Cochrane Library

Cochrane Database of Systematic Reviews

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

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

Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B.
Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012638.
DOI: 10.1002/14651858.CD012638.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Sheena Derry[1], Philip J Wiffen[1], R Andrew Moore[1], Ewan D McNicol[2], Rae F Bell[3], Daniel B Carr[4], Mairead McIntyre[5], Bee Wee[6]

[1]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [2]Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, Massachusetts, USA. [3]Research Fellow Regional Centre of Excellence in Palliative Care, Haukeland University Hospital, Bergen, Norway. [4]Pain Research, Education and Policy (PREP) Program, Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA. [5]West Hoe Surgery, Plymouth, UK. [6]Nuffield Department of Medicine and Sir Michael Sobell House, Churchill Hospital, Oxford, UK

Contact address: R Andrew Moore, Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. andrew.moore@ndcn.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012638. DOI: 10.1002/14651858.CD012638.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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

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 protocol is for 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. The other review will examine oral paracetamol (acetaminophen) for cancer pain in both adults and children.

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. 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 post-surgical pain related to surgery or neuropathic pain related specifically to chemotherapy or nerve pressure.

The current World Health Organisation (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 2016). 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) 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 aim to provide 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 synthesise prostaglandins that are involved in inflammation and pain. The analgesic and anti-inflammatory actions of NSAIDs are attributed to the inhibition of cyclooxygenase-2 (COX-2), while their adverse gastrointestinal effects are attributed to the inhibition of cyclooxygenase-1 (COX-1). 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 in a similar way to steroids, but without the side effects observed with steroids. Conventional NSAIDs (aspirin, ibuprofen, diclofenac, indomethacin, naproxen, and piroxicam) block COX-1 and COX-2 enzymes unselectively. Selective COX-2 inhibiting NSAIDs (celecoxib, etoricoxib) inhibit the COX-2 enzyme with a 5 to 50 fold selectivity (Brune 2004).

NSAIDs are responsible for 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 (Nabal 2011) 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 leaves many people with cancer at risk of severe life-limiting pain unless non-opioid analgesics can be used. This review will inform 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 2017). 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 2014a). 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 2013b). 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 associated with their use in clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

To be included, studies must:

- be randomised (described as 'randomised' anywhere in the manuscript);
- ideally be double-blind, but we will include single-blind or open studies because we expect there to be a limited literature on this important topic, and we desire to be as inclusive as possible;
- ideally include a minimum of 25 participants per treatment arm; for crossover studies this will mean 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 will exclude non-randomised studies, studies of experimental pain, case reports and clinical observations. Studies have to be fully

published or available as extended abstracts (e.g. from clinical trial websites); we will exclude 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

Studies will include adults (18 years or older) who experience cancer pain.

Types of interventions

Orally administered NSAID for cancer pain where the NSAID alone is 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 must 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 4-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 5-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).

When considering Patient Global Impression of Change (PGIC), 30% or greater reduction of pain over baseline equates to much improved and very much improved, and 50% or greater reduction of pain over baseline equates to very much improved. We will 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 will search the following databases, without language or date restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO).
- MEDLINE (via Ovid).
- Embase (via Ovid).

We will use a combination of MeSH or equivalent and text word terms and tailor search strategies to individual databases. The search strategy for MEDLINE is in Appendix 1.

Searching other resources

We will search 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 trials. In addition, we will check reference lists of reviews and retrieved articles for additional studies and perform citation searches on key articles. We do not plan to contact authors for additional information.

Data collection and analysis

Selection of studies

Two review authors (RAM, SD) will independently read the abstract of each study identified by the search, eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors (RAM, SD) will read these studies independently to select relevant studies for inclusion. In the event of disagreement, a third review author (PW) will adjudicate. We will not anonymise the studies before assessment. We will include 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 will include studies in the review, irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors (RAM, SD) will independently extract data using a standard form and check for agreement before entry into Review Manager (RevMan) (RevMan 2014). We will include 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 will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect 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) will independently assess 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 will complete a 'risk of bias' table for each included study, using the 'risk of bias' tool in RevMan (RevMan 2014). We will assess the following for each study.

- Random sequence generation (checking for possible selection bias). We will assess 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 will exclude 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 will assess 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 (studies that do not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess methods as: low risk of bias (study states that it was blinded and describes 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 states that it was blinded but does 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 will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks 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 will assess 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).
- Size of study (checking for possible biases confounded by small size (Dechartes 2013; Dechartres 2014; Moore 1998; Nüesch 2010; Thorlund 2011)). We will assess 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 will use dichotomous data to calculate risk difference (RD) or risk ratio (RR) with 95% confidence intervals (CI) 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 we will calculate this in the same manner.

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

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

We do 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 will be the individual participant.

Dealing with missing data

We plan 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 will report per-protocol data in the absence of ITT data.

Assessment of heterogeneity

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

Assessment of reporting biases

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

We will undertake an assessment of publication bias if there are 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).

Data synthesis

If data are sufficient, we will undertake a quantitative synthesis and present data in forest plots. In the event of substantial clinical heterogeneity, we will switch off the totals in the forest plots.

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

Quality of the evidence

We will use the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 2). Two review authors (RAM, SD) will independently rate the quality of each outcome.

We will pay 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 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 are no data reported for an outcome, we will report 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 will include 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 plan to include 'Summary of findings' table(s) to present the main findings in a transparent and simple tabular format. We will 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, and adverse events.

For the 'Summary of findings' table we will use 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 plan several possible subgroup analyses, depending on the availability of data.

1. Because we expect that many studies will have a cross-over design that can impede meta-analysis (Elbourne 2002), we plan to examine cross-over and parallel-group designs separately.
2. We will investigate whether subgroup analysis can be undertaken by individual drug or dose.
3. We will analyse separately studies with NSAID alone, and NSAID combined with opioid. These studies may also reflect different levels of initial pain intensity.

We plan no other subgroup analyses because the data are expected to be sparse, with small numbers of small trials.

Sensitivity analysis

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

ACKNOWLEDGEMENTS

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Review Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), or the Department of Health.

Institutional support was provided by the Oxford Pain Relief Trust.

REFERENCES

Additional references

AlBalawi 2013
AlBalawi Z, McAlister FA, Thorlund K, Wong M, Wetterslev J. Random error in cardiovascular meta-analyses: how common are false positive and false negative results? . *Interational Journal of Cardiology* 2013;**168**(2):1102–7. [DOI: 10.1016/j.ijcard.2012.11.048

Azevedo São Leão Ferreira 2006
Azevedo São Leão Ferreira K, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it?. *Support Care Cancer* 2006;**14**(11):1086–93. [DOI: 10.1016/j.critrevonc.2013.01.001

Bao 2016
Bao YJ, Hou W, Kong XY, Yang L, Xia J, Hua BJ, et al. Hydromorphone for cancer pain. *Cochrane Database of Systematic Reviews* 2016, Issue 10. [DOI: 10.1002/14651858.CD011108.pub2

Breivik 2009
Breivik H, Cherny N, Collett B, De Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Annals of Oncology* 2009;**20**(8):1420–33. [DOI: 10.1093/annonc/mdp001

Brok 2009
Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287–98. [DOI: 10.1093/ije/dyn188

Brune 2004
Brune K, Hinz B. The discovery and development of anti-inflammatory drugs. *Arthritis and Rheumatology* 2004;**50**(8):2391–9. [DOI: 10.1002/art.20424

Brune 2015
Brune K, Patrignani P. New insights into the use of currently available nonsteroidal anti-inflammatory drugs. *Journal of Pain Research* 2015;**8**:105–18. [DOI: 10.2147/JPR.S75160

Cancer Research UK 2016
Cancer Statistics for the UK. www.cancerresearchuk.org/health-professional/cancer-statistics (accessed 7 February 2017).

Carlson 2016
Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *Journal of Pain Research* 2016;**9**:515–34. [10.2147/JPR.S97759. eCollection 2016]

Chell 2005
Chell S, Patsos HA, Qualtrough D, H-Zadeh AM, Hicks DJ, Kaidi A, et al. Prospects in NSAID-derived chemoprevention of colorectal cancer. *Biochemical Society Transactions* 2005;**33**(Pt 4):667–71.

CNT 2014
Coxib and Traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of nonsteroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2014;**382**(9894):769–79. [DOI: 10.1016/S0140-6736(13)60900-9

Deandrea 2008
Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Annals of Oncology* 2008;**19**(12):1985–91. [DOI: 10.1093/annonc/mdn419

Dechartes 2013
Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;**346**:f2304. [DOI: 10.1136/bmj.f2304

Dechartres 2014
Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. *JAMA* 2014;**312**: 623–30. [DOI: 10.1001/jama.2014.8166

Deng 2012
Deng D, Fu L, Zhao YX, Wu X, Zhang G, Liang C, et al. The relationship between cancer pain and quality of life in patients newly admitted to Wuhan Hospice Center of China. *American Journal of Hospital Palliative Care* 2012;**29** (1):53–9. [DOI: 10.1177/1049909111418636

Derry 2014
Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 12. [DOI: 10.1002/14651858.CD009281.pub3

Dreidi 2016
Dreidi MM, Hamdan-Mansour AM. Pain, sleep disturbance, and quality of life among Palestinian patients diagnosed with cancer. *Journal of Cancer Education* 2016; **31**(4):796–803. [DOI: 10.1007/s13187-015-0946-5

Dwivedi 2015
Dwivedi AK, Gurjar V, Kumar S, Singh N. Molecular basis for nonspecificity of nonsteroidal anti-inflammatory drugs (NSAIDs). *Drug Discovery Today* 2015;**20**(7):863–73. [DOI: 10.1016/j.drudis.2015.03.004

Dworkin 2008
Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;**9**(2): 105–21. [DOI: 10.1016/j.jpain.2007.09.005

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

EMEA 2005
European Medicines Agency. EMEA public statement on the suspension of the marketing authorisation for Bextra (valdecoxib) in the European Union. ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018391.pdf (accessed 7 February 2017).

EPOC 2015
Effective Practice, Organisation of Care (EPOC). 23. Worksheets for preparing a Summary of Findings using GRADE. Resources for review authors. epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 7 February 2017).

Fanelli 2017
Fanelli D, Costas R, Ioannidis JP. Meta-assessment of bias in science. *Proceedings of the National Academy of Sciences of the United States of America* 2017;**epub**. [DOI: 10.1073/pnas.1618569114

FDA 2004
Food, Drug Administration. FDA Public Health Advisory: safety of Vioxx. fda.gov/drugs/drugSafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm106274.htm (accessed 7 February 2017).

Gavaghan 2000
Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. *Pain* 2000;**85**(3): 415–24.

Guyatt 2011
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Cinical Epidemiology* 2011;**64**(12):1294–302. [DOI: 10.1016/j.jclinepi.2011.03.017

Guyatt 2013a
Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *Journal of Clinical Epidemiology* 2013;**66**:151–7. [DOI: 10.1016/j.jclinepi.2012.01.006

Guyatt 2013b
Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**:158–72. [DOI: 10.1016/j.jclinepi.2012.01.012

Hadley 2013
Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD010270.pub2

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hinz 2007
Hinz B, Cheremina O, Bachmakov J, Renner B, Zolk O, Fromm MF, et al. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. *Federation of American Societies for Experimental Biology Journal* 2007;**21** (10):2343–51. [DOI: 10.1096/fj.06-8061com

Hinz 2008
Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *Federation of American Societies for Experimental*

Biology Journal 2008;**22**(2):383–90. [DOI: 10.1096/fj.07-8506com

Häuser 2012

Häuser W, Jung E, Erbslöh-Möller B, Gesmann M, Kühn-Becker H, Petermann F, et al. The German fibromyalgia consumer reports - a cross-sectional survey. *BMC Musculoskeletal Disorders* 2012;**13**:74. [DOI: 10.1186/1471-2474-13-74

IARC 2012

International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (accessed 7 February 2017).

IntHout 2015

IntHout J, Ioannidis JP, Borm GF, Goeman JJ. Small studies are more heterogeneous than large ones: a meta-meta-analysis. *Journal of Clinical Epidemiology* 2015;**68**:860–9. [DOI: 10.1016/j.jclinepi.2015.03.017

Jadad 1995

Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of Its evaluation. *JAMA* 1995;**274**(23):1870–3.

Laine 2001

Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;**120**(3):594–606. [DOI: 10.1053/gast.2001.21907

Mangoni 2010

Mangoni AA, Woodman RJ, Gaganis P, Gilbert AL, Knights KM. Use of nonsteroidal anti-inflammatory drugs and risk of incident myocardial infarction and heart failure, and all-cause mortality in the Australian veteran community. *British Journal of Clinical Pharmacology* 2010;**69**(6):689–700. [DOI: 10.1111/j.1365-2125.2010.03627.x

McQuay 1998

McQuay H, Moore A. *An Evidence-based Resource for Pain Relief*. Oxford: Oxford University Press, 1998. [ISBN: 0–19–263048–2]

McQuay 2005

McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005;**81**(953):155–60. [DOI: 10.1136/pgmj.2004.024737

McQuay 2007

McQuay HJ, Moore RA. Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *British Journal of Cinical Pharmacology* 2014;**63**(3):271–8. [DOI: 10.1111/j.1365-2125.2006.02723.x

Mercadante 2013

Mercadante S, Giarratano A. The long and winding road of nonsteroidal anti-inflammatory drugs and paracetamol in cancer pain management: a critical review. *Critical Reviews in Oncology/Hematology* 2013;**87**:140–5. [DOI: 10.1016/j.critrevonc.2013.01.001

Mikan 2016

Mikan F, Wada M, Yamada M, Takahashi A, Onishi H, Ishida M, et al. The association between pain and quality of life for patients with cancer in an outpatient clinic, an inpatient oncology ward, and inpatient palliative care units. *American Journal of Hospital Palliative Care* 2016;**33**(8):782–90. [DOI: 10.1177/1049909116630266

Moore 1998

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

Moore 2008

Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic Reviews in Pain Research: Methodology Refined*. Seattle: IASP Press, 2008:15–24. [ISBN: 978-0-931092-69-5]

Moore 2010

Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Annals of the Rheumatic Diseases* 2010;**69**(2):374–9. [DOI: 10.1136/ard.2009.107805

Moore 2013a

Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**(4):400–12. [DOI: 10.1111/anae.12148

Moore 2013b

Moore RA, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Practice* 2014;**14**(1):79–94. [DOI: 10.1111/papr.12050

Moore 2014a

Moore RA. What works for whom? Determining the efficacy and harm of treatments for pain. *Pain* 2013;**154 Suppl 1**:S77–86. [DOI: 10.1016/j.pain.2013.03.024

Moore 2014b

Moore RA, Derry S, Simon LS, Emery P. Nonsteroidal anti-inflammatory drugs, gastroprotection, and benefit-risk. *Pain Practice* 2014;**14**(4):378–95. [DOI: 10.1111/papr.12100

Nabal 2011

Nabal M, Librada S, Redondo MJ, Pigni A, Brunelli C, Caraceni A. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. a systematic review of the literature. *Palliative Medicine* 2012;**26**(4):305–12. [DOI: 10.1177/0269216311428528

Nguyen 2017

Nguyen TL, Collins GS, Lamy A, Devereaux PJ, Daurès JP, Landais P, et al. Simple randomization did not protect

against bias in smaller trials. *Journal of Clinical Epidemiology* 2017;**epub**. [DOI: 10.1016/j.jclinepi.2017.02.010

NICE 2016
National Institute for Health and Care Excellence. Palliative cancer care - pain. cks.nice.org.uk/palliative-cancer-care-pain (accessed 7 February 2017).

Nüesch 2010
Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515. [DOI: 10.1136/bmj.c3515

PaPaS 2012
Cochrane Pain, Palliative and Supportive Care Group. PaPaS author and referee guidance. papas.cochrane.org/papas-documents (accessed 7 February 2017).

Portenoy 1999
Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999;**353**(9165):1695–700. [DOI: 10.1016/S0140-6736(99)01310-0

Prommer 2015
Prommer EE. Pharmacological management of cancer-related pain. *Cancer Control* 2015;**22**(4):412–25. [PUBMED: 26678968]

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2015
Roberts I, Ker K, Edwards P, Beecher D, Manno D, Sydenham E. The knowledge system underpinning healthcare is not fit for purpose and must change. *BMJ* 2015;**350**:h2463. [DOI: 10.1136/bmj.h2463

Schmidt-Hansen 2015a
Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart JS. Buprenorphine for treating cancer pain. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD009596.pub4

Schmidt-Hansen 2015b
Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD003870.pub5

Sheen 2002
Sheen CL, Dillon JF, Bateman DN, Simpson KJ, MacDonald TM. Paracetamol pack size restriction: the impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen.. *Pharmacoepidemiology and Drug Safety* 2002;**11**(4):329–31. [DOI: 10.1002/pds.701

Straube 2014
Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD006601.pub4

Thorlund 2011
Thorlund K, Imberger G, Walsh M, Chu R, Gluud C, Wetterslev J, et al. The number of patients and events required to limit the risk of overestimation of intervention effects in meta-analysis - a simulation study. *PLOS One* 2011;**6**(10):e25491. [DOI: 10.1371/journal.pone.0025491

Turner 2013
Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLOS One* 2013;**8**(3):e59202. [DOI: 10.1371/journal.pone.0059202

Twycross 2014
Twycross R, Wilcock A, Howard P. *Palliative Care Formulary*. PCF5. Nottingham: Palliativedrugs.com Ltd, 2014. [ISBN: 978–0–9552547–9–6]

Van den Beuken-van Everdingen 2016
Van den Beuken-van Everdingen MHJ, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *Journal of Pain and Symptom Management* 2016;**51**:1070–90. [DOI: 10.1016/j.jpainsymman.2015.12.340

Wender 2015
Wender RC. Aspirin and NSAID chemoprevention, gene-environment interactions, and risk of colorectal cancer. *JAMA* 2015;**313**(11):1111–2. [DOI: 10.1001/jama.2015.1032

WHO 2016
Anonymous. WHO analgesic ladder. who.int/cancer/palliative/painladder/en/ (accessed 7 February 2017).

Wiffen 2014
Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD011056.pub2

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 2017
Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: 10.1002/14651858.CD012508

Wolfe 2014
Wolfe F, Walitt BT, Katz RS, Lee YC, Michaud KD, Häuser W. Longitudinal patterns of analgesic and central

acting drug use and associated effectiveness in fibromyalgia. *European Journal of Pain* 2014;**17**(4):581–6. [DOI: 10.1002/j.1532-2149.2012.00234.x

References to other published versions of this review

McNicol 2015

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*

APPENDICES

Appendix 1. Search strategy for MEDLINE (via Ovid)

1. exp Anti-Inflammatory Agents, Non-Steroidal/
2. (NSAID* or "non-steroidal anti-inflammatory drug*".tw.
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/
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
5. 1 or 2 or 3
6. exp Neoplasms/
7. (neoplasm* or malignan* or tumour* or tumor* or cancer* or carcinoma*).mp.
8. 5 or 6
9. exp Pain/
10. (pain* or nocicept* or neuropath*).mp.
11. 8 or 9
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 5 and 8 and 11 and 19

Appendix 2. 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.

CONTRIBUTIONS OF AUTHORS

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

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.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support

External sources

- The National Institute for Health Research (NIHR), UK.

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