen 4/50 Diclofenac 2/50
Yalçin 1998	Diflunisal 2 x 500 mg daily Dipyrone 3 x 500 mg daily Cross-over, n = 50	No rescue medication allowed	Any AE: no data SAE: 1 death due to disseminated malignancy (treatment at time not given)	Somnolence: Diflunisal 0/50 Dipyrone 2/50 Anorexia: Diflunisal 2/50 Dipyrone 1/50 Dyspepsia: Diflunisal 2/50 Dipyrone 1/50	AE: none 2 participants lost to follow-up
NSAID versus opioid					
Carlson 1990	Ketorolac tromethamine 4 x 10 mg daily, n = 34 Paracetamol + codeine 4 x 600 mg/60 mg daily, n = 40	No data	Any AE: Ketorolac 21/34 Paracetamol + codeine 19/40 SAE: none reported	Somnolence: Ketorolac 1/34 Paracetamol + codeine 3/40 Anorexia: Ketorolac 1/34 Paracetamol + codeine 1/40 Dry mouth: Ketorolac 0/34 Paracetamol + codeine 2/40 Dyspepsia: Ketorolac 5/34 Paracetamol + codeine 4/40	All cause: Ketorolac 17/34 Paracetamol + codeine 27/40 LoE: Ketorolac 8/34 Paracetamol + codeine 7/40 AE: Ketorolac 5/34 Paracetamol + codeine 4/40 AE and LoE: Ketorolac 3/34 Paracetamol+ codeine 0/40 Other medical problems Ketorolac 2/34 Paracetamol + codeine 1/40
Minotti 1989	See above				
Rodriguez 1994	Dipyrone 3 x 1000 mg daily, n = 41 Dipyrone 3 x 2000 mg daily, n = 38 Morphine 6 x 10 mg daily, n = 42 Dose could be increased on day	Dipyrone 3000 mg 17/41 Dipyrone 6000 mg 21/38 Morphine 60 mg 14/42	Any AE: Dipyrone 3000 mg 27/41 Dipyrone 6000 mg 25/38 Morphine 34/42 Incidence and severity lower with dipyrone than morphine,	Somnolence: Dipyrone 3000 mg 4/41 Dipyrone 600 mg 9/38 Morphine 18/42 Anorexia:	No AE withdrawals

(Continued)

	4: up to 3 x 2000 mg dipyrone, and 6 x 30 mg morphine	but not statistically significant Tolerability good, excellent: Dipyrone 3000 mg 77% (32/41) Dipyrone 6000 mg 62% (20/38) Morphine 60 mg 49% (20/42) SAE: none reported	Dipyrone 3000 mg 0/41 Dipyrone 600 mg 0/38 Morphine 1/42 Dyspepsia: Dipyrone 3000 mg 0/41 Dipyrone 600 mg 1/38 Morphine 1/42

AE: adverse event; GIH: gastrointestinal haemorrhage; LoE: lack of effect; Na: sodium; SAE: serious adverse event

WHAT'S NEW

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest.
7 February 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 4, 2017
Review first published: Issue 7, 2017

Date	Event	Description
28 May 2019	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

RAM, SD, and PW drafted the protocol, and other authors commented on that draft to produce the final version.

SD and RAM searched for studies, carried out data extraction, and assessed risk of bias. SD, RAM, and PW prepared a draft of the full review, and all authors contributed to the final version.

DECLARATIONS OF INTEREST

PW: none known.

SD: none known.

RAM has received grant support from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake

(2015). He has received honoraria from Omega Pharma (2016) and Futura Pharma (2016) for providing advice on trial and data analysis methods.

EDM: none known.

RFB: none known; RFB is a specialised pain physician and has managed patients with cancer pain.

DBC: none known; DBC is a specialised pain physician and has managed patients with cancer pain.

MM: none known.

BW: none known. BW is a specialist Palliative Medicine Consultant physician and manages patients with advanced life threatening illnesses, including cancer.

This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

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  NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Selective reporting bias added to risk of bias.

NOTES

A restricted search in January 2019 identified one potentially relevant study [Liu 2017; 342 participants], but we judged the results were unlikely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

Liu et al, Combined application of diclofenac and celecoxib with an opioid yields superior effcacy in metastatic bone cancer pain: a randomized controlled trial. Int J Clin Oncol (2017) 22:980–985. DOI 10.1007/s10147-017-1133-y

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics, Opioid [administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Cancer Pain [*drug therapy]; Randomized Controlled Trials as Topic; Withholding Treatment [statistics & numerical data]

MeSH check words

Adult; Humans