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Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD003868.

DOI: [10.1002/14651858.CD003868.pub4](https://doi.org/10.1002/14651858.CD003868.pub4).

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[Intervention Review]

Oral morphine for cancer pain

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 3, 2021.

Citation: Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD003868. DOI: [10.1002/14651858.CD003868.pub4](https://doi.org/10.1002/14651858.CD003868.pub4).

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ABSTRACT

Background

This is the third updated version of a Cochrane review first published in Issue 4, 2003 of *The Cochrane Library* and first updated in 2007. Morphine has been used for many years to relieve pain. Oral morphine in either immediate release or modified release form remains the analgesic of choice for moderate or severe cancer pain.

Objectives

To determine the efficacy of oral morphine in relieving cancer pain, and to assess the incidence and severity of adverse events.

Search methods

We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 9); MEDLINE (1966 to October 2015); and EMBASE (1974 to October 2015). We also searched ClinicalTrials.gov (1 October 2015).

Selection criteria

Published randomised controlled trials (RCTs) using placebo or active comparators reporting on the analgesic effect of oral morphine in adults and children with cancer pain. We excluded trials with fewer than 10 participants.

Data collection and analysis

One review author extracted data, which were checked by another review author. There were insufficient comparable data for meta-analysis to be undertaken or to produce numbers needed to treat (NNTs) for the analgesic effect. We extracted any available data on the number or proportion of participants with 'no worse than mild pain' or treatment success (very satisfied, or very good or excellent on patient global impression scales).

Main results

We identified seven new studies in this update. We excluded six, and one study is ongoing so also not included in this update. This review contains a total of 62 included studies, with 4241 participants. Thirty-six studies used a cross-over design ranging from one to 15 days, with the greatest number (11) for seven days for each arm of the trial. Overall we judged the included studies to be at high risk of bias because the methods of randomisation and allocation concealment were poorly reported. The primary outcomes for this review were participant-reported pain and pain relief.

Fifteen studies compared oral morphine modified release (Mm/r) preparations with morphine immediate release (MIR). Fourteen studies compared Mm/r in different strengths; six of these included 24-hour modified release products. Fifteen studies compared Mm/r with other opioids. Six studies compared MIR with other opioids. Two studies compared oral Mm/r with rectal Mm/r. Three studies compared MIR with MIR by a different route of administration. Two studies compared Mm/r with Mm/r at different times and two compared MIR with MIR given

at a different time. One study was found comparing each of the following: Mm/r tablet with Mm/r suspension; Mm/r with non-opioids; MIR with non-opioids; and oral morphine with epidural morphine.

In the previous update, a standard of 'no worse than mild pain' was set, equivalent to a score of 30/100 mm or less on a visual analogue pain intensity scale (VAS), or the equivalent in other pain scales. Eighteen studies achieved this level of pain relief on average, and no study reported that good levels of pain relief were not attained. Where results were reported for individual participants in 17 studies, 'no worse than mild pain' was achieved by 96% of participants (362/377), and an outcome equivalent to treatment success in 63% (400/638).

Morphine is an effective analgesic for cancer pain. Pain relief did not differ between Mm/r and MIR. Modified release versions of morphine were effective for 12- or 24-hour dosing depending on the formulation. Daily doses in studies ranged from 25 mg to 2000 mg with an average of between 100 mg and 250 mg. Dose titration was undertaken with both instant release and modified release products. A small number of participants did not achieve adequate analgesia with morphine. Adverse events were common, predictable, and approximately 6% of participants discontinued treatment with morphine because of intolerable adverse events.

The quality of the evidence is generally poor. Studies are old, often small, and were largely carried out for registration purposes and therefore were only designed to show equivalence between different formulations.

Authors' conclusions

The conclusions have not changed for this update. The effectiveness of oral morphine has stood the test of time, but the randomised trial literature for morphine is small given the importance of this medicine. Most trials recruited fewer than 100 participants and did not provide appropriate data for meta-analysis. Only a few reported how many people had good pain relief, but where it was reported, over 90% had no worse than mild pain within a reasonably short time period. The review demonstrates the wide dose range of morphine used in studies, and that a small percentage of participants are unable to tolerate oral morphine. The review also shows the wide range of study designs, and inconsistency in cross-over designs. Trial design was frequently based on titration of morphine or comparator to achieve adequate analgesia, then crossing participants over in cross-over design studies. It was not clear if these trials were sufficiently powered to detect any clinical differences between formulations or comparator drugs. New studies added to the review for the previous update reinforced the view that it is possible to use modified release morphine to titrate to analgesic effect. There is qualitative evidence that oral morphine has much the same efficacy as other available opioids.

PLAIN LANGUAGE SUMMARY

Oral morphine for cancer pain

Background

Morphine taken by mouth produced good pain relief for most people with moderate or severe cancer pain.

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. Morphine taken by mouth has been used since the 1950s for controlling cancer pain. In 1986 the World Health Organization recommended taking an oral solution of morphine every four hours. Morphine is now available in a number of different formats that release the morphine over various periods of time. Morphine immediate release is rapidly absorbed, and would usually be taken every four hours. Modified release tablets are available that release morphine more slowly, so that they can be taken only twice a day or even only once a day.

Study characteristics

In this updated review we set out to estimate how well morphine worked, how many people had side effects, and how severe those side effects were – for example, whether they were so severe that participants stopped taking their oral morphine.

We found 62 studies with 4241 participants. The studies were often small, compared many different preparations, and used different study designs. This made it difficult to work out whether any one tablet or preparation of oral morphine was better than any other. There did not seem to be much difference between them.

Key findings

More than 9 in 10 participants had pain that went from moderate or severe before taking morphine to pain that was no worse than mild when taking morphine. More than 6 in 10 participants were very satisfied with the morphine treatment, or considered the result to be very good or excellent. Only about 1 person in 20 stopped taking morphine because of side effects. Morphine is associated with some unwanted effects, mainly constipation, and nausea and vomiting.

Quality of the evidence

At one level these are good results. On another level, the quality of studies is generally poor and we could wish for more consistency in study design, and especially in study reporting, which should include the outcome of pain reduced to tolerable levels – no worse than mild pain – so that people with cancer are not bothered by pain.

BACKGROUND

This review is the third update of a previously published review in *The Cochrane Library* (Issue 4, 2013) and first updated in 2007, evaluating the analgesic effects of oral morphine for cancer pain.

Trials of morphine have been equivalence studies, which have attempted to show either that one form of release system is as effective as another, or compared a newer opioid with morphine. However, this literature presents a number of methodological challenges as trials may not be sufficiently powered to detect differences in efficacy or to show equivalence. Two systematic reviews of morphine pharmacokinetics have been published (Collins 1998; Faura 1998). No differences in either efficacy or adverse events between morphine modified release (Mm/r) or morphine immediate release (MIR) were discerned in a systematic review using narrow inclusion criteria (Goudas 2001). The present review will bring together the randomised controlled trial (RCT) literature for oral morphine.

The term 'modified release' replaces the term 'sustained release' used in the first version of this review.

Description of the condition

Cancer pain is perhaps one of the most feared symptoms associated with the disease. Pain may be the first symptom that causes someone to seek medical advice that leads to a diagnosis of cancer and some 30% to 50% of all sufferers will experience moderate to severe pain (Portenoy 1999b). 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 1999b). For those with advanced cancer some 75% to 90% will experience pain that has a major impact on daily living.

Description of the intervention

Morphine in one form or another has been available for centuries, and appeared in Pliny's *Historia Naturalis* (AD 77) as opium, the resin derived from poppy sap. Morphine was extracted from opium in 1803 and named as such by Sertürner, a German pharmacist from Einbeck, in 1817 (Rey 1993). Oral morphine was first recommended in England in the 1950s for the treatment of cancer pain. This was often in the form of the so-called 'Brompton cocktail' containing cocaine and alcohol in addition to morphine or diamorphine. Treatment moved towards oral morphine alone as morphine demonstrated effective pain relief without the side effects linked to the 'cocktail'.

Following the publication of World Health Organization (WHO) guidelines in the mid-1980s, the oral administration of aqueous morphine solution every four hours by the clock became commonplace for moderate to severe cancer pain (WHO 1986). Morphine in a modified release tablet was first marketed around the same time, allowing the dosage interval to be extended to 12 hours.

Morphine, usually as the sulphate or hydrochloride salt, is available in four oral formulations: an elixir or solution of morphine in various concentrations; an immediate release tablet; a number of different preparations of modified release tablets or capsules; and modified release suspensions. Modified release tablets are available in both 12-hour and 24-hour release patterns and should be swallowed whole. Modified release capsules contain small coated beads and can be sprinkled over food, etc, if necessary. This review considered

all RCTs for all forms of oral morphine for cancer-related pain, defined as "pain of unspecified origin in any patient with cancer or a history of cancer". This review uses the convention as used by the British National Formulary, which uses the abbreviation m/r to describe modified release.

The wide range of formulations and dosages (10 mg to 150 mg) allows great flexibility in the management of severe pain (Grahame-Smith 2002). Potent opioid analgesics are particularly indicated for the relief of pain in malignant disease and often have the additional very useful actions of relieving anxiety, producing drowsiness, and allowing sleep (Grahame-Smith 2002). However, all opioid analgesics have the potential to produce adverse events: respiratory depression, nausea and vomiting, constipation, and itching. During chronic opioid therapy, larger doses may be required to sustain the analgesic effect (tolerance) and people can be at risk of opioid withdrawal syndrome upon sudden cessation of the opioid or administration of an antagonist (physiological dependence).

How the intervention might work

Morphine is known to bind to opioid receptors to produce pain relief (Mandal 2015). Three different receptors have been identified.

- Mu receptors (subdivided into μ_1 , μ_2 , and μ_3). These are found in the brainstem and the thalamus. Activation can result in pain relief, sedation, and euphoria, and can also lead to respiratory depression, constipation, and physical dependence.
- Kappa receptor. This is found in the limbic system, the brain stem, and spinal cord. Activation can result in pain relief, sedation, loss of breath, and dependence.
- Delta receptor. This is found in the brain, spinal cord, and digestive tract. Activation can result in analgesic as well as antidepressant effects. It can also lead to respiratory depression.

Why it is important to do this review

Morphine has long been considered the preferred choice of opioid. It is widely, though still not universally, available across the world, is comparatively cheap, and is effective orally. It is listed in the WHO essential medicines list (WHO 2011). The review is important to determine the effectiveness of morphine compared to other interventions used in cancer pain.

OBJECTIVES

To determine the efficacy of oral morphine in relieving cancer pain, and to assess the incidence and severity of adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), single or multiple dose, parallel or cross-over, of any duration were eligible for inclusion in this review. We excluded studies that did not state that they were randomised. We excluded quasi-randomised studies and trials with 10 or fewer participants (Moore 1998). We excluded studies that did not deal with cancer-related pain, or did not assess pain as an outcome measure. Full journal publication was an inclusion criterion.

Types of participants

Adults and children with cancer pain requiring treatment with opioids.

Types of interventions

Oral morphine preparations compared with either placebo, an alternative presentation of morphine, or an active control.

Types of outcome measures

Data collection included the following outcomes:

- participant-reported pain (physician-, nurse- or carer-reported pain measures were not included in the analysis);
- pain relief expressed using validated pain scales such as pain intensity and pain relief in the form of visual analogue scales or categorical scales, or both;
- type of pain;
- rescue medication;
- discontinuation of treatment for any reason;
- adverse events, major and minor.

It is becoming clear that the pain outcome desired by patients can be summarised as 'no worse than mild pain' (Moore 2013a), therefore we also looked for outcomes that might be equivalent to this. This was no or mild pain, $\leq 3/10$ on a numerical rating scale, or $\leq 30/100$ mm on a visual analogue scale. We also included patient outcome measures of satisfaction (usually very satisfied), or treatment success, or global impression of change (very good, excellent).

Primary outcomes

- Participant-reported pain (physician-, nurse- or carer-reported pain measures were not included in the analysis).
- Pain relief expressed using validated pain scales such as pain intensity and pain relief in the form of visual analogue scales or categorical scales, or both.

Secondary outcomes

- Rescue medication.
- Discontinuation of treatment for any reason.
- Adverse events, major and minor.

Search methods for identification of studies

We ran the search for the original review in December 2002 and ran a subsequent search for this update in October 2015.

For the identification of studies included or considered for inclusion in this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database. Please see [Appendix 1](#) for the MEDLINE search strategy, [Appendix 2](#) for the EMBASE strategy, and [Appendix 3](#) for the CENTRAL strategy.

Electronic searches

We searched the following databases, without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 10)
- MEDLINE (OVID) (1966 to 7 October 2015)
- EMBASE (OVID) (1974 to 7 October 2015)

The search attempted to identify all relevant studies irrespective of language. We assessed non-English language papers and translated as necessary.

Searching other resources

We searched clinicaltrials.gov on 1 October 2015.

Handsearching

A database of pain trials was developed by handsearching 40 key journals (Jadad 1996a). We searched this resource for the original review, and undertook no further handsearching for this review update.

Unpublished studies

We asked six pharmaceutical companies that market oral morphine products, as part of the initial review process, to provide data on published and unpublished RCTs as a check on our search strategy. We did not contact any companies for this update.

Data collection and analysis

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and we obtained full copies of the remaining studies. Two review authors made the decisions. Two review authors read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We reported the reasons for excluding trials.

Data extraction and management

Two review authors extracted data independently using a standard form and checked for agreement before entry into Review Manager 5 (RevMan 2014). We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event).

We only extracted data from cross-over studies from the first arm to avoid carry-over effects and to ensure data were not double-counted.

Assessment of risk of bias in included studies

For the previous update we continued to assess quality using the Oxford Quality Scale (Jadad 1996b), which allocates points for randomisation, blinding, and the recording of study withdrawals. The maximum possible score (indicating a trial of high methodological quality) is five. We also used the Cochrane 'Risk of bias' tool. We used the following standard parameters.

We completed a 'Risk of bias' table for each included study, using methods adapted from those described by the Cochrane Pregnancy

and Childbirth Group. Two authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with any disagreements resolved by discussion. 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); high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) - we excluded these studies; unclear risk of bias: the trial may or may not be free of bias.
- Allocation concealment (checking for possible selection bias). We assessed the method used to conceal allocation to interventions prior to assignment to establish whether intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment. The methods were assessed as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed, opaque, envelopes); high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth) - these studies would be excluded; unclear risk of bias - the trial may or may not be free of bias.
- 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. We considered studies to be at low risk of bias if they stated that they were blinded and described the method used to achieve blinding (e.g. identical tablets, matched in appearance and smell); or at unknown risk if they stated that they were blinded, but did not provide an adequate description of how it was achieved.
- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Moore 2012; Nüesch 2010). We considered studies to be at low risk of bias if they had 200 or more participants, at unclear risk if they had between 50 and 200 participants, and at high risk if they had fewer than 50 participants.
- Selective outcome reporting. We considered studies to be at low risk of bias if all outcomes were pre-defined (for example, in a published protocol) and reported, or all clinically relevant and reasonably expected outcomes were reported; at uncertain risk of bias if it is unclear whether all pre-defined and clinically relevant and reasonably expected outcomes were reported; and at high risk of bias if one or more clinically relevant and reasonably expected outcomes were not reported, and data on these outcomes were likely to have been recorded.

Measures of treatment effect

We planned to calculate NNTs as the reciprocal of the absolute risk reduction (ARR).. For unwanted effects, the NNT becomes the number needed to treat for an additional harmful outcome (NNH) and is calculated in the same manner. We would use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless we found significant statistical heterogeneity (see below). We did not plan to use continuous data in analyses. In the event no data were available for these calculations.

Unit of analysis issues

We planned to split the control treatment arm between active treatment arms in a single study if there was more than one active treatment arm, and they were not combined for analysis. However, this was not possible as no data were available for analysis.

Dealing with missing data

We extracted data using intention-to-treat (ITT) analysis where the ITT population consists of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. We assigned zero improvement to missing participants wherever possible.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and assess statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. If the I^2 value was greater than 50%, we would consider possible reasons for this. In the event there was only one included study, so heterogeneity was not an issue.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to patients with pain (Hoffman 2010; Moore 2010a; Moore 2010b; Moore 2010c; Moore 2013b). We did not extract continuous data, as these poorly reflect efficacy and utility.

We planned to assess publication bias 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, this was not possible.

Data synthesis

We planned to use a fixed-effect model for meta-analysis, or a random-effects model if there was significant clinical heterogeneity and it was considered appropriate to combine studies. In this review it was not possible to generate forest plots. We planned to meta-analyse data in Review Manager 5 (RevMan 2014) and also to calculate numbers needed to treat (NNTs) and numbers needed to treat for harm (NNTHs) for adverse events (Cook 1995). However, there were no data that could be analysed in this way. Instead, we provided a qualitative overview of this literature.

Quality assessment

For previous versions of the review, we assessed trial quality using the Oxford Quality Scale, a five-point assessment tool (Jadad 1996b). The results of the assessments are recorded in the [Characteristics of included studies](#) table, but were not used to weight studies.

Subgroup analysis and investigation of heterogeneity

In an earlier version, had data been available, we planned subgroup analyses for the following areas:

- immediate versus modified release;
- opiate-naïve versus previous exposure to morphine;
- multiple dose versus single dose;
- enriched enrolment versus those without enriched enrolment;

- studies with a quality score of three or more versus those with a quality score of one or two.

However, there were no data that could be subjected to such analyses.

We did not plan to undertake subgroup analysis as we were aware that data would not be available.

Sensitivity analysis

We did not plan specific sensitivity analysis because the evidence base is known to be too small to allow reliable analysis. We had hoped to examine details of dose-escalation schedules to see if this could provide some basis for a sensitivity analysis.

RESULTS

Description of studies

This review contains 62 studies of 4241 participants. One study is included on the basis of an English language abstract but is waiting for full translation for data extraction ([Oztürk 2008](#)).

In total, over 150 potentially includable studies were identified by the combined searches. All studies were of adult participants. The 62 included studies are listed, together with details of the data extracted, in the [Characteristics of included studies](#) table. Thirty-six of the 62 studies used a cross-over design ranging from one day each arm to 15 days. Comparisons, together with numbers of studies and participants, are listed in Summary table A. The number of cross-over days and the number of studies is presented as Summary table B.

Results of the search

We identified seven potentially new studies in this update; we excluded six ([Corli 2012](#); [NCT00573937 2010](#); [NCT00660348 2014](#); [NCT00726830 2012](#); [NCT01541124 2012](#); [Shimoyama 2015](#)). See [Characteristics of excluded studies](#) for details. We placed one study in [Characteristics of ongoing studies](#) as the study is complete but no results have been published to date ([NCT01809106 2014a](#)).

Information on the flow of studies from the number of references identified in the search to the number of studies included in the review is available in [Figure 1](#).

Figure 1. Study flow diagram.

Included studies

The 62 studies that met the inclusion criteria contained 4241 enrolled participants. Trial size varied from 11 to 699 participants. Three studies used a single dose and the remainder were multi-dose studies, ranging in time from three days to six weeks. The majority compared morphine modified release (Mm/r) with morphine immediate release (MIR), either as tablets or solution. Many of these were cross-over studies over a variety of time periods, listed in Summary table B. Other comparators were noted and described, such as different opioids or morphine by different routes. The range of daily morphine doses across the studies, where

reported in sufficient detail to allow calculation, was 15 mg to 2000 mg. The majority of the studies were designed to show equivalence between two morphine products. It was not generally clear if they were sufficiently powered to detect a clinically meaningful difference.

For the first version of the review, responses were received from four pharmaceutical companies and yielded six studies (all published) not retrieved by the electronic search strategy. Attempts to contact researchers listed in www.controlledtrials.com proved fruitless, and we identified no unpublished studies.

Summary table A: Comparisons, studies, and participants

Types of studies	Number of studies	No of participants
Mm/r versus other opioids	16	1359
Mm/r versus Mm/r different strengths or times	15	1084
Mm/r versus MIR	15	500
MIR versus other opioids	5	849
Mm/r versus Mm/r rectal	3	84
MIR versus MIR different times	2	46
Mm/r tablet versus Mm/r suspension	1	52
Mm/r versus non-opioids	1	20
MIR versus non-opioids	1	121
MIR versus epidural morphine	1	30
MIR versus rectal morphine	1	34
MIR versus intravenous morphine	1	62
TOTALS	62	4241

Summary table B: Cross-over studies and days spent on each arm

Number of days per arm	Number of studies
1 + 1	1
2 + 2	4
3 + 3	3
4 + 4	2
5 + 5	2
6 + 6	6
7 + 7	11
10 + 10	1
14 + 14	4
15 + 15	2

Excluded studies

Excluded studies are listed together with reasons for exclusion in the [Characteristics of excluded studies](#) table. We excluded six studies for this update.

Risk of bias in included studies

In previous versions of this review, we assessed study quality using the Oxford Quality Scale ([Jadad 1996b](#)), which allocates points for randomisation, blinding, and the recording of study withdrawals. The maximum possible score (indicating a trial of high methodological quality) is five. We have retained those results in the [Characteristics of included studies](#) section but have also used the Cochrane 'Risk of bias' tool.

Overall, the methodological quality of included trials was high with a median quality score of four.

Thirty-two studies explicitly mentioned pharmaceutical industry support; the majority of these had a quality score of three or more.

For the previous update we incorporated the Cochrane 'Risk of bias' tool. The findings are listed in the 'Risk of bias' table linked to the [Characteristics of included studies](#) tables.

The overall findings are presented in the 'Risk of bias' summary graphs ([Figure 2](#) and [Figure 3](#)). Of note is that only 13 studies adequately reported the method of randomisation and few reported on allocation concealment. We considered the majority of studies to be at high risk of bias due to small study size.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Size
Ahmedzai 1997	?	?	+	+	+	+
Arkininstall 1989	?	?	+	+	+	+
Babul 1998	?	?	+	+	+	+
Boureau 1992	?	?	+	+	+	?
Broomhead 1997a	?	?	+	+	+	?
Bruera 1998	?	?	+	+	+	+
Bruera 2004	+	+	+	+	+	?
Cundiff 1989	?	?	+	+	+	+
Currow 2007	+	+	+	+	+	+
Dale 2009	+	+	+	+	+	+
De Conno 1995	?	?	+	+	+	+
Dellemijn 1994	?	?	+	+	+	+
Deschamps 1992	+	?	+	+	+	+
Ferrell 1989	?	?	+	+	?	?
Finn 1993	+	?	+	+	+	+
Flöter 1997	+	?	+	+	+	?
Gillette 1997	?	?	+	?	+	+
Gourlay 1997	?	?	+	?	+	+
Hagen 2005	?	?	+	+	+	+
Hanks 1987a	?	?	+	+	+	+
Hanks 1995	?	?	+	+	+	+
Hanna 2008	+	?	+	+	+	+
Harris 2003	?	?	+	+	+	?

Figure 2. (Continued)

Hanna 2008	+	?	+	+	+	+
Harris 2003	?	?	-	+	+	?
Heiskanen 2000	+	+	+	+	+	-
Homsy 2010	?	-	-	+	+	-
Hoskin 1989	?	+	+	+	+	-
Kalso 1990	?	?	?	?	+	-
Kerr 2000	?	?	-	+	+	?
Klepstad 2003	+	+	+	+	+	-
Knudsen 1985	?	?	?	+	+	-
Kossman 1983	?	?	-	-	+	-
Lauretti 2003	?	?	+	+	+	-
Leppart 2001	?	?	-	+	+	-
Melzack 1979	+	?	+	-	+	-
Mercadante 1998	?	?	-	+	+	-
Mercadante 2008	+	-	-	+	+	?
Mercadante 2010	?	?	-	+	+	-
Mignault 1995	?	?	+	+	+	-
Mizuguchi 1990	?	?	+	+	?	-
Moriarty 1999	+	?	+	+	+	?
Mucci LoRusso 1998	?	?	+	+	+	?
O'Brien 1997	?	?	+	+	+	?
Oztürk 2008	?	?	-	?	?	-
Panich 1993	?	?	-	?	+	?
Portenoy 1989	?	?	+	+	+	?
Ridgway 2010	?	?	?	+	-	-
Rodriguez 1994	?	?	?	+	+	?
Smith 1991	?	?	+	?	-	-
Thirlwell 1989	?	?	+	+	+	-
Todd 2002	?	?	-	+	+	-
Twycross 1977	?	?	+	+	+	+
Vainio 1988	?	?	-	+	+	-
Van Seventer 2003	?	?	-	+	+	?
Ventafridda 1986	?	?	-	+	+	?
Ventafridda 1989	?	?	-	+	+	?
Vielvoye-Kerkmeer 2002	?	?	-	-	+	?
Walsh 1985a	?	?	+	+	+	-
Walsh 1992	+	?	+	+	+	-
Wilder-Smith 1994	?	?	+	+	+	-
Wilkinson 1992	?	?	-	+	+	-
Wong 1997	?	?	-	+	+	-
Xu 1997	?	?	-	+	+	?

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

We judged only 10/62 studies to have an adequate description of the randomisation process used and for allocation concealment the figure dropped to 5/62.

Blinding

Of the 62 included studies 22 were not double-blind as far as we could tell.

Incomplete outcome data

Reporting of data was generally good so incomplete data were not an issue and it was possible to account for all participants.

Selective reporting

Reporting of data was generally good so selective reporting was not an issue.

Other potential sources of bias

Only 2/62 studies included over 200 participants and 17/62 contained 50 to 199 participants.

The quality of the evidence is generally poor. Studies are old, often small, and were largely carried out for registration purposes and therefore were only designed to show equivalence between different formulations.

Effects of interventions

1. Morphine modified release (Mm/r) compared to morphine immediate release (MIR)

This comparison is arguably the most important as it seeks to establish the efficacy of morphine modified release products, currently the mainstay of pain relief in cancer care. In spite of this importance the literature is small, with 15 studies consisting of 500 participants in total. None of the trials were large, having a median size of 27 participants (range 16 to 73). Eleven of the trials were of cross-over design. The results of these trials show that Mm/r and MIR are equivalent for pain relief. No new studies were found for this comparison in this update, or the previous update (2013).

(a) Studies not utilising a cross-over design

Four studies were parallel design. [Ventafridda 1989](#) conducted the largest of the trials. Seventy participants who were opioid-naïve

received either morphine solution or Mm/r. All participants received both oral diclofenac 225 mg and oral haloperidol 20 mg daily. The study duration was 14 days. Using an integrated pain score, greater pain relief was achieved by Mm/r with fewer side effects. This occurred despite the use of a higher mean daily dose of MIR (120 mg) compared to Mm/r (90 mg). [Hoskin 1989](#) randomised 19 participants who were stable on MIR to receive Mm/r with or without an additional dose of MIR. There was no difference in pain scores between those who received the additional dose and those receiving placebo, demonstrating that a loading dose may not be necessary when commencing Mm/r. [Kossman 1983](#) compared Mm/r with a morphine cocktail (content and strength not stated) in 20 participants. The study included a pharmacokinetic component but no doses were recorded. [Klepstad 2003](#) compared Mm/r 24-hour release with MIR in 40 participants. Acceptable pain relief was achieved in 2.1 days (95% confidence interval (CI) 1.4 to 2.7) for MIR and 1.7 days (95% CI 1.1 to 2.3) in the Mm/r group; 10/13 in the MIR group and 13/17 in the Mm/r group were satisfied or very satisfied with pain relief.

(b) Cross-over studies

The cross-over studies showed a wide variation in treatment periods, as with the rest of this literature. None of the studies addressed the issue of carry-over of analgesic effect for those who received the Mm/r product. In a study by [Cundiff 1989](#) it was difficult to determine exactly when cross-over occurred; however, as pain was assessed by a nurse and not by the participant the results of this trial are not considered here.

[Walsh 1992](#) took participants who were stable on morphine or on other opioids, which were then converted to morphine. The mean daily dose at trial entry was 109 mg per day. Participants were randomised either to Mm/r or MIR using a double-dummy technique. Cross-over occurred at two days. There was no significant difference detected in mean daily morphine dose, visual analogue score (VAS) pain data, breakthrough pain, or use of rescue analgesia. Equally, scores for adverse events, including nausea, confusion, constipation, and anxiety, were similar. A preference for Mm/r was stated by 22 of the 33 people who entered the study. Only 27 participants were evaluated.

[Hanks 1987a](#) conducted a similar study although one-third of the 27 participants dropped out early. Both intervention groups experienced adequate pain control but those on Mm/r experienced better quality sleep at night. Another study by [Walsh 1985a](#) used

cross-overs at day three and again at days five and eight. This study also reported no differences in either pain relief or side effects. The authors stated that they did not detect any carry-over effects. No difference was detected between treatments during five-day cross-overs by [Finn 1993](#) or by [Thirlwell 1989](#). A French study by [Gillette 1997](#) compared Mm/r as M-Eslon® with MIR solution in opioid-naïve participants in a double-dummy study with a pharmacokinetic component. The participants were crossed over at six days. Pain relief was similar in both groups and the kinetic parameters were comparable. Three studies used a seven-day cross-over design. [Knudsen 1985](#), in a Danish language paper, stated that the design was "consecutively randomised" but there was no explanation of what this meant. The English abstract stated that the study was a randomised, double-blind study and it has been included in the review on that basis. The authors reported no difference in pain relief or adverse events. Similar findings were recorded by [Deschamps 1992](#) and also by [Panich 1993](#). In this latter study, over 70% of the participants expressed a preference for morphine solution (MIR). As 60% of them had either neck or face cancers this may have influenced the response in favour of an easy to swallow product.

While 29 people entered the study by [Arkininstall 1989](#), only 17 completed it. Again, participants were as well controlled on Mm/r twice a day as on MIR six times a day, with no reported difference in adverse events. A small number of people with non-cancer pain were included in this sample.

2. Morphine modified release (Mm/r) comparisons - different strengths, formulations, and/or dose intervals

Fifteen studies (1084 participants) compared Mm/r at different strengths or release profiles. Three new studies (112 participants) were added at the previous update.

These studies can be subdivided as follows:

- (a) different dose strength combinations of 12-hour release;
- (b) studies of 24-hour release.

(a) Six studies (277 participants) examined different dose strengths or interval combinations of 12-hour release Mm/r

Using a double-blind design, [Mignault 1995](#), in a Canadian study, showed that 12-hourly dosage was as effective as eight-hourly administration. This was a small study of 19 participants; there were no differences in adverse events and the majority of participants felt that the 12-hour regimen had advantages in terms of convenience. The assessment of high-dose tablets of Mm/r was covered by three studies. [Portenoy 1989](#) compared three tablets of Mm/r 30 mg (MS Contin) with one tablet of 100 mg Mm/r. Participants were stabilised on MIR over a one- or two-day period then randomised to either Mm/r 100 mg or Mm/r 90 mg (3 x 30 mg) every 12 hours. Comparison of the pain intensity and rescue analgesic consumption (MIR) showed no significant differences. The reported side effect profiles were also similar. Two studies compared Mm/r 100 mg with Mm/r 200 mg (MS Contin). [Smith 1991](#) studied 20 participants who received either dose for three or four days. Doses ranged from 400 mg to 1800 mg per day. Pain assessment and pharmacokinetic monitoring confirmed similar analgesic efficacy and plasma profiles. In another three-day cross-over study consisting of the same formulations, [Hanks 1995](#) also showed comparable efficacy in a study of 25 participants.

People in this study used doses of 400 mg to 2000 mg per day. A comparative study of two different Mm/r products was undertaken in 45 participants by [Homsy 2010](#). This was an open-label study with no cross-over, based on mean pain scores and standard error of the means (SEM); the authors claim that one product was more effective on days three to five of a five-day study. Only the results of day three were statistically significant. The authors claim that this has clinical significance. It should be noted that the sponsors of the study produce the 'more effective' product.

A different brand of modified release capsule was used in a Chinese study by [Xu 1997](#). M-Eslon® was compared to MS Contin® in 120 participants. Both were designed for 12-hourly dose intervals. The study was conducted at two dose levels: 20 mg every 12 hours and 30 mg every 12 hours. No titration was permitted. Using a range of analgesic assessments there was no significant difference between the two products and adverse events were also similar.

(b) Studies of 24-hour release

Nine studies were found (807 participants) of once-daily morphine tablet or capsule (marketed under a number of trade names including Adprem®, Kadian®, Kapanol®, Morcap® or MXL® capsules).

MXL capsules were shown to be comparable to an equivalent dose of MS Contin in a study of 85 participants by [O'Brien 1997](#). The comparators were MXL 60 mg versus Mm/r 30 mg twice a day. The dose could be multiplied for participants requiring higher doses. While the majority of participants needed 60 mg a day, doses up to 300 mg per day were used. There were no significant differences in pain relief between participants. The study by [Flöter 1997](#) included people with cancer and non-cancer pain such as post-trauma and neuropathic pains. The authors claimed a significant difference in favour of the once-daily product for pain intensity (VAS) when measured immediately prior to the evening dose. Data were not available for a separate analysis of the participants with cancer pain. [Broomhead 1997a](#) conducted a study of 150 people with cancer pain in two separate phases. Phase one contained a placebo arm to demonstrate that the study could differentiate between active treatment and placebo. Rescue medication was available in the form of MIR. Phase two consisted of three arms: Kapanol every 24 hours, Kapanol every 12 hours, and Mm/r every 12 hours. There was no significant difference between the groups in terms of rescue medication requirement. Participants' global assessments of 'good' or 'very good' pain control was 89% for the Kapanol 24-hour group, 76% in the Kapanol 12-hour group, and 68% in the Mm/r group. Adverse events were similar between groups and there was no increase in adverse events associated with the larger unit dose of the once-daily product. [Gourlay 1997](#) showed that there were no significant differences between Kapanol once a day and Mm/r twice a day for either analgesic effect or adverse events. The pharmacokinetic profile was much flatter for Kapanol 24-hour, reflecting the designed release profile.

Twenty-nine participants were enrolled in a study comparing MS Contin XL with MS Contin ([Hagen 2005](#)). All participants experienced good pain relief though it was observed that pain scores were more stable through the day on the once daily formulation. One hundred and thirty-four participants were titrated to relief of cancer pain with MIR then randomised to either Mm/r 24-hour (Kadian) or Mm/r 12-hour (MS Contin) formulations ([Kerr 2000](#)). Only 104 participants entered the efficacy trial, which was a cross-over design. No dose adjustments were allowed but rescue

MIR was provided; 57/104 preferred Kadian, 34/104 MS Contin, and 13/104 expressed no preference. One hundred and fifty-three participants entered a study by [Vielvoye-Kerkmeer 2002](#) but only 110 were enrolled after a 14-day run-in period. It was not stated why the 43 participants dropped out. No significant differences were detected between groups in terms of pain intensity, rescue analgesia, or sleep quality. A study of 38 participants compared a new once daily matrix Mm/r with twice daily Mm/r ([Ridgway 2010](#)). The study demonstrated therapeutic equivalence and no difference for incidence of breakthrough pain or pain intensity measured for morning and evening.

In a study about timing of the dosing of a 24-hour Mm/r in 45 participants, [Currow 2007](#) showed that there was no difference in pain control or pain during the day for either morning or evening administration.

3. Morphine modified release (Mm/r) compared to other opioids

Sixteen studies (1359 participants) compared morphine modified release with other opioids as either modified release or immediate release formulations. This includes four studies (418 participants) added at the previous update.

Five comparator drugs were studied:

- (a) oxycodone (six studies: [Bruera 1998](#); [Ferrell 1989](#); [Heiskanen 2000](#); [Lauretti 2003](#); [Mercadante 2010](#); [Mucci LoRusso 1998](#));
- (b) hydromorphone (two studies: [Hanna 2008](#); [Moriarty 1999](#));
- (c) fentanyl transdermal (five studies: [Ahmedzai 1997](#); [Mercadante 2008](#); [Oztürk 2008](#); [Van Seventer 2003](#); [Wong 1997](#));
- (d) dextropropoxyphene (one study: [Mercadante 1998](#));
- (e) tramadol (one study: [Leppart 2001](#));
- (f) methadone (one study [Bruera 2004](#)).

(a) Mm/r versus oxycodone

Six studies (346 participants) compared modified release oxycodone with Mm/r ([Bruera 1998](#); [Ferrell 1989](#); [Heiskanen 2000](#); [Lauretti 2003](#); [Mercadante 2010](#); [Mucci LoRusso 1998](#)). All reported adequate analgesia with both agents when doses were titrated. One study reported the relative potency of oxycodone to morphine as 1:1.5 ([Mucci LoRusso 1998](#)). Another reported a similar relative potency of oxycodone to morphine as 1:1.6 ([Lauretti 2003](#)). There do seem to be some minor differences in side effect profiles, for example, no participants experienced hallucinations on oxycodone.

A separate Cochrane review assessing the effectiveness of oxycodone for cancer pain relief has been published ([Schmidt-Hansen 2015](#)).

A study by [Ferrell 1989](#) presented a number of problems. Participants who were already receiving short-acting analgesics (oxycodone, hydromorphone, codeine, or morphine) were randomised either to a 'no change' group or changed to Mm/r. However, no data were presented on the numbers of participants receiving each opioid. There appeared to be an assumption that the short-acting opioids were equally effective. The authors reported that pain intensity was reduced in the Mm/r group.

(b) Mm/r versus hydromorphone

Two studies (300 participants) compared hydromorphone modified release and Mm/r ([Hanna 2008](#); [Moriarty 1999](#)). Two hundred participants were recruited to a multi-national multicentre study by Hanna and colleagues. Using a double-dummy design, participants were randomised either to twice daily Mm/r or once daily hydromorphone OROS formulation with a placebo tablet in the evening. The authors claimed a small but statistically significant benefit for hydromorphone. In another randomised cross-over study of two three-day treatment periods ([Moriarty 1999](#)), the primary outcome was the use of rescue medication. Both treatments controlled pain satisfactorily and there was no difference between the number of occasions that rescue medication was used during the last 24 hours of each treatment period. Of a subgroup that expressed a preference, only five out of 38 participants preferred hydromorphone; 13 preferred morphine and the remainder had no preference. Hydromorphone is also the subject of a separate Cochrane review ([Quigley 2007](#)).

(c) Mm/r versus transdermal fentanyl

Transdermal (TD) fentanyl has gained in popularity over recent years; we found five studies (538 participants) comparing this agent with oral morphine ([Ahmedzai 1997](#); [Mercadante 2008](#); [Oztürk 2008](#); [Van Seventer 2003](#); [Wong 1997](#)). [Ahmedzai 1997](#) compared 202 participants in a cross-over study (not double-blind) comparing Mm/r with transdermal fentanyl patches. They found a significant carry-over effect so only the first phase of this trial has been analysed. Pain control was assessed by a variety of measures but no significant differences were found between Mm/r and fentanyl patches. More participants required rescue medication in the fentanyl group and the fentanyl dose more often needed to be titrated upwards. Fentanyl appeared to be less sedating than morphine both during the day and at night. Participants on fentanyl were significantly less constipated. Of 136 participants who expressed a preference, 14 had no preference, 73 preferred fentanyl, and 49 preferred morphine. In [Mercadante 2008](#), 108 participants were randomised to receive either Mm/r or fentanyl TD or methadone in an open study. All three were found to be effective and well tolerated. A Turkish study compared Mm/r with fentanyl TD in 50 participants. Again both analgesics were found to be safe and effective but with significantly less constipation experienced in the fentanyl group ([Oztürk 2008](#)). In the study by [Van Seventer 2003](#), 131 participants received either transdermal fentanyl or Mm/r. After dose titration both groups reported good pain relief. Participants reported less troublesome adverse events on fentanyl with a slightly lower incidence in the use of laxatives: 51/67 used laxatives on fentanyl and 47/64 on morphine. Both groups used MIR for breakthrough pain. A study by [Wong 1997](#) was also randomised and open without cross-over. Participants were converted to MIR for seven days prior to randomisation then assigned either to Mm/r or fentanyl patches. In this smaller study (20 participants per group) both groups reported good pain relief and adverse events were similar. The authors reported problems in using the manufacturer's guidance in converting the dose of morphine into an equivalent fentanyl dose. Transdermal fentanyl is the subject of a separate Cochrane review in preparation ([Hadley 2013](#)).

(d) Mm/r versus dextropropoxyphene

Dextropropoxyphene was compared to Mm/r in 32 opioid-naïve participants by [Mercadante 1998](#). Few data were presented so clear

conclusions could not be drawn. Pain relief was achieved at lower doses on dextropropoxyphene, possibly with fewer side effects, in this small study of 16 people per group. The median dose of dextropropoxyphene was 40 mg (range 10 mg to 120 mg) and for morphine it was 42 mg (range 20 mg to 600 mg).

(e) Mm/r versus tramadol

A Polish study compared modified release tramadol with Mm/r in 40 opioid-naïve participants (Leppart 2001). Satisfactory analgesia was achieved in both groups with a mean dose for tramadol of 322 +/- 116 mg and for morphine 123 +/- 78 mg. The authors reported that morphine was more effective at treating neuropathic pain.

(f) Mm/r versus methadone

Bruera 2004 compared methadone 7.5 mg every 12 hours (with an additional 5 mg every four hours for breakthrough) with Mm/r 15 mg 12-hourly (with an additional 5 mg every four hours for breakthrough) in a study of 103 participants. At day eight 37/49 methadone and 42/54 morphine participants had greater than 20% reduction in pain intensity. There were a greater number of adverse events reported in the methadone group.

4. Morphine immediate release (MIR) compared to other opioids

We identified five studies (849 participants) that compared MIR with four other opioids:

- (a) Brompton Cocktail (two studies: Melzack 1979; Twycross 1977);
- (b) methadone (one study: Ventafridda 1986);
- (c) tramadol (one study: Wilder-Smith 1994);
- (d) oxycodone (one study: Kalso 1990).

(a) MIR versus Brompton Cocktail

The largest study in this review enrolled 699 participants but only 146 of these crossed over after two weeks (Twycross 1977). The study compared elixirs containing diamorphine and cocaine with a morphine and cocaine elixir. 'Brompton Cocktail' was a generic term for mixtures and elixirs containing diamorphine or morphine and cocaine with or without chlorpromazine. These are now obsolete and should not be used (Parfitt 1999). This study is of historical interest because of the large number of participants. The study did not detect any difference between the groups when the medicines were given in equi-analgesic doses. Melzack 1979 compared morphine solution and a Brompton mixture containing a variable amount of morphine, 10 mg of cocaine, and 2.5 ml of 98% ethyl alcohol, in 44 participants. Thirty completed both phases of this cross-over study. There was no significant difference in pain scores or adverse events but it was noted that approximately 15% of participants did not obtain adequate pain relief. However, the average morphine dose was 25 mg. This study was valuable in demonstrating that cocaine did not enhance analgesia.

(b) MIR versus methadone

Sixty-six participants were entered into a study of oral morphine versus methadone, in Italy by Ventafridda 1986. Only those participants (N = 54) who completed the first 14 days titration were evaluated. All participants received 150 mg diclofenac and haloperidol 20 mg daily by injection. Morphine was given in a dose of 4 mg to 24 mg every four hours and methadone in a dose of 8 mg to 28 mg every six hours for the first three days then every

eight hours. Pain control was demonstrated with both treatments. More participants on morphine complained of dry mouth whereas more on methadone complained of headache. The authors argue that methadone has value in cancer pain but needs to be managed differently from morphine because of accumulation of methadone during treatment.

(c) MIR versus tramadol

Tramadol solution (5%) was compared to morphine solution (1%) in a cross-over study by Wilder-Smith 1994. Participants reported similar pain intensities on day four. Mean daily doses were morphine 101 mg (+/- 58 mg) and tramadol 375 mg (+/- 135 mg). Eight participants preferred morphine, three favoured tramadol, and nine expressed no distinct choice.

(d) MIR versus oxycodone

Oxycodone immediate release was studied against morphine immediate release in a trial of 20 participants by Kalso and Vainio (Kalso 1990). Participants were titrated by patient controlled analgesia (PCA) until free of pain then randomised to use either morphine or oxycodone. After 48 hours the intravenous dose was used to calculate the oral dose, divided into four-hourly doses. Oxycodone was provided at a concentration of 2.7 mg/ml and morphine at 4 mg/ml to reflect relative potencies. Participants could ask for the dose to be increased if not pain-free, or for it to be reduced if sedated at the end of each four-hour period. Participants were crossed over after 96 hours. The mean oral morphine consumption was 168 mg in group one and 228 mg in group two. The most frequent side effect with both treatments was sedation. Oral morphine caused significantly more nausea. Hallucinations occurred only with morphine. Five participants preferred morphine, five preferred oxycodone, and 10 had no preference.

5. Morphine modified release (Mm/r) administered rectally

Three studies (83 participants) compared Mm/r tablets with rectal morphine modified release. In one trial this was undertaken using Mm/r tablets administered rectally (Wilkinson 1992), in another controlled release suppositories were used (Babul 1998). One study compared Mm/r with morphine suppositories (Mizuguchi 1990).

Wilkinson 1992 conducted a small study of 10 participants who were stabilised on morphine and then randomised to receive Mm/r tablets either orally or rectally in a pharmacokinetic and efficacy study which was open and of cross-over design. No significant difference was found in the 'area under the curve' (i.e. that is they had similar pharmacokinetic profiles) for parenteral morphine but fewer metabolites were measured in the rectal group. No significant difference was found between the two routes in terms of pain relief. Participants expressed a preference for the oral route.

Twenty-seven participants were selected for a randomised, double-blind, double-dummy, two-way cross-over study of Mm/r tablets and a commercially available Mm/r suppository (Babul 1998). Participants stabilised on morphine were given Mm/r suppositories at the same dose as their oral requirement. Breakthrough pain was treated with approximately 10% of the daily morphine dose given orally as morphine immediate release. No other opioids or rescue medications were allowed but participants were allowed to continue on prior medication, which could include nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants,

anticonvulsants, or bisphosphonates. Twenty-two participants completed the study. There were no significant differences between pain scores or rescue medication requirements. There was a small but significant difference between nausea scores in favour of the rectal route. No difference was detected for other adverse events.

[Mizuguchi 1990](#) (published in Japanese) compared Mm/r as three 10 mg MS Contin tablets with three 20 mg morphine suppositories, each given twice daily for three days in a cross-over study of 46 participants. A total of 17/46 participants reported very good pain relief on Mm/r and 14/46 using suppositories. There were no significant differences in adverse events.

6. Morphine modified release (Mm/r) tablets compared to morphine modified release (Mm/r) oral suspension

A French study compared Mm/r suspension with tablets in a double-blind, double-dummy, cross-over study of 52 participants ([Boureau 1992](#)). Using visual analogue scores and categorical scales, there were no significant differences between the groups regarding pain relief or other measured indicators such as activity, mood, or sleep. There was no clear participant preference for any product. Adverse events were also comparable.

7. Morphine modified release (Mm/r) compared to non-opioids

In a small study by [Dellemijn 1994](#) 20 participants with malignant nerve pain were randomised to receive either naproxen 500 mg three times a day or Mm/r 30 mg twice a day with cross-over at seven days for each arm. Doses were fixed, not titrated, and rescue paracetamol up to 4 g per day was allowed. Pain was assessed on a 101-point numerical rating scale. Data from four participants were considered not evaluable so reported differences were based on only 16 participants. The authors stated that there was greater use of paracetamol as rescue medication in the morphine arms of the trial.

8. Morphine instant release (MIR) compared to non-opioids

A parallel, double-blind study of 121 participants conducted in Spain compared two doses of dipyrone (1 g three times a day or 2 g three times a day) with oral morphine solution at a dose of 10 mg every four hours ([Rodriguez 1994](#)). Dipyrone is not available in many countries but is widely used in Spain and South America. Both dipyrone 2 g and morphine 10 mg showed benefits over dipyrone 1 g; more side effects were reported in the morphine group but these were not statistically significant.

9. Oral morphine versus epidural morphine

A study by [Vainio 1988](#) compared oral morphine (MIR or Mm/r) with two techniques for epidural morphine administration in 30 participants with tumour involvement of the brachial or lumbar nerve plexuses. Epidural morphine was administered either via a conventional tunnelled epidural catheter or an epidural catheter connected to an implanted injection port. Participants were assigned randomly to either oral morphine (MIR or Mm/r) or to one of the two epidural groups. Doses were adjusted according to patient demand, daily during the first week and weekly thereafter. The initial dose of morphine was 46 mg to 150 mg orally or 2 mg to 12 mg epidurally. Treatment was continued for as long as possible, often until the participant died. Pain relief was similarly effective in all groups but those on epidural treatment reported significantly fewer side effects. There were some technical problems in the epidural groups with three dislocated catheters in the tunnelled

group and three blocked catheters in the port group. Mean length of treatment was 108 days (+/- 290) in the oral group, 43 days (+/- 13) in the tunnelled group, and 97 days (+/- 23) in the port group.

10. Morphine immediate release compared to rectal morphine

[De Conno 1995](#) compared morphine as a 10 mg oral solution with 10 mg of solution administered rectally as a micro enema in 34 cancer patients who had previously been treated with NSAIDs. This was a cross-over study (two days each arm) using a double-dummy technique. Significant pain relief was achieved faster in the rectal group, at 10 minutes compared to 60 minutes for the oral group. Pain relief remained better in the rectal group, up to 180 minutes. There was no significant difference in side effects.

11. Morphine instant release (MIR) compared to intravenous morphine

A study in India of 62 participants by [Harris 2003](#) compared intravenous morphine with MIR. More patients achieved satisfactory pain relief at four hours with intravenous morphine but numbers were similar at 24 hours.

12. Morphine instant release (MIR) given at different time points

Two studies (46 participants) examined the effects of different time points of administration of MIR in cross-over design studies. [Dale 2009](#) compared a single evening dose followed by a second dose four hours later with a double evening dose followed by a placebo four hours later. Each dose was for one night in this two-day study. The authors report that the two regimens were clinically equivalent. A similar study by [Todd 2002](#) provided an evening dose followed by a second dose after four hours and another dose after eight hours. This was compared with a double evening dose followed by a regular dose after eight hours. The study was two days for each phase. The authors claim that more participants on double-dose morphine required breakthrough analgesia than those on four-hourly dosing. The likelihood is that neither of these studies are long enough or large enough to provide a reliable answer.

Other aspects

No worse than mild pain

For the previous update we examined reports to ascertain whether a pain intensity of 'no worse than mild pain' was achieved based on a visual analogue scale of pain intensity (VASPI) of 30/100 mm or less on a pain intensity VAS, or the equivalent in other pain scales. Eighteen studies reported that average pain scores on morphine were below 30/100 mm, indicating that most treated participants had no worse than mild pain ([Arkinstall 1989](#); [Babul 1998](#); [Broomhead 1997a](#); [Bruera 1998](#); [Finn 1993](#); [Heiskanen 2000](#); [Homsy 2010](#); [Hoskin 1989](#); [Knudsen 1985](#); [Melzack 1979](#); [Mercadante 2008](#); [Mercadante 2010](#); [Mucci LoRusso 1998](#); [Ridgway 2010](#); [Ventafridda 1986](#); [Ventafridda 1989](#); [Vielvoye-Kerkmeier 2002](#); [Walsh 1992](#)). No study reported that average pain on treatment with oral morphine was above 30/100 mm or equivalent.

Eighteen studies recorded the proportion of participants achieving either no worse than mild pain ([Dale 2009](#); [Dellemijn 1994](#); [Deschamps 1992](#); [Gillette 1997](#); [Gourlay 1997](#); [Hanks 1987a](#); [Kossman 1983](#); [Moriarty 1999](#); [O'Brien 1997](#)), or some global outcome indicating satisfaction or success ([Ahmedzai 1997](#);

Broomhead 1997a; Bruera 2004; Currow 2007; Xu 1997; Hanna 2008; Klepstad 2003; Mignault 1995; Rodriguez 1994).

The outcome of 'no worse than mild pain' was achieved by 96% of participants (362/377), with consistently high levels of

response (Figure 4). For an outcome equivalent to treatment success, successful pain control, or participant global evaluation of very good or excellent, results were more variable, with an overall success rate of 63% (400/638; Figure 5).

Figure 4. Percentage of participants with oral morphine reporting no worse than mild pain. The size of the symbol is proportional to the size of the sample

Figure 5. Percentage of participants with oral morphine reporting an outcome equivalent to treatment success. The size of the symbol is proportional to the size of the sample

Effectiveness of morphine and dose

The effectiveness of morphine is demonstrated by the literature with titration to effect being common. The more important question concerns dose. The range of doses used in the reported studies was wide, varying from 25 mg/day (Melzack 1979), to 300 mg/day (Gillette 1997) for opioid-naïve participants. The maximum dose recorded was 2000 mg/day (Hanks 1995). Mean daily doses presented by a number of investigators were from 100 mg/day to 250 mg/day.

Study withdrawals

Withdrawals were common in these studies due to the frail nature of the participants. In spite of this, not every study reported the number of participants and reasons for withdrawals and dropouts. In the study by Twycross 1977, 699 participants were enrolled but only 146 were able to cross over to the second phase of the study after two weeks.

In many cases withdrawal was due to disease progression. Rates for withdrawal due to adverse events are reported below.

Nine studies reported withdrawals due to a lack of analgesic efficacy; all studies titrated participants to satisfactory pain relief and provided rescue medication. A total of 41 out of 544 participants (7%) withdrew. In one study this was linked to unstable pain control after the titration phase (Kalso 1990). Other reasons for withdrawal included death during the study and protocol violations.

Withdrawal due to adverse events

Twenty-six studies reported on participants withdrawing due to adverse events. In two studies, it was not possible to determine how many withdrew while on fentanyl and how many withdrew on morphine (Ahmedzai 1997; Wong 1997). In the remaining 24 studies, 154 participants out of a total of 2162 participants dropped out. This gives a dropout rate of 7% of participants who suffered adverse events of morphine of sufficient intensity that they could not continue treatment. While every effort has been made to identify all participants in each study, these estimates will be affected by any failures to report this information in the included studies.

DISCUSSION

This is the third update of the original Cochrane review first published in 2003. We identified no new studies for inclusion in this update, and the conclusions remain unchanged.

Summary of main results

This review has 62 included studies with 4241 participants. The main results of this review are that oral morphine works well in cancer pain, providing over 90% of participants with no worse than mild pain where this was reported. Over 60% of participants using oral morphine registered outcomes like measures of satisfaction. Oral morphine for routine use at the correct dose for an individual is as effective as other opioids.

This review might not change practice but it provides support for current practice. In particular, new studies included in the previous update confirmed that there is no significant difference

in pain relief whether 24-hour morphine modified release (Mm/r) preparations are administered in the morning or evening (Currow 2007), nor whether 12-hourly or 24-hourly Mm/r preparations are used (Ridgway 2010). The often-asked clinical question of whether or not a double dose at bedtime improves pain relief remains unanswered. In two new studies included in this review, there was no significant difference in achievement of no worse than mild pain, participant preference (Dale 2009), or use of breakthrough analgesia (Todd 2002), whether the participant had a single or double dose of morphine immediate release (MIR) at bedtime. However, both studies are probably too small to justify a change in practice in either direction. The 2007 update of this review indicated that titrating to analgesic effect with Mm/r was as effective as with MIR, and that there was no difference in achieving no worse than mild pain when Mm/r tablets are compared to Mm/r administered rectally or Mm/r oral suspension. Pain relief was also equally effective with oral morphine or epidural morphine: the latter caused fewer side effects but was associated with more technical problems. Based on the findings of this review, patient preference and other practical factors should continue to guide local practice.

There is also no conclusive evidence that other strong opioids are superior in efficacy to morphine. The new studies included in this review showed that there was no difference in pain intensity whether participants received Mm/r or fentanyl or methadone (Mercadante 2008), or oxycodone (Mercadante 2010). The Cochrane review by Quigley 2007 concluded that there was little difference between hydromorphone and morphine in terms of analgesic efficacy, adverse effect profile, and patient preference, but one of the new studies included in this review showed a small but statistically significant difference in benefit of hydromorphone over Mm/r (Hanna 2008). Fentanyl and oxycodone are both subjects of other Cochrane reviews (Hadley 2013; Schmidt-Hansen 2015).

Overall completeness and applicability of evidence

Most of the studies compared different formulations of oral morphine, or oral morphine with other oral opioids, or occasionally oral morphine with opioids using different routes of administration. There was no corpus of evidence for any particular comparison. The evidence would still have been useful if one of the outcomes reported consistently was that of participants obtaining good levels of pain relief, ideally no worse than mild pain, a patient-reported outcome of acknowledged benefit (Moore 2013a). Only nine of the 62 included studies reported this, although seven reported other outcomes of value from the patient perspective.

Most reported pain intensity as a mean, often with considerable variability around the mean. It was frequently the case that mean pain intensity scores were low and below (say) 30/100 mm. While average values are of questionable value in pain studies (Moore 2010a; Moore 2011), average values did support the results in individuals. It was frustrating that reporting was not more appropriate and applicable to individual patients.

Applicability of the evidence was also hindered by a general concentration on studies attempting to discern small differences in effect or harm between formulations or opioids, or both. The concentration was on statistical rather than clinically useful outcomes.

Quality of the evidence

The quality of the evidence was limited by an absence of double-blinding in a significant minority of studies, and small size in a substantial majority. Only 11 of the 62 studies included at least 100 participants and many had fewer than 50 participants (37/62).

Potential biases in the review process

We are unaware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

The results of this review are broadly in agreement with previous versions. A systematic review for the European Palliative Care Research Collaborative guidelines project included 17 studies, and concluded that their findings were identical to those of the Cochrane reviews on the topic (Caraceni 2011).

AUTHORS' CONCLUSIONS

Implications for practice

We identified no new studies for inclusion in this update, and the conclusions remain unchanged.

For people with cancer pain

This literature review, and many years of use, shows oral morphine to be an effective analgesic in patients who suffer pain associated with cancer. Oral morphine remains the gold standard for treating moderate to severe pain. Help may be needed to manage the more common undesirable adverse effects such as constipation and nausea.

For clinicians

This literature review, and many years of use, shows oral morphine to be an effective analgesic in patients who suffer pain associated with cancer. Oral morphine remains the gold standard for treating moderate to severe pain. This review demonstrates that it is possible to titrate with oral morphine of any formulation, and to be confident that most patients will achieve a high level of pain relief within at least two weeks. There is likely to be a small number of patients who do not benefit from morphine, or who may develop intolerable adverse events.

For policy makers

This literature review, and many years of use, shows oral morphine to be an effective analgesic in patients who suffer pain associated with cancer. Oral morphine remains the gold standard for treating moderate to severe pain.

For funders

This review demonstrates that it is possible to titrate with oral morphine of any formulation, and to be confident that most patients will achieve a high level of pain relief within at least two weeks. There is likely to be a small number of patients who do not benefit from morphine, or who may develop intolerable adverse effects and so other opioids need to be included in formularies. Oral morphine remains the gold standard for treating moderate to severe pain.

Implications for research

General

The quality of reporting of trials in this area continues to be disappointing. Despite this, the review shows that even with very variable descriptions of outcomes, it is possible to discern that a high proportion of patients with cancer pain can obtain good pain relief (or low pain levels) within a sensible time after beginning titration with oral morphine.

Design

Two methodological issues stand out. The quality of reporting of trials continues to be poor and small studies are far too common.

Measurement (endpoints)

Trials need to consider additional endpoints of no worse than mild pain as well as the impact of morphine on symptoms that raise serious concerns such as consciousness, appetite, and thirst.

Other

Given that most of the studies in this review were completed within the last 20 years the obvious implication for research is to instigate a morphine trialists' collaboration in order to undertake retrospective analyses of clinical trial data, using outcomes of clear patient benefit (no worse than mild pain within two weeks of starting morphine titration). Trialist collaborations have proved highly informative, with the Antiplatelet Trialists Collaboration probably the largest example of how retrospective analysis and pooling of clinical trial data can lead to improvements in treatment. With oral morphine in cancer pain, the 62 studies with 4241

participants should provide useful information about outcomes, titration schedules, and formulations to be translated into better results for patients, and a cost-effective approach for healthcare providers.

A second goal would be to extend the collaboration to include other drug interventions, including other oral opioids, and formulations of opioids other than oral.

A third goal of the collaboration would be to set guidelines for future clinical trials and systematic reviews to assess pain and pain relief by means of patient-reported validated scales, and to present data that can be related to individual participants rather than aggregated or mean data.

ACKNOWLEDGEMENTS

Thanks to Sylvia Bickley for developing the original search strategies for this review. Thanks also to Jayne Rees and Jodie Barden who were authors on the first published version of this review, and Henry McQuay who was an author the first two published versions.

Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS 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.

The 2015 review update was developed as part of the NIHR Cochrane Programme Grant: 13/89/29 - Addressing the unmet need of chronic pain: providing the evidence for treatments of pain.

REFERENCES

References to studies included in this review

Ahmedzai 1997 {published data only}

Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer. *Journal of Pain and Symptom Management* 1997;**13**(5):254-61.

Arkininstall 1989 {published data only}

* Arkininstall WW, Goughnour BR, White JA, Stewart JH. Control of severe pain with sustained-release morphine tablets versus oral morphine solution. *Canadian Medical Association Journal* 1989;**140**(6):653-7.

Goughnour BR, Arkininstall WW, Stewart JH. Analgesic response to single and multiple doses of controlled release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989;**63**(Suppl 11):2294-7.

Babul 1998 {published data only}

Babul N, Provencher L, Laberge F, Harsanyi Z, Moulin D. Comparative efficacy and safety of controlled-release morphine suppositories and tablets in cancer pain. *Journal of Clinical Pharmacology* 1998;**38**(1):74-81.

Boureau 1992 {published data only}

Boureau F, Saudubray F, D'Arnoux C, Vedrenne J, Estève M, Roquefeuil B, et al. A comparative study of controlled-release morphine (CRM) suspension and CRM tablets in chronic cancer pain. *Journal of Pain and Symptom Management* 1992;**7**(7):393-9.

Broomhead 1997a {published data only}

Broomhead A, Kerr R, Tester W, O'Meara P, Maccarrone C, Bowles R, et al. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *Journal of Pain and Symptom Management* 1997;**14**(2):63-73.

Bruera 1998 {published data only}

Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *Journal of Clinical Oncology* 1998;**16**(10):3222-9.

Bruera 2004 {published data only}

Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *Journal of Clinical Oncology* 2004;**22**(1):185-92.

Cundiff 1989 {published data only}

* Cundiff D, McCarthy K, Savarese JJ, Kaiko R, Thomas G, Grandy R, et al. Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. *Cancer* 1989;**63**(11 Suppl):2355-9.

Cundiff D, Savarese J, Grandy R, MacCarthy K, Kaiko R, Thomas G, et al. Evaluation of a controlled- and immediate

release morphine and a unique well-controlled study design in cancer pain. *Journal of Pain and Symptom Management* 1988;**3**(Suppl):18.

Currow 2007 {published data only}

Currow DC, Plummer JL, Cooney NJ, Gorman D, Glare PA. A randomized, double-blind, multi-site, crossover, placebo-controlled equivalence study of morning versus evening once-daily sustained-release morphine sulfate in people with pain from advanced cancer. *Journal of Pain and Symptom Management* 2007;**34**:17-23.

Dale 2009 {published data only}

Dale O, Piribauer M, Kaasa S, Moksnes K, Knobel H, Klestad P. A double-blind, randomized, crossover comparison between single-dose and double-dose immediate-release oral morphine at bedtime in cancer patients. *Journal of Pain and Symptom Management* 2009;**37**:68-76.

De Conno 1995 {published data only}

De Conno F, Ripamonti C, Saita L, MacEachern T, Hanson J, Bruera E. Role of rectal route in treating cancer pain: a randomized crossover clinical trial of oral versus rectal morphine administration in opioid-naïve cancer patients with pain. *Journal of Clinical Oncology* 1995;**13**(4):1004-8.

Dellemijn 1994 {published data only}

Dellemijn PL, Verbiest HB, Van Vliet JJ, Roos PJ, Vecht CJ. Medical therapy of malignant nerve pain. A randomised double-blind explanatory trial with naproxen versus slow-release morphine. *European Journal of Cancer* 1994;**30A**(9):1244-50.

Deschamps 1992 {published data only}

Deschamps M, Band PR, Hislop TG, Rusthoven J, Iscoe N, Warr D. The evaluation of analgesic effects in cancer patients as exemplified by a double-blind, crossover study of immediate-release versus controlled-release morphine. *Journal of Pain and Symptom Management* 1992;**7**(7):384-92.

Ferrell 1989 {published data only}

Ferrell B, Wisdom C, Wenzl C, Brown J. Effects of controlled released morphine on quality of life for cancer pain. *Oncology Nursing Forum* 1989;**16**(4):521-6.

Finn 1993 {published data only}

Finn JW, Walsh TD, MacDonald N, Bruera E, Krebs LU, Shepard KV. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *Journal of Clinical Oncology* 1993;**11**(5):967-72.

Flöter 1997 {published data only}

Flöter T, Koch EMW, and the Kap-Cas study group. Comparison of two oral morphine formulations for chronic severe pain of malignant and non malignant origin Kapanol (R) vs MST (R). *Clinical Drug Investigation* 1997;**14**(3):183-91.

Gillette 1997 {published data only}

Gillette JF, Ferme C, Moisy N, Mignot L, Schach R, Vignaux J, et al. Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. *Clinical Drug Investigation* 1997;**14**(Suppl 1):22-7.

Gourlay 1997 {published data only}

Gourlay GK, Cherry DA, Onley MM, Tordoff SG, Conn DA, Hood GM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain* 1997;**69**(3):295-302.

Hagen 2005 {published data only}

Hagen NA, Thirlwell M, Eisenhoffer J, Quiquley P, Harsanyi Z, Darke A. Efficacy, safety, and steady state pharmacokinetics of once-a-day controlled release morphine (MS Contin XL) in cancer pain. *Journal of Pain and Symptom Management* 2005;**29**(1):80-90.

Hanks 1987a {published data only}

Hanks GW, Twycross RG, Bliss JM. Controlled release morphine tablets: a double blind trial in patients with advanced cancer. *Anaesthesia* 1987;**42**(8):840-4.

Hanks 1995 {published data only}

Hanks GW, Hanna M, Finlay I, Radstone DJ, Keeble T. Efficacy and pharmacokinetics of a new controlled-release morphine sulfate 200-mg tablet. *Journal of Pain and Symptom Management* 1995;**10**(1):6-12.

Hanna 2008 {published data only}

Hanna M, Thipphawong J. A randomized, double-blind comparison of OROS hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC Palliative Care* 2008;**7**:17.

Harris 2003 {published data only}

Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. *Palliative Medicine* 2003;**17**:248-56.

Heiskanen 2000 {published data only}

Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997;**73**:37-45.

* Heiskanen TE, Ruismaki PM, Seppala TA, Kalso EA. Morphine or oxycodone in cancer pain? *Acta Oncologica* 2000;**39**(8):941-7.

Homs 2010 {published data only}

Homs J, Walsh D, Lasheen W, Nelson KA, Rybicki LA, Bast J, et al. A comparative study of 2 sustained-release morphine preparations for pain in advanced cancer. *American Journal of Hospice and Palliative Care* 2010;**27**:99-105.

Hoskin 1989 {published data only}

Hoskin PJ, Poulain P, Hanks GW. Controlled release morphine in cancer pain. Is a loading dose required when the formulation is changed? *Anaesthesia* 1989;**44**(11):897-901.

Kalso 1990 {published data only}

Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clinical Pharmacology and Therapeutics* 1990;**47**(5):639-46.

Kerr 2000 {published data only}

Kerr RO, Tester WJ. A patient preference study comparing two extended-release morphine sulfate formulations (once-daily Kadian™ versus twice-daily MS Contin™) for cancer pain. *Clinical Drug Investigation* 2000;**19**(1):25-32.

Klepstad 2003 {published data only}

Klepstad P, Kaasa S, Jystad A, Hval B, Borchgrevink PC. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain* 2003;**101**(1-2):193-8.

Knudsen 1985 {published data only}

Henriksen H, Knudsen J. Controlled evaluation and ongoing experience with sustained release morphine in patients with advanced cancer pain. In: *Advances in Cancer Pain Management. The International Symposium on Pain Control*. Toronto: Purdue Frederick Inc, 1986.

* Knudsen J, Mortensen SM, Eikard B, Henriksen H. Slow-release morphine tablets compared with conventional morphine tablets in the treatment of cancer pain [Morfin-depottabletter og konventionelle morfintabletter ved cancersmerter]. *Ugeskrift for Læger* 1985;**147**(9):780-4.

Kossman 1983 {published data only}

Kossman B, Dick W, Bowdler I, Kilian J, Hecht M. Modern aspects of morphine therapy. In: *Advances in Morphine Therapy. The 1983 International Symposium on Pain Control*. Royal Society of Medicine International Congress and Symposium Series no 64. London: Royal Society of Medicine, 1983:73-81.

Lauretti 2003 {published data only}

Lauretti GR, Oliveira GM, Pereira NL. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. *British Journal of Cancer* 2003;**89**(11):2027-30.

Leppart 2001 {published data only}

Leppart W. Analgesic efficacy and side effects of oral tramadol and morphine administered orally in the treatment of cancer pain. *Nowotwory* 2001;**51**(3):257-66.

Melzack 1979 {published data only}

Melzack R, Mount BM, Gordon JM. The Brompton mixture versus morphine solution given orally: effects on pain. *Canadian Medical Association Journal* 1979;**120**(4):435-8.

Mercadante 1998 {published data only}

Mercadante S, Salvaggio L, Dardanoni G, Agnello A, Garofalo S. Dextropropoxyphene versus morphine in opioid-naïve cancer patients with pain. *Journal of Pain and Symptom Management* 1998;**15**(2):76-81.

Mercadante 2008 {published data only}

Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *European Journal of Pain* 2008;**12**:1040-6.

Mercadante 2010 {published data only}

Mercadante S, Tirelli W, David F, Arcara C, Fulfaro F, Casuccio A, et al. Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study. *Clinical Journal of Pain* 2010;**26**(9):294-7.

Mignault 1995 {published data only}

Mignault GG, Latreille J, Viguie F, Richer P, Lemire F, Harsanyi Z, et al. Control of cancer-related pain with MS Contin: a comparison between 12-hourly and 8-hourly administration. *Journal of Pain and Symptom Management* 1995;**10**(6):416-22.

Mizuguchi 1990 {published data only}

Mizuguchi K, Takeda F, Hiraga K, Nakashima M. Utility evaluation of morphine hydrochloride suppository, AN-631, in the treatment of cancer pain. *Rinshou Igaku* 1990;**6**(11):2357-76.

Moriarty 1999 {published data only}

Moriarty M, McDonald CJ, Miller AJ. A randomised crossover comparison of controlled release hydromorphone tablets with controlled release morphine tablets in patients with cancer pain. *Journal of Clinical Research* 1999;**2**:1-8.

Mucci LoRusso 1998 {published data only}

Mucci LoRusso P, Berman BS, Silberstein PT, Citron ML, Bressler L, Weinstein SM, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. *European Journal of Pain* 1998;**2**:239-49.

O'Brien 1997 {published data only}

O'Brien T, Mortimer PG, McDonald CJ, Miller AJ. A randomized crossover study comparing the efficacy and tolerability of a novel once-daily morphine preparation (MXL capsules) with MST Continus tablets in cancer patients with severe pain. *Palliative Medicine* 1997;**11**(6):475-82.

Oztürk 2008 {published data only}

Oztürk T, Karadibak K, Catal D, Cakan A, Tugsavul F, Cırak K. Comparison of TD-fentanyl with sustained-release morphine in the pain treatment of patients with lung cancer [Akciğer Kanseri Hastalarının Ağrılarının Tedavisinde Transdermal Fentanil ve Yavaş Salımlı Morfinin Karşılaştırılması.]. *Agri* 2008;**20**:20-5.

Panich 1993 {published data only}

Panich A, Charnvej L. Comparison of morphine slow release tablet (MST) and morphine sulphate solution (MSS) in the treatment of cancer pain. *Journal of Medical Association of Thailand* 1993;**76**(12):672-6.

Portenoy 1989 {published data only}

* Portenoy R, Maldonado M, Fitzmartin R, Kaiko R, Kanner R. Oral controlled release morphine sulfate. Analgesic efficacy and

side effects of a 100 mg tablet in cancer pain patients. *Cancer* 1989;**63**(Suppl 11):2284-8.

Portenoy RK, Maldonado M, Fitzmartin R, Kaiko R, Kanner R. Controlled-release morphine sulfate: analgesic efficacy and side effects of a 100 mg tablet. *Journal of Pain and Symptom Management* 1988;**3**(3):Suppl 16.

Ridgway 2010 {published data only}

Ridgway D, Sopata M, Burneckis A, Jespersen L, Andersen C. Clinical efficacy and safety of once-daily dosing of a novel, prolonged-release oral morphine tablet compared with twice-daily dosing of a standard controlled-release morphine tablet in patients with cancer pain: a randomized, double-blind, exploratory crossover study. *Journal of Pain and Symptom Management* 2010;**39**:712-20.

Rodriguez 1994 {published data only}

Rodriguez M, Barutell C, Rull M, Gálvez R, Pálles J, Vidal F, et al. Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. *European Journal of Cancer* 1994;**30A**(5):584-7.

Smith 1991 {published data only}

Smith KJ, Miller AJ, McKellar J, Court M. Morphine at gramme doses: kinetics, dynamics and clinical need. *Postgraduate Medical Journal* 1991;**67**(Suppl 2):S55-9.

Thirlwell 1989 {published data only}

Thirlwell MP, Sloan PA, Maroun JA, Boos GJ, Besner JG, Stewart JH, et al. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989;**63**(Suppl 11):2275-83.

Todd 2002 {published data only}

Todd J, Rees E, Gwilliam B, Davies A. An assessment of the efficacy and tolerability of a 'double dose' of normal-release morphine sulphate at bedtime. *Palliative Medicine* 2002;**16**:507-12.

Twycross 1977 {published data only}

Twycross R. The measurement of pain in terminal carcinoma. *Journal of International Medical Research* 1976;**4**(Suppl 2):58-67.

* Twycross RG. Choice of strong analgesic in terminal cancer: diamorphine or morphine? *Pain* 1977;**3**:93-104.

Vainio 1988 {published data only}

Vainio A, Tigerstedt I. Opioid treatment for radiating cancer pain: oral administration vs. epidural techniques. *Acta Anaesthesiologica Scandinavica* 1988;**32**(3):179-85.

Van Seventer 2003 {published data only}

Van Seventer R, Smit JM, Schipper RM, Wicks MA, Zuurmond WW. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. *Current Medical Research and Opinion* 2003;**19**(6):457-69.

Ventafridda 1986 {published data only}

Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F. A randomized study on oral administration of morphine and

methadone in the treatment of cancer pain. *Journal of Pain and Symptom Management* 1986;**1**(4):203-7.

Ventafridda 1989 {published data only}

Ventafridda V, Saita L, Barletta L, Sbanotto A, De Conno F. Clinical observations on controlled release morphine in cancer pain. *Journal of Pain and Symptom Management* 1989;**4**(3):124-9.

Vielvoye-Kerkmeier 2002 {published data only}

Vielvoye-Kerkmeier A, Van Tinteren H, Mattern C, Schüller J, Farnell A. Sustained release morphine in cancer pain. *European Journal of Palliative Care* 2002;**9**(4):137-40.

Walsh 1985a {published data only}

Walsh TD. A controlled study of MST Continus tablets for chronic pain in advanced cancer. In: Wilkes E, editors(s). *Advances in Morphine Therapy: International Symposium on Pain Control*. London: Royal Society of Medicine, 1984:99-102.

* Walsh TD. Clinical evaluation of slow release morphine tablets. *Advances in Pain Research and Therapy* 1985;**9**:727-31.

Walsh 1992 {published data only}

Walsh TD, MacDonald N, Bruera E, Shepard KV, Michaud M, Zanes R. A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. *American Journal of Clinical Oncology* 1992;**15**(3):268-72.

Wilder-Smith 1994 {published data only}

Wilder-Smith CH, Schimke J, Osterwalder B, Senn HJ. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Annals of Oncology* 1994;**5**(2):141-6.

Wilkinson 1992 {published data only}

Wilkinson TJ, Robinson BA, Begg EJ, Duffull SB, Ravenscroft PJ, Schneider JJ. Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients. *Cancer Chemotherapy and Pharmacology* 1992;**31**(3):251-4.

Wong 1997 {published data only}

Wong JO, Chiu GL, Tsao CJ, Chang CL. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiologica Sinica* 1997;**35**(1):25-32.

Xu 1997 {published data only}

Xu GZ, Cai ZJ, Deng YP, Zhou J, Xie GR, Liu SJ. Clinical evaluation of the analgesic effect of sustained release morphine sulfate microgranules in patients with terminal cancer. *Clinical Drug Investigation* 1997;**Suppl 14**(1):34-42.

References to studies excluded from this review

Babul 1992 {published data only}

Babul N, Darke AC, Anslow JA, Krishnamurthy TN. Pharmacokinetics of two novel rectal controlled-release morphine formulations. *Journal of Pain and Symptom Management* 1992;**7**(7):400-5.

Beaver 1977 {published data only}

Beaver WT, Wallenstein SL, Houde RW, Rogers A. Comparisons of the analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. *Journal of Clinical Pharmacology* 1977;**17**(4):186-98.

Beaver 1978 {published data only}

Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *Journal of Pharmacology and Experimental Therapeutics* 1978;**207**(1):92-100.

Bosek 1994 {published data only}

Bosek V, Miguel R. Comparison of morphine and ketorolac for intravenous patient-controlled analgesia in postoperative cancer patients. *Clinical Journal of Pain* 1994;**10**(4):314-8.

Brooks 1989 {published data only}

Brooks I, De Jager R, Blumenreich M, George E, Savarese JJ. Principles of cancer pain management. Use of long-acting oral morphine. *Journal of Family Practice* 1989;**28**(3):275-80.

Broomhead 1997b {published data only}

Broomhead A, West R, Kadigamanathan G, Knox K, Krueger D, Malick J. Comparative bioavailability of sustained-release morphine sulfate capsules versus pellets. *Clinical Drug Investigation* 1997;**14**(2):137-45.

Bruera 1995 {published data only}

Bruera E, Fainsinger R, Spachynski K, Babul N, Harsanyi Z, Darke AC. Clinical efficacy and safety of a novel controlled-release morphine suppository and subcutaneous morphine in cancer pain: a randomized evaluation. *Journal of Clinical Oncology* 1995;**13**(6):1520-7.

Buxton 1987 {published data only}

Buxton B. A comparison of morphine sulphate solution and MST Continus tablets in the treatment of pain in terminally ill at home. In: Derek Doyle, editors(s). *International Symposium on Pain Control*. Royal Society of Medicines Services International Congress and Symposium Series 123. London: Royal Society of Medicines Services Ltd, 1987:132.

Carlson 1990 {published data only}

Carlson RW, Borrison RA, Sher HB, Eisenberg PD, Mowry PA, Wolin EM. A multiinstitutional evaluation of the analgesic efficacy and safety of ketorolac tromethamine, acetaminophen plus codeine, and placebo in cancer pain. *Pharmacotherapy* 1990;**10**(3):211-6.

Cherny 1994 {published data only}

Cherny NI, Thaler HT, Friedlander-Klar H, Lapin J, Foley KM, Houde R, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. *Neurology* 1994;**44**(5):857-61.

Chrubasik 1987 {published data only}

Chrubasik J, Geller E, Niv D, Zindler M. Morphine inhalation versus intravenous infusion in pain treatment after abdominal surgery. *Anesthesia and Analgesia* 1987;**66**:Suppl 29.

Citron 1992 {published data only}

Citron ML, Kalra JM, Seltzer VL, Chen S, Hoffman M, Walczak MB. Patient-controlled analgesia for cancer pain: a long-term study of inpatient and outpatient use. *Cancer Investigation* 1992;**10**(5):335-41.

Cleeland 1996 {published data only}

Cleeland CS, Nakamura Y, Howland EW, Morgan NR, Edwards KR, Backonja M. Effects of oral morphine on cold pressor tolerance time and neuropsychological performance. *Neuropsychopharmacology* 1996;**15**(3):252-62.

Coluzzi 2001 {published data only}

* Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001;**91**(1-2):123-30.

Coluzzi PH, Schwartzberg L, Conroy Jr JD, Charapata S, Gay M, Busch M, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Docteurs* 2002;**3**(1):26-35.

Coluzzi PH, Schwartzberg L, Conroy Jr JD, Charapata S, Gay M, Busch M et al. Irruptive pain in cancer: A randomized comparative trial of oral transmucosal fentanyl citrate (OTFC) versus immediate-release morphine sulphate (MSIR). *Revista De La Sociedad Espanola Del Dolor* 2002;**9**(5):306-16.

Corli 2012 {published data only}

Corli O, Montanari M, Deandrea S, Greco MT, Villani W. An exploratory analysis on the effectiveness of four strong opioids in patients with cancer pain. *Pain Medicine* 2012;**13**:897-907. [DOI: [10.1111/j.1526-4637](https://doi.org/10.1111/j.1526-4637)]

Cowen 1997 {published data only}

Cowen D, Tardieu C, Schubert M, Peterson D, Resbeut M, Faucher C, et al. Low energy helium-neon laser in the prevention of oral mucositis in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 1997;**38**(4):697-703.

Davis 1993 {published data only}

Davis T, Miser AW, Loprinzi CL, Kaur JS, Burnham NL, Dose AM, et al. Comparative morphine pharmacokinetics following sublingual, intramuscular, and oral administration in patients with cancer. *Hospice Journal* 1993;**9**(1):85-90.

De Bernardi 1997 {published data only}

De Bernardi M, De Bernardi F, Colombo P. Randomised crossover comparison of the pharmacokinetic profiles of two sustained release morphine sulfate formulations in

patients with cancer-related pain. *Clinical Drug Investigation* 1997;**14**(Suppl 1):28-33.

De Conno 1997 {published data only}

De Conno F. Analgesic efficacy and side effects of opioids in different routes of administration for terminal cancer patients: a clinical, pharmacokinetic and neurophysiological study. *Journal of Clinical Oncology* 1997;**13**:49-51.

Deng 1997 {published data only}

Deng Y, Xu G, Wang K. The steady-state concentration of morphine sulphate tablets and its clinical analgesic effect in cancer patients. *Chinese Pharmaceutical Journal* 1997;**32**(6):356-9.

Donner 1998 {published data only}

Donner B, Zenz M, Strumpf M, Raber M. Long-term treatment of cancer pain with transdermal fentanyl. *Journal of Pain and Symptom Management* 1998;**15**(3):168-75.

Drexel 1989 {published data only}

Drexel H, Dzien A, Spiegel RW, Lang AH, Breier C, Abbrederis K, et al. Treatment of severe cancer pain by low-dose continuous subcutaneous morphine. *Pain* 1989;**36**(2):169-76.

Du 1999 {published data only}

Du X, Skopp G, Aderjan R. The influence of the route of administration: a comparative study at steady state of oral sustained release morphine and morphine sulfate suppositories. *Therapeutic Drug Monitoring* 1999;**21**(2):208-14.

Dudgeon 2007 {published data only}

Dudgeon DJ, Bruera E, Gagnon B, Watanabe SM, Allan SJ, Warr DG, et al. A phase III randomized, double-blind, placebo-controlled study evaluating dextromethorphan plus slow-release morphine for chronic cancer pain relief in terminally ill patients. *Journal of Pain and Symptom Management* 2007;**33**:365-71.

Ernst 1992 {published data only}

Ernst DS, MacDonald RN, Paterson AH, Jensen J, Brasher P, Bruera E. A double-blind, crossover trial of intravenous clodronate in metastatic bone pain. *Journal of Pain and Symptom Management* 1992;**7**(1):4-11.

Farrar 1998 {published data only}

Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *Journal of the National Cancer Institute* 1998;**90**(8):611-6.

Faura 1996 {published data only}

Faura CC, Moore RA, Horga JF, Hand CW, McQuay HJ. Morphine and morphine-6-glucuronide plasma concentrations and effect in cancer pain. *Journal of Pain and Symptom Management* 1996;**11**(2):95-102.

Forman 1993 {published data only}

Forman WB, Portenoy RK, Yanagihara RH, Hunt C, Kush R, Shepard K. A novel morphine sulphate preparation: clinical trial

of a controlled-release morphine suspension in cancer pain. *Palliative Medicine* 1993;**7**(4):301-6.

Georgiou 2000 {published data only}

Georgiou L, Louizos A, Sklavou C, Manolopoulos L, Yiotakis I, Adamopoulos G. Cervical versus thoracic epidural morphine for the treatment of head and neck cancer pain. *Annals of Otolaryngology & Laryngology* 2000;**109**(7):676-8.

Glare 1993 {published data only}

Glare PA, Walsh TD. Dose-ranging study of oxycodone for chronic pain in advanced cancer. *Journal of Clinical Oncology* 1993;**11**(5):973-8.

Gourlay 1986 {published data only}

Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986;**25**(3):297-312.

Gourlay 1995 {published data only}

Gourlay GK, Plummer JL, Cherry DA. Chronopharmacokinetic variability in plasma morphine concentrations following oral doses of morphine solution. *Pain* 1995;**61**(3):375-81.

Griffith 1990 {published data only}

Griffith S, Dewberry HM, Titcombe JM, McNamara PJG, Harcourt JMV, Twycross RG. Evaluation of the palatability of Oramorph - a proprietary preparation of oral morphine sulphate. *Palliative Medicine* 1990;**4**:205-9.

Hagen 1995 {published data only}

Hagen N, Thirlwell MP, Dhaliwal HS, Babul N, Harsanyi Z, Darke AC. Steady-state pharmacokinetics of hydromorphone and hydromorphone-3-glucuronide in cancer patients after immediate and controlled-release hydromorphone. *Journal of Clinical Pharmacology* 1995;**35**(1):37-44.

Hanks 1984 {published data only}

Hanks GW, Trueman T. Controlled release morphine tablets in chronic cancer pain. *Pain* 1984;**Suppl**:406.

Hasselstrom 1991 {published data only}

Hasselstrom J, Alexander N, Bringel C, Svensson JO, Sawe J. Single dose and steady state kinetics of morphine and its metabolites in cancer patients - a comparison of two oral formulations. *European Journal of Clinical Pharmacology* 1991;**40**(6):585-91.

Hill 1990 {published data only}

Hill HF, Chapman CR, Kornell JA, Sullivan KM, Saeger LC, Benedetti C. Self-administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 1990;**40**(2):121-9.

Hill 1992 {published data only}

Hill HF, Coda BA, Mackie AM, Iverson K. Patient-controlled analgesic infusions: alfentanil versus morphine. *Pain* 1992;**49**(3):301-10.

Hoffman 1997 {published data only}

Hoffman M, Xu JC, Smith C, Fanelli C, Pascal V, Degaetano C, et al. A pharmacodynamic study of morphine and its glucuronide metabolites after single morphine dosing in cancer patients with pain. *Cancer Investigation* 1997;**15**(6):542-7.

Houde 1981 {published data only}

Houde RW, Kaiko RF, Wallenstein SL, Rogers AG. Analgesic assay of oral zomepirac and intramuscular morphine in advanced cancer patients. *Pain* 1981;**Suppl**:247.

Kaiko 1979 {published data only}

Kaiko R, Wallenstein S, Rogers A, Heidrich G 3rd, Houde R. Relative analgesic potency of intramuscular heroin and morphine in cancer patients with postoperative pain: a preliminary report. *National Institute on Drug Abuse Research Monograph* 1979;**27**:254-60.

Kaiko 1984 {published data only}

Kaiko RF, Wallenstein SL, Lapin J, Houde RW. Oral fenoprofen compared to intramuscular morphine and oral aspirin in cancer patients with postoperative pain. *National Institute on Drug Abuse Research Monograph* 1984;**49**:205-11.

Kaiko 1987 {published data only}

Kaiko RF, Kanner R, Foley KM, Wallenstein SL, Canel AM, Rogers AG, et al. Cocaine and morphine interaction in acute and chronic cancer pain. *Pain* 1987;**31**(1):35-45.

Kaiko 1989 {published data only}

Kaiko RF, Grandy RP, Oshlack B, Pav J, Horodniak J, Thomas G, et al. The United States experience with oral controlled release morphine (MS Contin tablets). Parts I and II. Review of nine dose titration studies and clinical pharmacology of 15 mg, 30 mg, 60 mg, and 100 mg tablet strengths in normal subjects. *Cancer* 1989;**63**(Suppl 11):2348-54.

Kalso 1996 {published data only}

Kalso E, Heiskanen T, Rantio M, Rosenberg PH, Vainio A. Epidural and subcutaneous morphine in the management of cancer pain: a double-blind cross-over study. *Pain* 1996;**67**(2-3):443-9.

Khojasteh 1987 {published data only}

Khojasteh A, Evans W, Reynolds R, Thomas G, Savarese J. Controlled release oral morphine sulfate in the treatment of cancer pain with pharmacokinetic correlation. *Journal of Clinical Oncology* 1987;**5**(6):956-61.

Lakdja 1997 {published data only}

Lakdja F, Dixmerias F, Bussieres E, Fonrouge J-M, Lobera A. Preemptive analgesia on postmastectomy pain syndrome with ibuprofen-arginine [Effet analgesique preventif d'une administration perioperatoire d'ibuprofene-arginine sur le syndrome douloureux postmastectomie]. *Bulletin Du Cancer* 1997;**84**(3):259-63.

Lauretti 1999 {published data only}

Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants

to oral morphine therapy for cancer pain management. *Anesthesiology* 1999;**90**(6):1528-33.

Lazarus 1990 {published data only}

Lazarus H, Fitzmartin RD, Goldenheim PD. A multi investigator clinical evaluation of oral controlled release morphine (MS Contin tablets) administered to cancer patients. *Hospice Journal* 1990;**6**(4):1-15.

Li 1994 {published data only}

Li QS, Cao SH, Xie GM, Gan YH, Ma H, Lu JZ, et al. Combined traditional Chinese medicine and Western medicine. Relieving effects of Chinese herbs, ear-acupuncture and epidural morphine on postoperative pain in liver cancer. *Chinese Medical Journal* 1994;**107**(4):289-94.

Marinangeli 2004 {published data only}

Marinangeli F, Ciccozzi A, Leonardi M, Aloisio L, Mazzei A, Paladini A, et al. Use of strong opioids in advanced cancer pain: a randomized trial. *Journal of Pain and Symptom Management* 2004;**27**(5):409-16.

Masood 1995 {published data only}

Masood AR, Subhan MM, Reed JW, Thomas SH. Effects of inhaled nebulized morphine on ventilation and breathlessness during exercise in healthy man. *Clinical Science* 1995;**88**(4):447-52.

Masood 1996 {published data only}

Masood AR, Thomas SH. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *British Journal of Clinical Pharmacology* 1996;**41**(3):250-2.

Meed 1987 {published data only}

Meed SD, Kleinman PM, Kantor TG, Blum RH, Savarese JJ. Management of cancer pain with oral controlled-release morphine sulfate. *Journal of Clinical Pharmacology* 1987;**27**(2):155-61.

Minotti 1989 {published data only}

Minotti V, Patoia L, Roila F, Basurto C, Tonato M, Pasqualucci V, et al. Double-blind evaluation of analgesic efficacy of orally administered diclofenac, nefopam, and acetylsalicylic acid (ASA) plus codeine in chronic cancer pain. *Pain* 1989;**36**(2):177-83.

Minotti 1998 {published data only}

Minotti V, De Angelis V, Righetti E, Celani MG, Rossetti R, Lupatelli M, et al. Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* 1998;**74**(2-3):133-7.

Morgan 1992 {published data only}

Morgan DJ, McCormick Y, Cosolo W, Roller L, Zalberg J. Prolonged release of morphine alkaloid from a lipophilic suppository base in vitro and in vivo. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1992;**30**(12):576-81.

Moulin 1996 {published data only}

Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996;**347**(8995):143-7.

NCT00573937 2010 {published data only}

Prommer E (lead investigator). Methadone versus morphine for cancer-related pain. <https://clinicaltrials.gov/ct2/show/NCT00573937> 2010.

NCT00660348 2014 {published data only}

Erdek M (lead investigator). A randomized study of optimal pain management: standard pain control versus early intervention with intrathecal therapy in patients with advanced pancreatic cancer. <https://clinicaltrials.gov/ct2/show/NCT00660348> 2014.

NCT00726830 2012 {unpublished data only}

Fisch M, Bearden J (lead investigators). A randomized comparison of oral methadone as a "first-switch" opioid versus opioid switching between sustained-release morphine and oxycodone for oncology-hematology outpatients with pain management problems: the "simply rotate" study. <https://clinicaltrials.gov/ct2/show/NCT00726830> 2010.

NCT01541124 2012 {published data only}

Nunes B, Garcia J, Sakata R. Morphine as the first drug for treatment of cancer pain. *Journal of Palliative Medicine* 2012;**15**:963-4.

Sakata R (lead investigator). Morphine as the first drug for the treatment of cancer pain. <https://clinicaltrials.gov/ct2/show/NCT01541124> 2010.

Penn 1992 {published data only}

Penn RD, Paice JA, Kroin JS. Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992;**49**(1):13-9.

Portenoy 1999a {published data only}

Portenoy RK, Payne R, Coluzzi P, Rashko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* 1999;**79**(2-3):303-12.

Repas 1992 {published data only}

Repas C. Tramadol and the possibilities for its use with cancer patients [Tramadol i vozmozhnosti ego primeneniia u onkologicheskikh bol'nykh]. *Terapevticheskii Arkhiv* 1992;**64**(10):91-6.

Ripamonti 1992 {published data only}

Ripamonti C, Sita L, De Conno F, Ventafridda V, MacEachern T, Hanson J, et al. Rectal versus oral morphine for the management of cancer pain. A double-blind, double dummy cross-over trial. In: Proceedings of the Annual Meeting of the American Society of Clinical Oncology. ASCO, 1992:397.

Roca 1996 {published data only}

Roca G, Aguilar JL, Gomar C, Mazo V, Costa J, Vidal F. Nimodipine fails to enhance the analgesic effect of slow release morphine in the early phases of cancer pain treatment. *Pain* 1996;**68**:239-43.

Santillan 1998 {published data only}

Santillan R, Hurlle MA, Armijo JA, De los Mozos R, Florez J. Nimodipine-enhanced opiate analgesia in cancer patients requiring morphine dose escalation: a double-blind, placebo-controlled study. *Pain* 1998;**76**(1-2):17-26.

Savarese 1988 {published data only}

Savarese JJ, Thomas GB, Homesley H, Hill CS. Rescue factor: a design for evaluating long-acting analgesics. *Clinical Pharmacology and Therapeutics* 1988;**43**(4):376-80.

Säwe 1983 {published data only}

Säwe J, Dahlstrom B, Rane A. Steady-state kinetics and analgesic effect of oral morphine in cancer patients. *European Journal of Clinical Pharmacology* 1983;**24**:537-42.

Schaer 1992 {published data only}

Schaer H, Baasch K, Prochacka K. Intrathecal morphine for postoperative pain [Intrathekales morphin für postoperativen schmerz]. *Der Anaesthetist* 1992;**41**(11):689-93.

Shimoyama 2015 {published data only}

Shimoyama N, Gomyo I, Teramoto O, Kojima K, Higuchi H, Yukitoshi N, et al. Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined from oral morphine rescue doses in the treatment of breakthrough cancer pain. *Japanese Journal of Clinical Oncology* 2015;**45**:189-96. [DOI: [10.1093/jjco/hyu182](https://doi.org/10.1093/jjco/hyu182)]

Sjogren 1989 {published data only}

Sjogren P, Banning AM, Henriksen H. High-dose epidural opioid treatment of malignant pain [Højdosid epidural opioidbehandling af miligne smerter]. *Ugeskrift for Læger* 1989;**151**(1):25-8.

Sloan 1998 {published data only}

Sloan PA, Moulin DE, Hays H. A clinical evaluation of transdermal therapeutic system fentanyl for the treatment of cancer pain. *Journal of Pain and Symptom Management* 1998;**16**(2):102-11.

Stambaugh 1981 {published data only}

Stambaugh JE. Comparison of the analgesic effect of parenteral levonantradol to morphine and placebo in patients with moderate to severe pain of cancer. *Pain* 1981;**Suppl**:97.

Stambaugh 1990 {published data only}

Stambaugh J, Drew J, Davis M. Comparison of immediate vs. sustained released oral morphine in cancer patients - acute pain novel study design. *Journal of Clinical Pharmacology* 1990;**30**:838.

Stambaugh 2001 {published data only}

Stambaugh JE, Reder RF, Stambaugh MD, Stambaugh H, Davis M. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *Journal of Clinical Pharmacology* 2001;**41**(5):500-6.

Sykes 1996 {published data only}

Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliative Medicine* 1996;**10**(2):135-44.

Takeda 1987 {published data only}

Takeda F. A clinical evaluation of S-8114 (morphine sulphate controlled-release tablets) in the management of cancer pain: comparison with oral morphine hydrochloride. *Kiso to Rinsho (The Clinical Report)* 1987;**21**(17):6889-906.

Tawfik 1990 {published data only}

Tawfik MO, Elborolossy K, Nasr F. Tramadol hydrochloride in the relief of cancer pain. A double blind comparison against sustained release morphine. *Pain* 1990;**Suppl**:S377.

Wallenstein 1980 {published data only}

Wallenstein SL, Rogers A, Kaiko RF, Heidrich G 3d, Houde RW. Relative analgesic potency of oral zomepirac and intramuscular morphine in cancer patients with postoperative pain. *Journal of Clinical Pharmacology* 1980;**20**(4):250-8.

Walsh 1984 {published data only}

Walsh TD. Controlled study of slow release morphine for chronic pain in advanced cancer. *Pain* 1984;**Suppl**:S202.

Walsh 1985b {published data only}

Walsh TD. Controlled study of oral slow release morphine in pain due to advanced cancer. In: Proceedings of the Annual Meeting of the American Society of Clinical Oncology. Vol. 9. ASCO, 1985:Abs No 1035.

Weingart 1985 {published data only}

Weingart W, Sorkness C, Earhart R. Analgesia with oral narcotics and added ibuprofen in cancer patients. *Clinical Pharmacy* 1985;**4**(1):53-8.

Westerling 1993 {published data only}

Westerling D, Frigren L, Höglund P. Morphine pharmacokinetics and effects on salivation and continuous reaction times in healthy volunteers. *Therapeutic Drug Monitoring* 1993;**15**(5):364-74.

References to ongoing studies
NCT01809106 2014a {unpublished data only}

Corli O (lead investigator). RCT comparing the analgesic efficacy of 4 therapeutic strategies based on 4 different major opioids (fentanyl, oxycodone, buprenorphine vs morphine) in cancer patients with moderate/severe pain, at the moment of starting 3rd step of WHO analgesic ladder (CERP). <https://clinicaltrials.gov/ct2/show/NCT01809106> 2014.

Additional references
Caraceni 2011

Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care

Research Collaborative guidelines project. *Palliative Medicine* 2011;**25**(5):402-9. [DOI: [10.1177/0269216310392102](https://doi.org/10.1177/0269216310392102)]

Collins 1998

Collins SL, Faura CC, Moore RA, McQuay HJ. Peak plasma concentrations after oral morphine - a systematic review. *Journal of Pain and Symptom Management* 1998;**16**:388-402.

Cook 1995

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

Faura 1998

Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. *Pain* 1998;**74**:43-53.

Goudas 2001

Goudas L, Carr DB, Bloch R, Balk E, Ioannides JP, Terrin N, et al. Management of cancer pain. Evidence report/Technology Assessment No 35 ARHQ Publication No 02-E002. Rockville MD: ARHQ, 2001.

Grahame-Smith 2002

Grahame-Smith DG, Aronson JK. Oxford Textbook of Clinical Pharmacology and Drug Therapy. 3rd edition. Oxford: Oxford University Press, 2002.

Hadley 2013

Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No: CD010270. [DOI: [10.1002/14651858.CD010270.pub2](https://doi.org/10.1002/14651858.CD010270.pub2)]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoffman 2010

Hoffman DL, Sadosky A, Dukes EM, Alvir J. How do changes in pain severity levels correspond to changes in health status and function in patients with painful diabetic peripheral neuropathy? *Pain* 2010;**149**(2):194-201. [DOI: [10.1016/j.pain.2009.09.017](https://doi.org/10.1016/j.pain.2009.09.017)]

Jadad 1996a

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

Jadad 1996b

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

L'Abbé 1987

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

Mandal 2015

Mandal A. Morphine pharmacology. <http://www.news-medical.net/health/Morphine-Pharmacology.aspx> (accessed December 2015).

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything--large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16.

Moore 2008

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

Moore 2010a

Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain--establishing best practice in the reporting of systematic reviews. *Pain* 2010;**14**(7):386-9. [DOI: [10.1016/j.pain.2010.05.011](https://doi.org/10.1016/j.pain.2010.05.011)]

Moore 2010b

Moore RA, Derry S, McQuay HJ, Straube S, Aldington D, Wiffen P, et al. Clinical effectiveness: an approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. *Pain* 2010;**149**(2):173-6. [DOI: [10.1016/j.pain.2009.08.007](https://doi.org/10.1016/j.pain.2009.08.007)]

Moore 2010c

Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. *Pain* 2010;**149**(2):360-4. [DOI: [10.1016/j.pain.2010.02.039](https://doi.org/10.1016/j.pain.2010.02.039)]

Moore 2011

Moore RA, Mhuirheartaigh RJ, Derry S, McQuay HJ. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 2011;**28**(6):427-32. [DOI: [10.1097/EJA.0b013e328343c569](https://doi.org/10.1097/EJA.0b013e328343c569)]

Moore 2012

Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No: CD008242. [DOI: [10.1002/14651858.CD008242.pub2](https://doi.org/10.1002/14651858.CD008242.pub2)]

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](https://doi.org/10.1111/anae.12148)]

Moore 2013b

Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. *BMJ* 2013;**346**:f2690. [DOI: [10.1136/bmj.f2690](https://doi.org/10.1136/bmj.f2690)]

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](https://doi.org/10.1136/bmj.c3515).]

Parfitt 1999

Parfitt K (editor). Martindale. The Complete Drug Reference. 32nd edition. London: Pharmaceutical Press, 1999.

Portenoy 1999b

Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999;**353**:1695-700.

Quigley 2007

Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No: CD003447. [DOI: [10.1002/14651858.CD003447](https://doi.org/10.1002/14651858.CD003447).]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rey 1993

Rey R. History of Pain. Paris: Editions La Decouverte, 1993. [ISBN 2-7071-2256-4]

Schmidt-Hansen 2015

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No: CD003870. [DOI: [10.1002/14651858.CD003870.pub5](https://doi.org/10.1002/14651858.CD003870.pub5).]

WHO 1986

World Health Organization. Cancer Pain Relief. Geneva: WHO, 1986.

WHO 2011

World Health Organization. WHO Essential Medicines List 17th Edition. whqlibdoc.who.int/hq/2011/a95053_eng.pdf 2011 (accessed 20 June 2013).

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahmedzai 1997

Study characteristics

Methods	Design: multicentre cross-over study. Pts' other medication was unchanged. Allowed other analgesics e.g. NSAIDs. MIR used freely to titrate pain control at start of study + cross-over. Mean age 61.5 (range 18 to 89) yrs; 55% men
Participants	Cancer pain Setting: palliative care centres, UK 202 pts (adults)
Interventions	Dosing regimen: Mm/r vs transdermal fentanyl for 15 d each arm (morphine SR 12-hourly patches every 72 h) Length of treatment: 30 d (15 d cross-over then 15 d)
Outcomes	Outcome measures: Self rated QOL, EORTC QLQ-C30 diary for sleep, rescue medication, drowsiness (VAS), MPAC used twice a day for mood, pain Analgesic outcome results: 94/122 fentanyl, 99/122 morphine recorded as successful by pt. Other outcome results 73/136 preferred patches, 19/136 morphine
Notes	Withdrawals and adverse events: 110/202 completed, 41 withdrew due to AE: Abdominal pain 18/126 women, 0/126 men; constipation 6/126 women, 15/126 men; diarrhoea 35/126 women, 7/126 men; nausea 32/126 women, 23/126 men; somnolence 17/126 women, 19/126 men; deaths 14 QS: 2 (R1, W1)

Risk of bias

Oral morphine for cancer pain (Review)

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Ahmedzai 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Low risk	202 participants crossed over

Arkinstall 1989

Study characteristics

Methods	Design: randomised, 2-phase cross-over in 10 days treatment phase. No further dose adjustment allowed apart from MIR for breakthrough. Mean age 63 yrs; mean weight 61.1 kg
Participants	Cancer pain Setting: hospital/acute/surgery/community 29 pts
Interventions	Dosing regimen: Mm/r 12-h vs MIR 4-hourly with MIR for breakthrough. All pts treated under double-blind conditions Length of treatment: 20 d (10 d cross-over then 10 d)
Outcomes	Outcome measures: Extra MIR and pt preference. Plasma morphine concentrations last 3 d of both phases. Side effects Analgesic outcome results: No sig diff between Mm/r and MIR pain scores. Rescue MIR no sig diff between groups. Preferred Mm/r - 8, MIR - 6. No preference - 3 Achieved no worse than mild pain with scores of < 2 on a 10-point VAS
Notes	Withdrawals and AEs: No sig diff for nausea or tiredness. 11/29 dropped out (10 during titration). Withdrawal due to AE 3 pts. 17 pts completed study QS: 4 (R1, DB2, W1)

Oral morphine for cancer pain (Review)

Arkinstall 1989 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"by means of random allocation"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebos were used to maintain blinding"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	29 pts

Babul 1998
Study characteristics

Methods	Design: DB, randomised, 2-way cross-over study. Dose stabilisation on morphine. Non-morphine pts transferred to morphine. Mean age 55 yrs
Participants	Cancer pain 27 pts Setting not specified
Interventions	Dosing regimen: Pts received rectal controlled release morphine or Mm/r every 12 hours for 7 d dose ratio M/rectal to M/oral 1:1. ?Cross-over after 7 d (not clear in methods). Non-opioid analgesics continued Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: Pain intensity (VAS) 4 x daily and PPI (6-point categorised scale). No pain 0, mild pain 1, discomforting pain 2, distressing pain 3, horrible pain 4, excruciating pain 5. Nausea, sedation - 100 mm VAS - spontaneous + investigator-reported Analgesic outcome results: No sig diff in pain intensity, PPI or rescue between groups. Mean daily doses were 226 mg morphine rectally and 235 mg orally. Pts preference: no preference 45%, MSC R 23%, MSC T 27% Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: M/rectal 2/27 Mm/r 2/27 as inadequate pain control. Less nausea on M/rectal (significant). Sedation similar between groups

Babul 1998 (Continued)

QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"DB conditions maintained by use of matching placebos"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	27 participants

Boureau 1992
Study characteristics

Methods	Design: randomised, DB cross-over study with 2 x 7-d periods. Pts on stable dose morphine for previous 48 h with adequate pain relief. Pts all on < 400 mg morphine/24 h
Participants	Cancer pain Multicentre, setting not stated 52 pts
Interventions	Dosing regimen: Modified release suspension and tablets. Previous daily dose of morphine given in 2 doses (12-hourly) Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: Pain severity (VAS) 3 x day. Verbal rating scale (5-point). Rescue medication. Pt preferences. Quality of life indices (activity mood sleep) by pt and investigator Analgesic outcome results: 44 pts available for analysis. No sig diff for pain score or rescue analgesia or QOL measures. Preference: none 21 pts, tablets 10, suspension 7. Morphine dose 108 mg (+/- 57 SD) /24 h. Range 40 to 260 mg
Notes	Withdrawals and AEs: 9 withdrew, 8 excluded, 4 withdrew for AE. Constipation 25/33 tablet, 26/33 suspension, drowsiness 20/29 tablet, 25/29 suspension. No sig diff between AEs. No cases of respiratory depression QS: 5

Boureau 1992 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"four patient block randomisation method"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design with placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Unclear risk	52 pts

Broomhead 1997a

Study characteristics

Methods	Design: randomised, DB, DD, parallel-group. 4 treatments. Moderate to severe cancer pain
Participants	Cancer pain Multicentre outpatient study 150 pts
Interventions	Dosing regimen: Pts titrated with MIR during 3 to 14 d run-in period Phase 1: Kadian every (a) 24 h or every (b) 12 h, (c) Mm/r every 12 h, (d) Placebo every 12 h Phase 2 (main study): as 1 but no placebo; other non-opioids were allowed. MIR as rescue medication for all groups. Mean age 61 yrs Length of treatment: 7 days +/- 1 day
Outcomes	Outcome measures: 1. Elapsed time to re-medication (ETR) and total amount of rescue medication 2. Pain intensity (VAS) daily 3. Verbal PI (4-point) 4. Verbal PR (4-point) 5. Sleep quality 6. Global assessment over 7 days 7. AE (5-point) Analgesic outcome results:

Oral morphine for cancer pain (Review)

Broomhead 1997a (Continued)

Phase1: 17 pts demonstrated that morphine compounds better than placebo. Global rating for good or very good K 24 h 89%; K 12 h 76%; Mm/r 68%.

Phase 2: 152 pts completed - No diff between groups for rescue medication. Mean elapsed time to re-medication: K 24 16 h; K 12 9.1 h; Mm/r 8.7 h

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS

Notes	<p>Withdrawals and AEs:</p> <p>3/54 K 24 h withdrew. 6/45 K 12 h withdrew. 1/53 MSC withdrew due to AE. Serious AEs - 7/54 K 24 h, 10/45 K 12 h, 5/53 MSC. 46 pts had > 1 AE; 20.7% related to MIR. Pts with AE; K 24 h 16.4%, K 12 h 25%, MSC 7.1%. Significantly more AEs with K 12 h than MSC. 4 deaths</p> <p>QS: 4 (R1, DB2, W1)</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design with placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Unclear risk	172 pts

Bruera 1998

Study characteristics

Methods	Design: SR oxycodone vs Mm/r. DB, DD, randomised cross-over 7 d each arm. Rescue IR oxycodone or MIR. No other opioids or analgesics allowed
Participants	<p>Cancer pain</p> <p>Setting Palliative care programme 32 pts; 23 women</p>
Interventions	<p>Dosing regimen: Oxycodone 12-h morphine 12 h for 7 d, cross-over on d 8. Dose adjustment allowed if greater than 3 rescue doses in previous 24 h</p> <p>Length of treatment: 14 d (2 x 7 d)</p>

Oral morphine for cancer pain (Review)

Bruera 1998 (Continued)

Outcomes	<p>Outcome measures</p> <ol style="list-style-type: none"> 1. Pain intensity (VAS) 4 times a day 2. Cat PI (5-point) 3. Pt preferences 4. Nausea and sedation scale 5. AE checklist 6. Rescue analgesia <p>Analgesic outcome results: No sig diff in Pl. Av. daily rescue doses 2.3 +/- 2.3 for oxycodone vs morphine 1.7 +/- 2.1. Preference: oxycodone 8, morphine 11, no preference 4</p> <p>Achieved no worse than mild pain with scores of < 30 on a 100-point VAS</p>
Notes	<p>Withdrawals and AEs: 9/32 withdrew. No sig diff in nausea or sedation between groups. Withdrew for AEs: 3 morphine, 2 oxycodone. Lack of efficacy 1 morphine, 1 oxycodone QS: 4 (R1, DB2, W1)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinding was maintained by double dummy technique using matching placebos"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	32 pts

Bruera 2004
Study characteristics

Methods	Design: randomised, DB, parallel-group study for 4 weeks
Participants	<p>103 pts with cancer-related pain requiring the initiation of strong opioids</p> <p>Age 26 to 87</p> <p>Median age 60 yrs</p>

Oral morphine for cancer pain (Review)

Bruera 2004 (Continued)

Interventions	Methadone 7.5 mg orally every 12 h with 5 mg every 4 h as needed for breakthrough pain Or Mm/r every 12 h with 5 mg every 4 h as needed for breakthrough pain
Outcomes	VAS for pain, sedation, confusion, nausea, and constipation. Edmonton staging system for cancer pain. Daily assessments for 8 d then weekly assessment. Global impression of change. Results: at d 8, 37/49 methadone and 41/54 morphine had > 20% improvement in pain. 26/49 methadone and 33/54 morphine reported at least moderate global benefit. Methadone was not superior to morphine
Notes	Opioid adverse effects: 11/49 methadone, 3/54 morphine QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"the random allocation sequence was generated centrally by computer generated numbers"
Allocation concealment (selection bias)	Low risk	"allocation code was kept in a sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"capsules containing the drug were identical"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for in flow chart
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Unclear risk	103 pts

Cundiff 1989
Study characteristics

Methods	Mm/r or MIR titrated upwards until not more than 20% total daily morphine given as rescue over a 2-d period (time to reach steady state 4 to 7 d). Cross-over to start at 1/3 pre-study equivalent then titrate up. 23 pts Age 31 to 72 yrs, mean 45 yrs
Participants	Cancer pain Setting: in- and outpatients
Interventions	Dosing regimen: Mm/r 30 mg every 12 h or MIR tablets 15 mg 4-hourly. 15 mg MIR tablets as rescue Length of treatment: 4 to 7 d per arm
Outcomes	Outcome measures:

Oral morphine for cancer pain (Review)

Cundiff 1989 (Continued)

Quality and frequency of rescue medication. Nurse assessed PI and frequency. AE

Analgesic outcome results:

Total morphine dose in last 24 h significantly higher in immediate release group (496 mg MIR vs 369 mg Mm/r) Final doses approx 400 mg/d

Notes	Withdrawals and AEs: 3/23 MIR and 1/23 Mm/r experienced AEs No respiratory depression QS: 4 (R1, DB2, W1)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"random assignment"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique.... placebo physically indistinguishable from the alternative therapy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	23 pts

Currow 2007
Study characteristics

Methods	Design: randomised DB cross-over study of 15 d in total
Participants	Cancer pain Setting: community and hospital 42 pts
Interventions	Dosing regimen Mm/r in the morning with placebo in the evening for 7 d OR Mm/r evening with placebo in the morning for 7 d. Cross-over d 8
Outcomes	Outcome measures VAS PI every 4 h while awake, CATPR daily Other outcomes: AEs, CAT for sleep, nausea and vomiting, constipation, confusion, somnolence

Oral morphine for cancer pain (Review)

Currow 2007 (Continued)

Analgesic outcome results:

No sig diff between outcomes for primary outcome (PR). 24/26 satisfied or very satisfied with morning dose

25/26 satisfied or very satisfied with evening dose

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS

Notes	Withdrawals and AEs 16 withdrew (4 lack of efficacy) QS: 5
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was allocated from a central computer generated random no sequence"
Allocation concealment (selection bias)	Low risk	"the process was blinded at all times to participants and treating clinicians"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported
Size	High risk	42 pts

Dale 2009

Study characteristics

Methods	Design: randomised, DB, cross-over of single dose vs double dose if MIR at bedtime
Participants	Cancer pain Setting: hospital inpatients 22 pts
Interventions	Dosing regimen: After titration of dose, randomised to receive either a single dose of MIR at bedtime followed by another dose 4 h later or a double dose of MIR with a placebo dose 4 h later. 1 night on each treatment
Outcomes	Outcome measures:

Dale 2009 (Continued)

11-point NRS for pain, pt preference
BPI, Edmonton symptom assessment scale

Analgesic outcome results:

No sig diff in pt preference

Achieved no worse than mild pain with scores of < 3 on a 11-point VAS in 9/11 in single-dose and 9/9 in double-dose arms

Notes

Withdrawals and AEs:

3 excluded (2 protocol violation, 1 not stated)

QS: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"concealed procedure performed by hospital pharmacist using restricted randomisation table"
Allocation concealment (selection bias)	Low risk	"concealed procedure performed by hospital pharmacist using restricted randomisation table"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"placebo tablets identical in appearance and taste"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consort flow chart presented
Selective reporting (reporting bias)	Low risk	All outcomes reported
Size	High risk	22 pts

De Conno 1995

Study characteristics

Methods	Design: randomised DB DD. VASPI > 30 mm at baseline for inclusion. NSAIDS allowed. Mean age 59 +/- 8.8 (range 38 to 70) 34 pts (17 per group then cross-over)
Participants	Cancer pain Setting: 34 advanced/metastatic cancer pts
Interventions	Dosing regimen: 2 d either oral or rectal morphine 10 mg cross-over for d 3 and 4 Length of treatment: 4 d (2 x 2 d)
Outcomes	Outcome measures:

Oral morphine for cancer pain (Review)

De Conno 1995 (Continued)

1. Pain, nausea and sedation on VAS @ 10, 20, 30, 40, 60, 90, 120, 180 and 240 mins daily
2. No of vomiting episodes
3. Time to pain relief

Analgesic outcome results:

Sig relief rectally after 10 mins vs 60 mins orally. Rectal gave greater relief than oral after 180 mins. All pts were assessable

Notes	Withdrawals and AEs: No sig diff in intensity of sedation, nausea or no of vomiting episodes between rectal and oral QS 3 (R1, DB2)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated...according to a predetermined allocation sequence"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"all patients were assessable"
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	34 pts

Dellemijn 1994

Study characteristics

Methods	Design: randomised, DB, DD 2 x 1-week cross-over study. Baseline VASPI 82/83b mm. 6-h washout period
Participants	Cancer pain Setting: Pain clinic Malignant nerve pain 20 pts
Interventions	Dosing regimen: Naproxen 500 mg 3 times a day vs MS Contin 30 mg twice a day. Rescue medication - paracetamol and domperidone Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: 101-point numerical rating scale. 6-point Cat PR at end of each 7 d Pt preference

Oral morphine for cancer pain (Review)

Dellemijn 1994 (Continued)

Rescue medication use

Analgesic outcome results:

Pain VAS $\leq 30/100$ 2/8 in each arm

Naproxen group used significantly less rescue paracetamol than MSC group. Numbers very small

Notes

Withdrawals and AEs:

More nausea and vomiting in morphine group. Death x 1 disease progression

QS 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind, dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	20 pts

Deschamps 1992

Study characteristics

Methods	Design: randomised cross-over trial with titration phase. DB, DD. MIR for breakthrough. 2 x 7-d phases. No other opioids/analgesics allowed. Mean age 57 yrs (40 to 72)
Participants	Cancer pain Setting: cancer outpatients 20 pts
Interventions	Dosing regimen: Mm/r 30, 60, 100 mg vs MIR 1 mg/ml and 5 mg/ml. Mm/r given 12-hourly (8 am and 8 pm) MIR 4-hourly with double dose at night Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: VASPI, verbal (6-point) side effects severity. Pt preference

Oral morphine for cancer pain (Review)

Deschamps 1992 (Continued)

Analgesic outcome results:
No sig diff in pain scores or supplemental morphine

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS in 11/12 pts with data

Notes	Withdrawals and AEs: 4 died during titration and 2 withdrew due to AE. 1 withdrew consent. 8/20 dropped out. QS: 5
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by Pharmaceutical company...using randomisation table"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"titration and trial phases conducted under double blind conditions with double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	20 pts

Ferrell 1989

Study characteristics

Methods	Design: randomised parallel group - short-acting analgesics: oxycodone, hydromorphone, codeine or short-acting morphine vs Mm/r. Third group on Mm/r remained on this (75% receiving active treatment) Mean age 60 yrs
Participants	Cancer pain Oncology units in 2 US hospitals 83 pts
Interventions	Dosing regimen: Doses not stated. 41 on MIR, 42 on Mm/r Length of treatment: 6 weeks
Outcomes	Outcome measures: Pain experience measure PPI - (6-point) Karnofsky. City of Hope QOL Analgesic outcome results:

Oral morphine for cancer pain (Review)

Ferrell 1989 (Continued)

Pts on Mm/r had lower pain intensity than those on short-acting analgesics. Pts on Mm/r experience decreased pain but took medication regularly. Those on short-acting analgesics did not take all the prescribed doses

Notes	Withdrawals and AEs: Increased constipation in Mm/r group QS 1 (R1, DB0, W0)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	High risk	No information
Selective reporting (reporting bias)	Unclear risk	Unclear
Size	Unclear risk	83 pts

Finn 1993
Study characteristics

Methods	Design: randomised, DB, DD, cross-over. Mm/r 30 mg 12-hourly, MIR 20 mg/ml. Severe pain required > 60 mg MIR. Rescue: paracetamol, MIR or sub-cut/IM morphine. Non-opioid medications continued. Mean age 59 yrs
Participants	Cancer pain Setting: outpatients. 37 pts entered, 34 pts completed
Interventions	Dosing regimen: D 1: Usual MIR; D 2 and 3 either Mm/r or MIR (with matched placebo); D 4 and 5 cross-over. (15/34 MIR/Mm/r) (19/34 Mm/r/MIR) Length of treatment: 6 d
Outcomes	Outcome measures: VASPI 3 x d CATPI (4-point) Karnofsky. S/E profile. Use of rescue and pt preference Analgesic outcome results:

Finn 1993 (Continued)

No sig diff between groups on VAS scores. No sig diff on breakthrough medication. All pts in both groups reported either no pain or mild/mediate pain. No diff in side effects between groups. Av daily dose 150 mg

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS

Notes	Withdrawals and AEs: 3/37 withdrew; reasons not clear. 1 death. QS: 5
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation by using randomisation schedule provided to the responsible pharmacist"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinded drug supplies packaged daily by the responsible pharmacist"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	37 pts

Flöter 1997
Study characteristics

Methods	Design: Initial 7 to 14 d titration with Kapanol or Mm/r. Randomised, open study to Kapanol or Mm/r. Mean age 55 yrs, weight 69 kg
Participants	Mixed pain - 27/91 Kapanol and 26/74 MST had cancer pain Setting: multicentre study Germany 165 pts
Interventions	Dosing regimen: Kapanol 12-hourly vs Mm/r 12-hourly with MIR for breakthrough. Kapanol N = 91, Mm/r N = 74 Length of treatment: 14 d
Outcomes	Outcome measures: Main - physician assessment pain control (VASPI) Quality of sleep Rescue medication Well-being etc (patient diary)

Oral morphine for cancer pain (Review)

Flöter 1997 (Continued)

Analgesic outcome results:
Physician-reported - more pts on Kapanol achieved adequate analgesia. Sleep improved on Kapanol and greater pain relief on Kapanol. Kapanol "more effective" than Mm/r. Average daily dose 80 mg

Notes
Withdrawals and AEs:
14/91 Kapanol 7/74 Mm/r - treatment-related ADRs. 5/91 Kapanol 13/74 Mm/r - inadequate pain relief. In total 22/91 Kapanol and 31/74 Mm/r withdrew.

QS 3 (R2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation performed using a random number generator"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Unclear risk	165 pts

Gillette 1997
Study characteristics

Methods	Design: randomised, DB, DD 6-d treatment then cross-over. Initial dose titration 5 d. Mean age 61.3 yrs, weight 60 kg. Rescue: drugs other than morphine. Severe pain
Participants	Cancer pain Setting: hospital 27 pts
Interventions	Dosing regimen: Mm/r capsules 30 mg or 60 mg 12-hourly. MIR 5 ml/ml 4 h. No washout Length of treatment: 12 d (2 x 6 d)
Outcomes	Outcome measures: VASPI 4 x daily. Verbal scale (5-point) S/E, sleep quality (d 6 and 12). Morphine concentrations on d 6 and d 12 Analgesic outcome results:

Gillette 1997 (Continued)

No sig diff between treatments. No breakthrough analgesia required by any subject. AEs similar in both groups

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS in 27/27 pts (derived from mean and SD demonstrating that all pts should be below 30/100 mm)

Notes

Withdrawals and AEs:
Dry mouth, constipation, somnolence, and nausea most frequently reported. Incidence AEs - none withdrew because of AE.

QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind, dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only partly described
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	35 pts

Gourlay 1997

Study characteristics

Methods	Design: randomised, DB, DD cross-over study. Dose optimisation during run in. Moderate to severe pain
Participants	Cancer pain Cancer pts requiring at least 40 mg morphine/24 h 29 pts
Interventions	Dosing regimen: Dose optimised using MIR. Kapanol once a day vs Mm/r 12-hourly for 7 d (+/- 1 d) then cross-over for 7 d. Rescue: dextromoramide Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: Diary - admin times, PI, PR, sleep, side effects, pt global assessment, VASPI and CATPI, CATPR, plasma morphine concentrations Analgesic outcome results:

Oral morphine for cancer pain (Review)

Gourlay 1997 (Continued)

Similar amounts of rescue medication in both groups. % taking rescue medication time to rescue. Total dose rescue mg/day on d 7. No sig diff in VAS score. No sig diff in pt global assessment. Pt preference: K 4/24 MS Contin 11/24, both equally 9/24. Pt global good/very good pain relief: K 16/24, MS Contin 21/24. Mean morphine dose 199 +/- 275 (40 to 1200) mg/24 h in 24 evaluable pts.

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS in 24/24 pts (derived from mean and SD demonstrating that all pts should be below 30/100 mm)

Notes	Withdrawals and AEs: 5/29 withdrew, 2 disease progression, 3 protocol violation. No SE details. QS: 4 (R1, DB2, W1)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebo opaque capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	29 pts

Hagen 2005

Study characteristics

Methods	Design: randomised, DB, DD, multicentre cross-over study for 2 weeks
Participants	29 chronic cancer pain pts stable analgesic requirements Age 53 years +/- 10 yrs
Interventions	Once a day Mm/r (MS Contin XL) for 1 week vs twice-daily Mm/r (MS Contin). No dose adjustments permitted but MIR allowed for breakthrough pain. NSAIDs allowed to continue at pre-trial doses
Outcomes	Outcome measures: VASPI, CATPI, VAS for nausea and sedation. Least, worse, and average pain on VAS every 12 h. CATPR and pt preference. Blood levels of morphine Analgesic outcome results: 25 completed. All pts experienced good pain relief. No sig diff between once daily and twice daily pain scores. Pain scores on once daily stable through day but twice daily lower in

Hagen 2005 (Continued)

morning then increasing through the day. 8/25 had no preference, 4/25 preferred once a day, 13/25 preferred twice a day; however 68% expressed a preference for a once-a-day regimen.
Mean daily dose of morphine: 238 mg +/- 319 mg. Mean rescue 22 mg +/- 37 mg

Notes
4 dropouts: 1 for inadequate PR, 2 for AEs, 1 voluntary withdrawal. No difference in AEs between groups, nausea, constipation, somnolence, asthenia, and headache all reported.
QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinding maintained using the double placebo technique" (double-dummy)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	29 pts

Hanks 1987a
Study characteristics

Methods	Design: randomised, DB, DD, cross-over study 2 d each arm Age mean men 72 (range 59 to 78), women 68 (53 to 82)
Participants	Cancer pain Setting: continuing care unit 27 entered but 18 completed
Interventions	Dosing regimen: Mm/r twice a day vs MIR 4-hourly Length of treatment: 4 d (2 x 2 d)
Outcomes	Outcome measures: VASPI, VAS alertness, nausea, mood, sleep assessment, and appetite. Global rating CATPI (5-point) Analgesic outcome results: No diff in pain scores, but pts on Mm/r slept better. Baseline PI MIR 86.1 (SE 2.8) Mm/r 80.2 (SE 5.0). Final PI MIR 82.4 (4.8) Mm/r 75.3 (7.2). Pt preference: 14 no preference, 3 MIR, 1 Mm/r

Hanks 1987a (Continued)

No or mild pain in 14/18 pts on both arms

Notes

Withdrawals and AEs:
18 completed (abstract) withdrawals due to breakthrough pain: 1 MIR AEs, 1 Mm/r (drowsiness)
QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	27 pts

Hanks 1995
Study characteristics

Methods	Design: randomised, DB, DD, cross-over Age 35 to 69 yrs, mean 56 200 mg to 1000 mg Mm/r 12-hourly
Participants	Cancer pain Setting: Not stated Advanced malignant disease. At least 400 mg morphine/day 25 pts
Interventions	Dosing regimen: Mm/r 100 mg vs Mm/r 200 mg 3 d cross-over Length of treatment: 6 d (2 x 3 d)
Outcomes	Outcome measures: VASPI, symptom score categorical 4-point. Scores taken 4 times on d 3 and 6. Morphine plasma concentrations in 4 pts Analgesic outcome results:

Hanks 1995 (Continued)

No sig diff in treatments except in the 12 h post-dose ratings. Pts had less pain on 200 mg formulation. No sig diff in rescue medication. Kinetic data shows no dose "dumping". No sig diff in use of rescue.

Notes

Withdrawals and AEs:
5 withdrew: 2 constipation, 1 dysphagia, 1 increasing pain, 1 anxiety. Sedation 15/23 100 mg 17/21 200 mg (not sig) Nausea and vomiting 8/23 100 mg 10/23 200 mg (not sig). 1 pt excluded as unreliable data.

QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind double dummy crossover..."; "identical tablets"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	25 pts

Hanna 2008
Study characteristics

Methods	Design: randomised, DB, DD, parallel-group comparing hydromorphone (HM) to Mm/r
Participants	Cancer pain Setting: inpatients and outpatients 200 pts
Interventions	Dosing regimen: Dose titration with either HM IR or MIR on d 2 to 9 then either Mm/r or HM-OROS for 10 to 15 d. HM-OROS at 10 am with placebo at 10 pm or Mm/r at 10 am and 10 pm
Outcomes	Outcome measures: worst pain in previous 24 h, BPI, VASPI, VASPR Analgesic outcome results: Small but statistically sig diff benefit for HM-OROS Achieved no worse than mild pain with scores of < 3 on an 11-point VAS on average

Hanna 2008 (Continued)

Pt judgement of very good/excellent pain relief in 35/77 on HM-OROS and 36/86 on Mm/r

Notes	Withdrawals and AEs Lack of efficiency: 11/77 withdrew on HM, 4/86 withdrew on Mm/r AEs: Constipation: 30/77 HM, 19/86 Mm/r Nausea and vomiting 22/77 HM, 44/84 Mm/r Somnolence 8/77 HM, 12/86 Mm/r QS: 5
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised 1:1 with central computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebo capsules and tablets were used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problem identified
Size	Low risk	200 pts

Harris 2003
Study characteristics

Methods	Design: randomised controlled study
Participants	62 pts with end-stage cancer and severe pain, some opioid-naïve
Interventions	Dosing regimen: Morphine IV 1.5 mg every 10 mins with close monitoring of AEs to achieve either total pain relief or drowsiness. Pts then transferred to oral based on IV dosage required Or MIR 5 mg every 4 h (if opioid-naïve) or 10 mg every 4 h. Equivalent dose of rescue allowed. All pts also received paracetamol or diclofenac.
Outcomes	Outcome measures:

Harris 2003 (Continued)

Pain relief on 3-point scale: 1) total PR, 2) satisfactory PR, 3) unsatisfactory PR

Use of rescue medication

Adverse events

Follow-up every h for 12 h then every day for 2 d then weekly

Notes

1 in MIR group withdrew due to severe vomiting, 1 in morphine IV group had severe rash but continued. 1 in morphine IV excluded as opioid unresponsive. 2 withdrew from oral arm due to difficulty in taking oral morphine.

QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised was achieved by sampling with replacement"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems identified
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	62 pts

Heiskanen 2000
Study characteristics

Methods	Design: randomised, DB, DD, cross-over comparison study. Randomised open titration for 21 d; when stable for 48 h randomised to either morphine or oxycodone modified release. After 3 to 6 d, blood samples taken and crossed over, doses calculated in ratio of oxycodone 2: morphine 3. This treatment assessed after 3 to 6 d. No washout.
Participants	Chronic stable cancer pain Age 39 to 76, mean 60 years Setting: Not stated 45 pts
Interventions	Dosing regimen:

Heiskanen 2000 (Continued)

Mm/r 30 mg, oxycodone modified release 20 mg, matching placebo, rescue medication as morphine or oxycodone solutions

Outcomes	<p>Outcome measures:</p> <p>CATPI, categorical acceptability, pharmacodynamic assessments</p> <p>Analgesic outcome results: no correlation between VASPI or AEs and plasma opioid concentrations. Both opioids provide adequate stable analgesia. Mean daily morphine dose: 204 mg +/- 24 mg, oxycodone 148 mg +/- 18 mg</p> <p>Achieved no worse than mild pain with scores of < 30 on a 100-point VAS</p>
Notes	<p>Withdrawals and AEs:</p> <p>18 withdrew: 7 morphine, 11 oxycodone. Constipation more common in oxycodone, vomiting occurred more often on morphine</p> <p>QS: 5</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomisation. . . was performed"
Allocation concealment (selection bias)	Low risk	"list of randomisation codes was kept by the hospital pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"tablets and matched placebo were packed by the hospital pharmacy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	45 pts

Homsy 2010

Study characteristics

Methods	Design: randomised, parallel-group, open-label of 2 brands of Mm/r
Participants	<p>Cancer pain</p> <p>Setting: inpatients and outpatients</p> <p>37 pts</p>
Interventions	Dosing regimen:

Homsi 2010 (Continued)

Dose stabilised prior to randomisation, then MS Contin or Oramorph SR for 5 d. MIR as rescue. Adjuvant analgesics permitted if morphine dose stable.

Outcomes	<p>Outcome measures:</p> <p>CATPR 4-point scale, rescue dose and frequency, pt preference (author note: how is this possible? not a cross-over). AEs</p> <p>Analgesic outcome results:</p> <p>Authors claim Oramorph better on d 3 to 5 but not supported by data</p> <p>12/16 would chose to continue on MS Contin, 16/16 would chose to continue on Oramorph SR</p> <p>Achieved no worse than mild pain with scores of < 30 on a 100-point VAS</p>
Notes	<p>Withdrawals and AEs</p> <p>Drowsiness and dry mouth reported in both groups. No difference in AEs</p> <p>Study supported by manufacturers of Oramorph SR</p> <p>QS: 2 (R1, W1)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomised based on a number list"
Allocation concealment (selection bias)	High risk	Open-label study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	32 pts

Hoskin 1989
Study characteristics

Methods	Design: randomised DB study: 1 dose of Mm/r together with either additional MIR or placebo
Participants	<p>Cancer pain</p> <p>Setting: inpatients on MIR</p>

Hoskin 1989 (Continued)

19 pts

Interventions	Dosing regimen: 1st dose Mm/r with 4-hourly equivalent of MIR or placebo (1 dose) Length of treatment: single-dose 12-hour study
Outcomes	Outcome measures: Plasma morphine levels, VASPI and CATPI (4-point), VASPR. S/E categorical + nurse assessment Analgesic outcome results: No sig effect noted by giving a loading dose of MIR with first Mm/r dose. No sig diff in PI and PR scores Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: 1/20 withdrew - deteriorating condition QS: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"prospectively randomised"
Allocation concealment (selection bias)	Low risk	"randomisation code was kept in the hospital pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"preparations were prepared so as to have an identical taste and physical appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	19 pts

Kalso 1990
Study characteristics

Methods	Design: randomised DB cross-over MIR vs oxycodone IR. PCA titration with allocated drug until pain-free. After 48 h conversion to oral every 4 h. Dose adjustment allowed. After 96 h cross-over - again PCA titration followed by oral.
Participants	Severe cancer pain Setting: Not stated probably inpatient 20 pts
Interventions	Dosing regimen:

Oral morphine for cancer pain (Review)

Kalso 1990 (Continued)

MIR 4 mg/ml or oxycodone IR 2.7 mg/ml every 4 h with dose increase of 1 ml at a time if not pain-free
Length of treatment: 8 d (2 x 2 d with pre- and post-phase)

Outcomes	Outcome measures: VASPI (0 to 10) S/E profile and quality of sleep Analgesic outcome results: No sig diff between morphine and oxycodone on VASPI. 5/20 preferred morphine 5/20 preferred oxycodone 10/20 no preference
Notes	Withdrawals and AEs: Sedation most common effect QS: 2 (R1, DB1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in a randomised double blind crossover study"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"in a randomised double blind crossover study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	20 pts

Kerr 2000
Study characteristics

Methods	Design: randomised, multicentre, open-label, cross-over study. 2 x 10 d study periods (+/- 1 d) No washout. 28 centres.
Participants	134 pts requiring treatment for chronic cancer pain
Interventions	Dosing regimen: 3 to 14 d lead-in period using MIR, once stable then randomised to either Mm/r (24 h - Kadian) given at 8 am or Mm/r (12 h MS contin) given at 8 am and 8 pm. No dose adjustment allowed but rescue MIR provided
Outcomes	Outcome measures:

Kerr 2000 (Continued)

VASPI, average pain, least pain and worst pain in 24 h. Interference with daily activities, pt preference.

Secondary outcomes: average daily dose of MIR, investigator global assessment, QOL
Analgesic outcome results: at least 114 received at least 1 dose in each arm but only 104 stated a preference: 57/104 preferred Kadian, 34/104 preferred MS Contin, 13/104 no preferred treatment. Demand for rescue was similar in each arm. No sig diff for investigator global assessment or QOL. Average dose of morphine: 100 mg (range 15 mg to 800 mg)

Notes	Withdrawals and AEs: Kadian 19/134 (1 due to AE); MS Contin 17/134 (7 due to AE) QS: 3 (R2, DB0, W1)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"balanced randomisation"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	134 pts

Klepstad 2003

Study characteristics

Methods	Design: randomised DB, DD, parallel-group study terminated 2 d after achieving stable analgesic dose
Participants	40 pts with pain despite treatment with weak opioids for mild to moderate pain. Only 36 started the titration phase. Age 57 to 71
Interventions	Dosing regimen: Mm/r 24 h release or MIR 4-hourly. Dummy tablets given to Mm/r group for additional doses. Initial dose 60 mg per day then titrated to pain relief. Ketobemidone provided as rescue analgesia
Outcomes	Outcome measures: VASPI, rescue medication, nausea, loss of sleep, tiredness, loss of appetite, constipation, vertigo (4-point categorical scales)

Oral morphine for cancer pain (Review)

Klepstad 2003 (Continued)

analgesia outcome results: 10/17 satisfied or very satisfied with Mm/r, 10/13 satisfied or very satisfied with MIR. It took no longer to achieve acceptable pain relief with Mm/r than MIR. Av daily dose of morphine 88 mg (range 68 mg to 117 mg)

Notes	Withdrawals and AEs: 6 withdrawals, none for lack of pain relief or AEs QS: 5 NB Data in section 3.4 of paper are incorrect (typo). Table 4 correct - confirmed with author
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"hospital pharmacy performed a computerised randomisation"
Allocation concealment (selection bias)	Low risk	"none of the pharmacists arranging the study drugs were involved in other parts of the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind, double dummy", "placebo tablets identical in appearance and taste"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	40 pts

Knudsen 1985

Study characteristics

Methods	Design: randomised, DB, cross-over trial
Participants	Chronic pain due to advanced cancer Setting: not stated 18 pts
Interventions	Dosing regimen: Mm/r 12-hourly vs MIR tablets 4-hourly Length of treatment: 14 d
Outcomes	Outcome measures: VASPI for pain and sedation Analgesic outcome results: No sig diff for pain. Greater sedation on first 3 d of Mm/r which then resolved

Oral morphine for cancer pain (Review)

Knudsen 1985 (Continued)

Achieved no worse than mild pain with scores of < 30 on a 100-point VAS

Notes	Withdrawals and AEs: Not stated QS: 2 (R1, DB1)
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"consecutively randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	18 pts

Kossman 1983
Study characteristics

Methods	Design: randomised, parallel-group
Participants	Cancer pain Setting: Not stated 20 pts
Interventions	Dosing regimen: Mm/r vs morphine cocktail (MIR) Length of treatment: 7 d
Outcomes	Outcome measures: Daily PI, pain duration, and quality of sleep Analgesic outcome results: Marked fall in pain intensity on d 1. Then majority either wholly pain-free or only slight residual pain Achieved no worse than mild pain with scores of < 30 on a 100-point VAS on average, in 7/9 ps overall
Notes	Withdrawals and AEs: Not stated

Oral morphine for cancer pain (Review)

Kossman 1983 (Continued)

QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	20 pts

Lauretti 2003
Study characteristics

Methods	Design: randomised, DB, cross-over study of 2 x 14 d. 7-day open-label titration with MIR pre-study to determine suitable morphine dose
Participants	Cancer pain not adequately controlled with tramadol/NSAID combination Setting: Not stated 26 pts; age 59 +/- 19 yrs
Interventions	Dosing regimen: Either Mm/r or oxycodone modified release for 14 d then crossed over. Doses assigned by pharmacist. All pts allowed MIR 10 mg for breakthrough
Outcomes	Outcome measures: PI, pt satisfaction, AEs, use of rescue medications, VASPI and VAS for nausea and vomiting Analgesic outcome results: mean daily dose at 4 wks: oxycodone 40 mg, morphine 75 mg (1:1.6). Daily pain scores were less than 4 cm in all pts. MIR consumption higher in morphine group than oxycodone group. (Was this due to inadequate titration in morphine group?)
Notes	Withdrawals and AEs: 4 withdrew, 2 for lack of pain relief, 1 nausea and vomiting, 1 died. Range of AEs reported, mostly similar between groups. Less nausea and vomiting reported in oxycodone group. QS: 3 (R1, DB1, W1)

Oral morphine for cancer pain (Review)

Lauretti 2003 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" and blind assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	26 pts

Leppart 2001
Study characteristics

Methods	Design: open, randomised, prospective study
Participants	Cancer pain Setting: outpatients 40 pts
Interventions	Dosing regimen: Tramadol IR vs MIR. After 7 d converted to SR products for further 28 d. Length of treatment: 35 d
Outcomes	Outcome measures: VASPI and 5-point verbal scale. EORTC C30 for QOL Analgesic outcome results: No sig diff on pain intensity between groups either in IR or modified release phase. Morphine superior for neuropathic pain. Tramadol better than morphine on 1 QOL measure
Notes	Withdrawals and AEs: 3/20 withdrew tramadol (1 S/E, 1 poor analgesia, 1 disease progression). 2/20 withdrew morphine (1 S/E, 1 died). Morphine group more drowsy and constipated. QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Oral morphine for cancer pain (Review)

Leppart 2001 (Continued)

Random sequence generation (selection bias)	Unclear risk	"open randomised prospective study"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	40 pts

Melzack 1979
Study characteristics

Methods	Design: randomised, DB, cross-over trial. Cross-over after about 2 wks. 20 pts completed cross-over in same environment. 7 pts completed cross-over in diff environments.
Participants	Cancer pain Setting: in- and outpatients single centre 44 pts. 30 completed both phases
Interventions	Dosing regimen: Brompton mixture with morphine 10 mg, cocaine 10 mg, alcohol 2.5 ml in 20 ml vs morphine - variable amount in 20 ml Length of treatment: 4 wks (2 x 14 d)
Outcomes	Outcome measures: PPI 6-point categorical scale. Ratings for confusion, nausea, drowsiness, by pts, nurse and relative Analgesic outcome results: No sig diff in pain scores or adverse effects. Approx. 15% pts did not get adequate pain relief on either arm. Average morphine dose 25 mg
Notes	Withdrawals and AEs: 17 pts too ill to cross over QS: 4 (R2, DB2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Gellerman randomised table was used"

Melzack 1979 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"solutions prepared by pharmacist using random table"
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	44 pts

Mercadante 1998
Study characteristics

Methods	Design: randomised open study of dextropropoxyphene (variable dose) vs Mm/r 10 mg twice a day. Non-opioid drugs were continued. Records made on 1st 10 d of therapy and last 4 wks of life.
Participants	Cancer pain Setting: advanced cancer pts not responding to non-opioids. Home setting 32 pts
Interventions	Dosing regimen: Dextropropoxyphene 120 mg to 240 mg daily (?frequency) vs Mm/r 20 mg daily. Pts allowed to switch from dextropropoxyphene to Mm/r. Dextropropoxyphene N = 16, Mm/r N = 16 Length of treatment: long-term. Average length in study 38 d
Outcomes	Outcome measures: 1. Performance status 2. Mean opioid dose 3. Days on dextropropoxyphene in group 1 4. Days on morphine in each group 5. VAS PI 6. Symptoms and side effects on 4-point cat scale Analgesic outcome results: 13 switched from dextropropoxyphene to Mm/r. 3 switched from Mm/r to dextropropoxyphene due to intolerable side effects. Authors argue dextropropoxyphene has a place in WHO ladder (not proven)
Notes	Withdrawals and AEs: More favourable analgesia - side effects balance for dextropropoxyphene claimed - all figures low QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Oral morphine for cancer pain (Review)

Mercadante 1998 (Continued)

Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	32 pts

Mercadante 2008
Study characteristics

Methods	Design: multicentre, randomised, parallel-group, open study of 3 treatments
Participants	Cancer pain Setting: outpatients requiring strong opioids 108 pts
Interventions	Dosing regimen: One of Mm/r 60 mg/day, or TD fentanyl 0.6 mg/day (25 micrograms/hr) or methadone 15 mg/day. MIR for breakthrough pain at 1/3 of the 24 h morphine equivalent. Dose escalation, adjuvant analgesics (inc NSAIDs, antidepressants, and anti-convulsants) all allowed. 4-week study
Outcomes	Outcome measures: Numerical PI (0 to 10), AEs, time to dose stabilisation Analgesic outcome results: no difference in pain intensity and in non-opioid analgesic consumption between groups. Methadone more difficult to titrate doses. Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: Withdrawals: Mm/r 14/36, fentanyl 11/36, methadone 13/23 (reasons stated in study - not for AEs) QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Oral morphine for cancer pain (Review)

Mercadante 2008 (Continued)

Random sequence generation (selection bias)	Low risk	"randomisation was computer generated"
Allocation concealment (selection bias)	High risk	Open study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	108 pts

Mercadante 2010
Study characteristics

Methods	Design: parallel-group randomised open study of 8 wks duration comparing Mm/r and oxycodone SR. Oral morphine for breakthrough pain. Mean age 63 years approximately
Participants	Pancreatic cancer pain. Pain intensity at least 4/10 requiring opioids. Setting: outpatient or home care 60 pts randomised but only 46 completed baseline observations
Interventions	Dosing regimen: Mm/r 30 mg/day initially or oxycodone 20 mg/day initially. Dose escalated according to clinical need base if > 3 breakthrough pain meds per day
Outcomes	Outcome measures: Average PI in last 24 h (numerical scale of 0 to 10). Opioid-related symptoms: nausea and vomiting, drowsiness and confusion. Constipation rating scale Analgesic outcome results: no sig diff in PI between the 2 groups at 4 wks. Few pts survived to 8 wks Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: 14 lost to follow-up before baseline evaluation completed. 39 achieved 4 wks. No withdrawals due to AEs reported QS: 2 (R1, W1)

Risk of bias
Oral morphine for cancer pain (Review)

Mercadante 2010 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised by computer system"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	No problems detected
Selective reporting (reporting bias)	Low risk	No problems detected
Size	High risk	46 pts entered the study after baseline assessment

Mignault 1995
Study characteristics

Methods	Design: randomised, DB, cross-over 5-day study of either Mm/r 8-hourly or Mm/r 12-hourly. Oral morphine for breakthrough pain. Mean age 57 (38 to 69); weight 65 (47 to 104) kg
Participants	Moderate/severe cancer pain Setting: not stated 27 pts (19 included in analysis)
Interventions	Dosing regimen: Mm/r 8 h vs Mm/r 12 h Length of treatment: 10 d (2 x 5 d)
Outcomes	Outcome measures: VASPI 4 times daily. 4-point categorical scale for opioid S/E, 4-point global rates, pt preference Analgesic outcome results: No sig diff in treatment. D 4 pain relief greater in Mm/r 12 h than Mm/r 8 h (P value = 0.016) No advantage for 8 h Mm/r administration Pt global scoring excellent/good 8-hourly dosing 7/19; 12 hourly 10/19 Av daily dose 300 mg
Notes	Withdrawals and AEs: 8 withdrew - 2 found study demanding, 2 AE, 1 sick, 1 did not complete study, 2 unknown. No sig diff between treatments QS: 4 (R1, DB2, W1)

Risk of bias
Oral morphine for cancer pain (Review)

Mignault 1995 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"blinding maintained by administration of active and placebo tablets each day"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	27 pts

Mizuguchi 1990
Study characteristics

Methods	Design: multicentre, randomised, single-blind, DD, cross-over study for 3 d on each treatment. No washout
Participants	Cancer pain Setting: not clear, probably inpatient 46 pts
Interventions	Morphine HCL 20 mg suppository 3 times a day or MS Contin 3 x 10mg tablets twice a day. Cross-over after 3 d
Outcomes	Outcome measures: Pt-reported CATPI (4-point), CATPR (6-point) 1. Analgesic works well, 2. works quite well, 3. works a little, 4. no effect, 5. pain worse, 6 don't know Sleep, AEs and global assessment also recorded. Suppository reported to be effective as Mm/r at same daily dose.
Notes	Withdrawals and AEs: 7 withdrew; due to AEs (3), lack of pain relief (1), protocol violation (1) other (2) QS: 3 (R2, DB0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Mizuguchi 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	"randomisation by code"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebos were prepared"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Unclear risk	Not clear
Size	High risk	46 pts

Moriarty 1999
Study characteristics

Methods	Design: randomised, DB, DD, cross-over
Participants	Cancer pain Setting: multicentre 100 pts
Interventions	Dosing regimen: Hydromorphone modified release vs Mm/r. No washout. Pts stabilised on Mm/r during 1 to 3-day run-in. Range of escape medication MIR solution, diamorphine solution, diamorphine tabs and dextromoramide. Length of treatment: 6 d (2 x 3 d)
Outcomes	Outcome measures: Pt-reported VASPI, 6-point CAT scale, 4-point nausea Analgesic outcome results: Both treatments controlled pain. No sig diff in escape medication, incidence and severity of pain or tolerability. Preference: 42% no preference, 30% Mm/r, 12% HM Achieved no worse than mild pain with scores of < 30 on a 100-point VAS in all pts on Mm/r and hydromorphone
Notes	Withdrawals and AEs: 11 did not complete. AEs reported by 35 pts. 15 due to medication (HM 8, Mm/r 7) QS: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
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Oral morphine for cancer pain (Review)

Moriarty 1999 (Continued)

Random sequence generation (selection bias)	Low risk	"randomisation schedule prepared by clinical supplies dept"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"matching placebos", "double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	100 pts

Mucci LoRusso 1998
Study characteristics

Methods	Design: randomised, DB, parallel-group study. Pts receiving 30 mg to 340 mg oxycodone eligible.
Participants	Cancer pain Setting: general cancer pts. Multicentre 100 pts
Interventions	Dosing regimen: Oxycodone modified release vs Mm/r 12-hourly with immediate release oxycodone 5 mg and MIR15 mg for breakthrough Oxycodone N = 48 Mm/r N = 52. No other opioids permitted during study. Length of treatment: 12 d
Outcomes	Outcome measures: CATPI - 4-point scale - assessment pre-involvement then before each 12-hr dose. Global rating of therapy - 5-point cat scale. QOL using FACT-G 28-item questionnaire. Specific drug effect questionnaire. Analgesic outcome results: Slight decreases in pain intensity but no sig diff between groups - scores provided. No clear preference. Oral oxycodone SR as effective as Mm/r. Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: 7/48 oxycodone and 9 morphine withdrew before stable dose established. 2/48 oxycodone 2/52 morphine withdrew after stable dose. 40/48 oxycodone had S/E, 39/52 morphine profiles similar. Withdrew AEs: 2 oxycodone, 6 morphine - 2 disease-related deaths. AEs - Table 3 QS 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Oral morphine for cancer pain (Review)

Mucci LoRusso 1998 (Continued)

Random sequence generation (selection bias)	Unclear risk	"block randomisation was used"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	100 pts

O'Brien 1997
Study characteristics

Methods	Design: randomised, DB, DD, cross-over
Participants	Cancer pain Setting: over 30 GP practices, hospitals or hospices 85 pts
Interventions	Dosing regimen: One MXL capsule 60 mg in the morning plus placebo Mm/r 30 mg twice daily or Mm/r 30 mg twice a day plus placebo MXL 60 mg daily. Cross-over at 1 wk. MIR tablets for breakthrough pain. Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: PI using BS 11 scale. Escape medication and sleep. Analgesic outcome results: No sig diff between treatments. Breakthrough analgesia similar. Av daily dose 99 mg Achieved no worse than mild pain with scores of < 30 on a 100-point VAS in all pts on MXL or Mm/r
Notes	Withdrawals and AEs: 16/85 withdrew. 13 for non-treatment reasons. 3 from MXL (1 S/E, 2 lack of analgesia). 52% pts reported 110 symptoms. Most frequent: constipation, drowsiness, nausea and vomiting. QS: 4 (R1, B2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"

Oral morphine for cancer pain (Review)

O'Brien 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" and "double dummy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	85 pts

Oztürk 2008
Study characteristics

Methods	Design: randomised open study of TD fentanyl vs Mm/r (awaiting translation for full details)
Participants	50 chronic lung cancer pts
Interventions	TD-fentanyl vs Mm/r
Outcomes	Pain scores and adverse effects
Notes	Constipation significantly lower in fentanyl group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Awaiting assessment
Allocation concealment (selection bias)	Unclear risk	Awaiting assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Awaiting assessment
Selective reporting (reporting bias)	Unclear risk	Awaiting assessment
Size	High risk	50 pts

Oral morphine for cancer pain (Review)

Panich 1993

Study characteristics

Methods	Design: randomised cross-over at 7 d. Paracetamol or narcotic injection for breakthrough pain. Mean age 53 +/- 10, weight 46.5 kg +/- 10.6 kg
Participants	Severe cancer pain Setting: pain clinic in Thailand 73 pts (49 reported)
Interventions	Dosing regimen: Mm/r 10 mg or 30 mg every 12 h for 7 d, then cross-over to MIR solution (local formula) 5 mg to 10 mg every 4 h (or reverse order). No washout Length of treatment: 14 d (2 x 7 d)
Outcomes	Outcome measures: Nurse assessment of pain (VAS), nurse assessment - cat (4-point) duration of sleep Analgesic outcome results: no sig diff between Mm/r and MIR. Pt preference for MIR (71%). All pts had improved sleep. Pain scores provided.
Notes	Withdrawals and AEs: Withdrawals not included in analysis. Constipation, nausea, vomiting, dizziness - Table 6 no sig diff between groups. QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All pts accounted for but 24 not included in results
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	73 pts

Portenoy 1989

Study characteristics

Methods	Design: randomised, DB, parallel-group comparison of 2 strengths of Mm/r Mean age 52 yrs, weight 66.3 kg
Participants	Cancer pain Setting: pts with severe pain (using approx. 200 mg morphine/24h) 51 pts
Interventions	Dosing regimen: MIR 30 mg every 4 h with 15 mg every 2 h for breakthrough. When stabilised (1 to 2 d) randomised to 1 x 100 mg Mm/r or 3 x 30 mg Mm/r every 12 h for 3 d with 15 mg morphine as rescue available every 2 h as required. Length of treatment: 3 d
Outcomes	Outcome measures: PI 3 x daily, 5-point CAT scale, S/E, bowel Analgesic outcome results: No difference in pain intensity between groups. Rescue medication similar between groups. No significant difference in adverse effects.
Notes	Withdrawals and AEs: 2/51 not included for protocol violation therefore excluded from efficacy analysis 100 mg: N = 24, 30 mg N = 25. Total of 49 included and evaluable QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the blind condition was maintained by dispensing. . . in opaque capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	51 pts

Ridgway 2010

Study characteristics

Methods	Design: multicentre randomised, DB, cross-over study of once a day Mm/r formulation vs twice a day Mm/r formulation
Participants	Cancer pain Setting: not stated but 8 sites in Lithuania and Poland 38 pts
Interventions	Dosing regimen: Run-in period for dose stabilisation then fixed dose treatment period of 2 wks followed by cross-over treatment for 2 wks. ADPREM 30 mg once a day compared with Mm/r 15 mg twice a day (Napp). Placebo used for 2nd dose to maintain blinding. MIR allowed for breakthrough at approx 10% of the daily dose
Outcomes	Outcome measures: Av no of daily rescue doses during last 7 d of treatment. PI and average PI based on 11-point numerical scale. Pt impression and global assessment of preference Analgesic outcome results: Doses ranged from 30 to 210 mg/day. No diff in amount of rescue medication used and average PI similar Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: No difference in terms of AEs Study funded by Egalet who make ADPREM QS: 3 (R1, DB1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised to a treatment sequence"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"blinded by over encapsulating with gelatin capsules" but does not say identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	High risk	Summary results only

Oral morphine for cancer pain (Review)

Ridgway 2010 (Continued)

Size	High risk	38 pts
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Rodriguez 1994
Study characteristics

Methods	Design: randomised, DB, parallel-group trial, 7 d study vs other no medication except rescue (paracetamol 300 mg and codeine 15 mg). Baseline VASPI > 70. Mean age 61 yrs, 70% men Dipyrone pts given placebo to maintain blinding
Participants	Cancer pain Setting: oncology departments, Spain, multicentre 149 eligible; 121 pts participated
Interventions	Dosing regimen: 1. Dipyrone 1 g 8 h increasing to 2 g 8 h 2. MIR 10 mg 4 h increasing to 30 mg 4 h 3. Dipyrone 2 g 8 h Length of treatment: 7 d
Outcomes	Outcome measures: Daily VASPI, pre-study > 70 mm required. AE checklist - severity judged by investigators Analgesic outcome results: No sig diff between dipyrone 2 g 8-hourly and morphine. Dipyrone 1 g less effective (sig diff). % pts with > 50% improvement day 5: dipyrone 1 g 12%; morphine 39%; dipyrone 2 g 48%. Pt global for efficacy good/excellent: dipyrone 1 g 38%; morphine 46%; dipyrone 2 g 46%.
Notes	Withdrawals and AEs: Dipyrone 1 g 52 ADRs in 27 pts. Morphine 92 ADRs in 34 pts. Dipyrone 2 g 63 ADRs in 25 pts. No pts withdrew due to S/E but S/E more severe in morphine group. Detailed table of S/E provided in text. 149 pts in total, 28 excluded QS: 2 (R1, DB0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind"

Rodriguez 1994 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	121 pts

Smith 1991
Study characteristics

Methods	Design: randomised, DB, controlled, cross-over study. 3 to 4 d on each treatment
Participants	Cancer pain Setting: multicentre 25 pts
Interventions	Dosing regimen: Mm/r 100 mg with 200 mg placebo 12 h for 3/4 days, or Mm/r 200 mg with 100 mg placebo 12 h for 3/4 days. Aqueous morphine, dextromoramide, Solpadeine (paracetamol codeine, caffeine) available as rescue medication Length of treatment: up to 8 d (2 x 3 d or 4 d)
Outcomes	Outcome measures: VASPI 3 to 4 times daily. Morphine levels Analgesic outcome results Equivalence between treatments on VAS
Notes	Withdrawals and AEs: 5 did not complete the study, no reasons given QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"patients received wither MSC 100mg or 200mg with appropriate alternative placebo tablets"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated

Oral morphine for cancer pain (Review)

Smith 1991 (Continued)

Selective reporting (reporting bias)	High risk	Pain scores not reported
Size	High risk	20 pts

Thirlwell 1989
Study characteristics

Methods	Design: randomised, DB, DD, cross-over. Each phase > 5 d to stabilise morphine dose. No non-study opioids allowed. Non-opioids were allowed.
Participants	Cancer pain Setting: Not stated 28 pts
Interventions	Dosing regimen: Mm/r 30 mg 12-hourly or Mm/r 30 mg 8-hourly vs MIR 4-hourly Length of treatment: 10 d (2 x 5 d)
Outcomes	Outcome measures: PI PPI (4-point CAT scale) x 4 daily. Breakthrough analgesia. Plasma morphine concentrations Analgesic outcome results: No diff between treatments. Morphine bioavailability for Mm/r over 12 h similar to MIR 4 h. Av daily dose 160 mg
Notes	Withdrawals and AEs: 1 withdrew due to AE - somnolence + disorientation, 5/28 withdrew in total = 2 somnolence + disorientation, 2 difficulty in obtaining blood sample, 1 excluded as received extra dose of morphine on pharmacokinetic sampling day. Mm/r nausea 3, MIR nausea 3 QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned allocation technique"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Thirlwell 1989 (Continued)

Selective reporting (re-reporting bias)	Low risk	No problems noted
Size	High risk	28 pts

Todd 2002
Study characteristics

Methods	Design: multicentre, randomised, open, cross-over study of 2 dosing regimens of MIR
Participants	Cancer pain Setting: inpatients 24 pts
Interventions	Dosing regimen: Randomised to receive regular dose of MIR at bedtime followed by regular dose at 4 h and 8 h later for 2 d, OR double dose of MIR at bedtime followed by regular dose 8 h later for 2 days, cross-over design
Outcomes	Outcome measures: Use of breakthrough medication during night, subjective pain scores for overnight and morning pain, AEs Analgesic outcome results: Median dose 120 mg daily (range 30 mg to 600 mg). Use of breakthrough 4/20 on standard dose, 1/20 on double dose.
Notes	Withdrawals and AEs: 4 withdrew (2 due to deterioration in condition, 1 due to poor pain control, 1 due to hallucinations). Higher incidence of moderate or severe nausea on double dose; also higher incidence of sleep disturbance on double dose. QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"the order....was randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias)	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Todd 2002 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	24 pts

Twycross 1977
Study characteristics

Methods	Design: randomised, DB, cross-over after 15 to 20 d Median age 67 yrs
Participants	Cancer pain Setting: terminal cancer pts 699 pts
Interventions	Dosing regimen: Diamorphine elixir with cocaine 10 mg 1 dose. Morphine elixir with cocaine 10 mg 1 dose Length of treatment: 4 wks approx. Cross-over after 15 to 20 d
Outcomes	Outcome measures: VAS for pain, nausea and mood x 2 daily. Sleep - (though many also on sedation), appetite Analgesic outcome results: Men experienced more pain and lower mood when on diamorphine
Notes	Withdrawals and AEs: 67 withdrew as required parental therapy Withdrew due to AEs: nausea and vomiting: 25 diamorphine, 20 morphine Lack pain relief: 9 diamorphine, 7 morphine, 6 other reasons QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind", "two treatments in indistinguishable solutions"
Incomplete outcome data (attrition bias)	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Twycross 1977 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	No problems identified
Size	Low risk	699 pts

Vainio 1988
Study characteristics

Methods	Design: randomised 2-wk study. Baseline VAS (mean) 8.4/8.7
Participants	Cancer pain Setting: cancer pts with tumour compression or infiltration of brachial or lumbar plexus 30 pts
Interventions	Dosing regimen: Randomised to 1 of 3 groups: oral morphine, epidural via catheter, epidural implanted Oral morphine HCl 4 mg/ml (6 x daily) or Mm/r (2 to 3 times daily). Dose 46 to 150 mg/day. Epidural preservative-free morphine 2 mg/ml diluted to 10 ml either conventionally tunnelled catheter or totally implanted with a port (dose 2 mg to 12 mg) Length of treatment: 14 d
Outcomes	Outcome measures: VASPI. PID calculation after 24 h and 2 wks. Karnofsky performance. S/E profile Analgesic outcome results: No sig diff in VAS between groups. More S/E in oral than epidural. Av daily oral dose 190 mg
Notes	Withdrawals and AEs: Nausea and vomiting more prominent in oral group. Confusion, hallucinations, and dizziness only in oral group QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias)	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Vainio 1988 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	30 pts

Van Seventer 2003
Study characteristics

Methods	Design: randomised, multicentre, open-label study of 4 wks duration
Participants	Moderate/severe cancer pain - approx 30% opioid-naive. Pts who used opioids in previous 30 days were excluded. Setting: Not stated 131 pts, mean age 65 yrs (range 26 to 91)
Interventions	Dosing regimen: Either TD-fentanyl 25 micrograms/h for 3 d or Mm/r 30 mg 12-hourly then titrated to adequate pain relief. MIR for breakthrough pain.
Outcomes	Outcome measures: Short version Wisconsin pain inventory, pt global assessment at entry, 7 d and 28 d. Reports of constipation, respiratory depression, nausea and vomiting, drowsiness, and sleep quality also collected. Analgesic outcome results: both treatments equally effective for pain. Av dose: fentanyl 67 micrograms/hour (range 25 to 400); morphine 105 mg (30 to 400 mg)
Notes	Withdrawals and AEs: 23/64 morphine and 3/67 fentanyl dropped out due to AEs. Constipation reported by 18/64 morphine and 12/67 fentanyl. No sig diff in overall occurrence of AEs. No reports of clinically relevant respiratory depression. QS: 2 (R1, DB0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"centrally randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Van Seventer 2003 (Continued)

Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	131 pts

Ventafridda 1986

Study characteristics

Methods	Design: randomised to morphine or methadone orally
Participants	Cancer pain Setting: chronic pain with severe pain. Home setting 66 randomised, 54 included
Interventions	Dosing regimen: Methadone 1 mg/ml dose 4 mg to 24 mg every 4 h (N = 27); morphine 4 mg/ml dose 8 mg to 28 mg every 6 h (N = 27) for 3 d, then every 8 h. All pts received diclofenac 150 mg daily and haloperidol 20 mg/day by injection. Length of treatment: > 14 d
Outcomes	Outcome measures: Categorical PI 5-point scale (integrated pain score) Analgesic outcome results: adequate pain relief observed with both drugs Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: More experienced dry mouth with morphine, 4 headache with methadone. 7 pts died during treatment of disease. Withdrew AE: 2 x methadone; withdrew lack efficiency: 2 on methadone, 1 on morphine QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	"not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Ventafridda 1986 (Continued)

Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	54 pts

Ventafridda 1989
Study characteristics

Methods	Design: randomised, parallel-group Mean age 57 (28 to 88)
Participants	Cancer pain; no previous strong opiates Setting: Not stated 70 pts
Interventions	Dosing regimen: Mm/r 20 mg/day to 120 mg/day (N = 35); MIR 4% solution 24 mg/day to 144 mg/day (N = 35); also diclofenac 75 mg 3 x d; haloperidol 20 mg in 2 doses daily Length of treatment: 14 d
Outcomes	Outcome measures: Integrated score PI scale 0 to 240! S/E. Slight 1, troublesome 2.5, exhausting 5, terrible 7.5, killing 10 Analgesic outcome results: No diff between groups for analgesia. S/E frequency lower in Mm/r Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: MIR 2 died, 1 withdrew - lack of analgesia; Mm/r 1 died, 2 withdrew (1 with hallucinations, 1 morphine intolerant) QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Ventafridda 1989 (Continued)

Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	51 pts

Vielvoye-Kerkmeier 2002
Study characteristics

Methods	Design: stabilised on morphine then randomised to either once daily or twice daily Mm/r
Participants	Moderate to severe chronic cancer pain Setting: Not stated 153 enrolled, 110 entered treatment phase
Interventions	Dosing regimen: 14-day lead in of Mm/r twice a day. Once participants stable for 3 d, randomised to once daily or twice daily Mm/r for 6 to 7 d. Length of treatment: 6 to 7 d
Outcomes	Outcome measures: VAS pain, sleep verbal rating, sleep disturbance, alternate day telephone interviews re AEs, global assessment (4-point cat scale), treatment preference, AEs Analgesic outcome results: No sig diff in rescue doses between groups, pain intensity or sleep quality Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: 4/58 in twice-daily group, 1/52 once-daily (most disease-related). 12/58 nausea and vomiting on twice-daily. 10/52 nausea and vomiting on once-daily QS: 2 (R1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Not stated

Oral morphine for cancer pain (Review)

Vielvoye-Kerkmeer 2002 (Continued)

Selective reporting (reporting bias)	Low risk	No problems identified
Size	Unclear risk	110 pts

Walsh 1985a
Study characteristics

Methods	Design: randomised, DB, DD, cross-over MIR vs Mm/r Mean age 67 +/- 8 yrs
Participants	Cancer pain Setting: hospital inpatients 36 pts (30 completed)
Interventions	Dosing regimen: Pts stabilised on MIR, randomised to MIR/Mm/r cross-over d 3, cross-over d 5, cross-over d 8 Length of treatment: 10 d
Outcomes	Outcome measures: Pt-reported VASPI. Mood. Nurse-reported - pain sedation, nausea and vomiting, constipation, orientated. Pain breakthrough. Assessment of blinding Analgesic outcome results: no diff in pain, mood, sedation or anxiety. No evidence of pain breakthrough on Mm/r
Notes	Withdrawals and AEs: Not described QS: 3 (R1, DB2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical SRM placebo/pills were used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated
Selective reporting (reporting bias)	Low risk	No problems identified

Oral morphine for cancer pain (Review)

Walsh 1985a (Continued)

Size	High risk	36 pts
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Walsh 1992
Study characteristics

Methods	Design: randomised, DB, DD, cross-over
Participants	Cancer pain Setting: advanced cancer, hospitalised 33 pts, mean age 60 yrs
Interventions	Dosing regimen: Pre-study non-opioids allowed. Rescue - morphine (IR), paracetamol, IM/SC morphine. Pre-study morphine dose 92 to 108 mg/day. Required > 60 mg IR oral morphine to enter study. Mm/r 30 mg 12-hourly or multiple MIR equivalent mg/24 h every 4 h; cross-over at 2 d then 3 d further treatment Length of treatment: 5 d (cross-over d 2)
Outcomes	Outcome measures: VASPI. VAS for anxiety, depression, sedation, nausea, constipation and confusion. Pt preference, breakthrough pain Analgesic outcome results: No sig diff in pain scores, no diff in breakthrough pain (Table 3). No diff in S/Es. Achieved no worse than mild pain with scores of < 30 on a 100-point VAS
Notes	Withdrawals and AEs: AE scores recorded - no sig diff. 3 pts had nausea which necessitated withdrawal, 1 pt - protocol violation. 2 pts - rapid deterioration in health. QS: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was performed by pharmacist using a random number table"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double dummywith identical placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Walsh 1992 (Continued)

Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	33 pts

Wilder-Smith 1994
Study characteristics

Methods	Design: randomised, DB, cross-over study
Participants	Cancer pain Setting: cancer patients, hospitalised, 2 centres 20 pts, mean age 55
Interventions	Dosing regimen: Rescue - study treatment. Non-opioids stopped where possible. Tramadol solution 5% - initial dose 50 mg 6 x daily. MIR 1% solution - initial dose 16 mg 6 x daily with additional dose of same size for breakthrough. After 4 d pts cross-over for further 4 d. Length of treatment: 8 d (2 x 4 d)
Outcomes	Outcome measures: Daily 5-point verbal PI. 5-point verbal S/E Analgesic outcome results: Daily pain scores - higher in tramadol group on d 1 to 2 but similar on d 4. Nausea less on tramadol. 9 pts no preference, 8/20 preferred morphine, 3/20 preferred tramadol
Notes	Withdrawals and AEs: 4 pts on tramadol withdrew as insignificant analgesic effect. 3 pts withdrew on morphine, 2 due to nausea and vomiting, 1 with dizziness. QS: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind fashion. . . to taste, smell and look identical"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for

Oral morphine for cancer pain (Review)

Wilder-Smith 1994 (Continued)

Selective reporting (re-reporting bias)	Low risk	No problems identified
Size	High risk	20 pts

Wilkinson 1992
Study characteristics

Methods	Design: randomised, 4-dose, cross-over of Mm/r orally or rectally
Participants	Cancer pain Setting: hospital inpatients on stable morphine doses 11 pts
Interventions	Dosing regimen: Mm/r tablets every 12 h either orally or rectally. Breakthrough treatment with paracetamol or pethidine (oral) Length of treatment: 4 d
Outcomes	Outcome measures: VASPI every 12 h. VAS S/Es profile. Pharmacokinetic measurement after each 4th dose Analgesic outcome results: No sig diff in VASPI for oral or rectal. No sig diff in S/E. Preferred oral 8/10, rectal 1/10, no preference 1/10. Rectal Mm/r tablets may be useful if pts unable to swallow. Av daily dose 105 mg
Notes	Withdrawals and AEs: Not stated. 1 pt died. QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (re-reporting bias)	Low risk	No problems identified

Wilkinson 1992 (Continued)

Size	High risk	10 pts
------	-----------	--------

Wong 1997
Study characteristics

Methods	Design: randomised, open study of Mm/r vs TD-fentanyl
Participants	Cancer pain Setting: terminal cancer and treated with oral morphine 47 pts, mean age 59 yrs (30 to 79), weight 54 kg
Interventions	Dosing regimen: Pt stabilised on MIR tablets then Mm/r 12-hourly or TD fentanyl - every 3 d or 14 d. Patches overlapped by 24 h. MIR for rescue. Length of treatment: 14 d
Outcomes	Outcome measures: Verbal PI 5-point scale, frequency of pain 4-point, verbal PR 5-points, mood, sleep quality, activity status, breakthrough pain and S/E profile Analgesic outcome results: No sig diff in pain intensity between groups. Dose of fentanyl 40 to 60 micrograms/h.
Notes	Withdrawals and AEs: 7 dropped out in initial treatment phase. 6/10 Mm/r and 5/10 fentanyl reported drowsiness. Withdrew due to lack of efficacy: 3, 2 pts died, 2 withdrew AEs. QS: 2 (R1, DB0, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts accounted for
Selective reporting (reporting bias)	Low risk	No problems identified
Size	High risk	47 pts

Oral morphine for cancer pain (Review)

Xu 1997

Study characteristics

Methods	Design: randomised parallel group study comparing 2 doses of Mm/r capsules with 2 doses of Mm/r tablets (4 groups in total). Not blind. No dose titration. Lower dose given to those who had not used or rarely used opiates previously
Participants	Cancer pain Setting: cancer pts at 3 centres near Beijing 120 pts
Interventions	Dosing regimen: Mm/r 20 mg or 30 mg every 12 h for 7 d Length of treatment: 7 d
Outcomes	Outcome measures: Pain intensity - 10-point numerical scale. Pain relief - 5-point categorical scale. SPID, TOTPAR and TOTANS calculated. AEs Analgesic outcome results: No sig diff between the groups for SPID, TOTPAR, and TOTANS Pain relief moderate or complete in 65/120
Notes	Withdrawals and AEs: Withdrawals not recorded. Detailed tables of AEs. Reduction of side effects over 7 d for most symptoms except constipation, which increased QS: 1 (R1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	No problems detected
Size	Unclear risk	120 pts

ADR: adverse drug reaction

AE: adverse effect

Oral morphine for cancer pain (Review)

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Av: average
 BPI: Brief pain inventory
 BS: Box Score
 CAT: categorical scale
 CATPI: categorical pain intensity
 CATPR: categorical pain relief
 d: days
 DB: double-blind
 DD: double-dummy
 EORTC: European Organisation for Research and Treatment of Cancer
 h: hours
 HM: hydromorphone
 IR: immediate release
 IV: intravenous
 K: Kadian
 M: morphine
 Meds: medicines
 MPAC: memorial pain assessment card
 MIR: morphine instant release
 Mm/r: morphine modified release
 MSC R: morphine sustained release rectal
 MSC T: morphine sustained release tablet
 NRS: numerical rating scale
 NSAIDs: nonsteroidal anti-inflammatory drugs
 PCA: patient controlled analgesia
 PI: pain intensity
 PID: pain intensity difference
 PPI: present pain intensity
 PR: pain relief
 Pts: patients/participants
 QOL: quality of life
 QS: quality score (on Oxford Quality Scale)
 R: randomisation
 SD: standard deviation
 SE: standard error
 S/E: side effects
 Sig diff: significant difference
 Soln: solution
 SPID: sum of pain intensity difference
 SR: sustained release
 TD: transdermal
 TOTANS: total analgesic score
 TOTPAR: total pain relief
 VAS: visual analogue scale
 VASPI: VAS for pain intensity
 W: withdrawals
 WHO: World Health Organization
 Wks: weeks
 Yrs: years

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

Study	Reason for exclusion
Babul 1992	Healthy volunteers
Beaver 1977	Not oral morphine
Beaver 1978	Not morphine

Oral morphine for cancer pain (Review)

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Study	Reason for exclusion
Bosek 1994	Not oral morphine
Brooks 1989	Not a RCT
Broomhead 1997b	Healthy volunteers
Bruera 1995	Not oral morphine
Buxton 1987	Not a full journal publication - poster only
Carlson 1990	Not morphine
Cherny 1994	Not oral morphine
Chrubasik 1987	Acute pain study
Citron 1992	Not oral morphine
Cleeland 1996	Healthy volunteers
Coluzzi 2001	Study of breakthrough pain
Corli 2012	Observational study
Cowen 1997	Not morphine
Davis 1993	Only 7 patients in the study
De Bernardi 1997	Pain not evaluated - pharmacokinetics
De Conno 1997	Not a RCT
Deng 1997	Stated to be randomised but not clear if this is the case. Pain relief was physician-reported
Donner 1998	Morphine only used as rescue
Drexel 1989	Not a RCT
Du 1999	Not a RCT
Dudgeon 2007	Study of dextromethorphan
Ernst 1992	Morphine not assessed
Farrar 1998	Morphine not assessed
Faura 1996	Not a RCT
Forman 1993	Not a RCT
Georgiou 2000	Not oral morphine
Glare 1993	Not morphine

Study	Reason for exclusion
Gourlay 1986	Pharmacokinetic study
Gourlay 1995	Not a RCT
Griffith 1990	Pain not assessed
Hagen 1995	Not morphine
Hanks 1984	Abstract only
Hasselstrom 1991	No pain assessment - pharmacokinetics
Hill 1990	Acute pain
Hill 1992	Not oral morphine
Hoffman 1997	Inadequate randomisation
Houde 1981	Not oral morphine
Kaiko 1979	Acute pain
Kaiko 1984	Not oral morphine
Kaiko 1987	Not oral morphine
Kaiko 1989	Not oral morphine
Kalso 1996	Not oral morphine
Khojasteh 1987	Not oral morphine
Lakdja 1997	Acute pain
Lauretti 1999	Transdermal nitroglycerine added to morphine, so not a study of morphine alone
Lazarus 1990	Not a RCT
Li 1994	Not oral morphine
Marinangeli 2004	RCT comparing 2 stages on WHO analgesic ladder. Not specifically about morphine and while morphine included, no information about the form used
Masood 1995	Healthy volunteers
Masood 1996	Healthy volunteers
Meed 1987	Not a RCT
Minotti 1989	Not morphine
Minotti 1998	Not morphine
Morgan 1992	Not oral morphine

Study	Reason for exclusion
Moulin 1996	Not cancer pain
NCT00573937 2010	Only 1 patient enrolled
NCT00660348 2014	Only 1 patient enrolled
NCT00726830 2012	Only 1 patient enrolled
NCT01541124 2012	Results published as a letter only
Penn 1992	Not morphine
Portenoy 1999a	Opioids used calculated as morphine equivalents
Repas 1992	Not a RCT
Ripamonti 1992	Abstract only
Roca 1996	Abstract only
Santillan 1998	Morphine not used as a comparator
Savarese 1988	Inadequate randomisation
Säwe 1983	Fewer than 10 patients
Schaer 1992	Intrathecal study
Shimoyama 2015	Study of breakthrough pain
Sjogren 1989	Not prospective study
Sloan 1998	Not a RCT
Stambaugh 1981	Not oral morphine
Stambaugh 1990	Abstract only
Stambaugh 2001	RCT of oxycodone not morphine
Sykes 1996	Not pain study - constipation
Takeda 1987	Not randomised
Tawfik 1990	Abstract only
Wallenstein 1980	Acute pain
Walsh 1984	Abstract only
Walsh 1985b	Abstract only
Weingart 1985	Mixed opioids not morphine
Westerling 1993	Healthy volunteers

RCT: randomised controlled trial
WHO: World Health Organization

Characteristics of ongoing studies [ordered by study ID]

NCT01809106 2014a

Study name	RCT comparing the analgesic efficacy of 4 therapeutic strategies based on 4 different major opioids (fentanyl, oxycodone, buprenorphine vs morphine) in cancer patients with moderate/severe pain, at the moment of starting 3rd step of who analgesic ladder
Methods	RCT
Participants	550
Interventions	4 therapeutic strategies based on 4 different major opioids (fentanyl, oxycodone, buprenorphine vs morphine)
Outcomes	Proportion of non-responders
Starting date	2011
Contact information	Oscar Corli, Mario Negri Institute for Pharmacological Research
Notes	Author stated October 2015: "I am posting the results on clinicaltrials.gov and will be available soon after PRS review process."

RCT: randomised controlled trial

APPENDICES

Appendix 1. MEDLINE search strategy

The subject search used a combination of controlled vocabulary and free text terms based on the following search strategy for searching MEDLINE.

```
#1 MORPHINE*:ME
#2 MORPHINE
#3 DELAYED-ACTION-PREPARATIONS:ME
#4 TABLETS-ENTERIC-COATED:ME
#5 ((#1 or #2) and (#3 or #4))
#6 (MORPHINE NEAR "SUSTAINED RELEASE")
#7 (MORPHINE NEAR SUSTAINED-RELEASE)
#8 (MORPHINE NEAR "CONTROLLED RELEASE")
#9 (MORPHINE NEAR CONTROLLED-RELEASE)
#10 (MORPHINE NEAR "IMMEDIATE RELEASE")
#11 (MORPHINE NEAR IMMEDIATE-RELEASE)
#12 (MORPHINE NEAR "MODIFIED RELEASE")
#13 (MORPHINE NEAR MODIFIED-RELEASE)
#14 (MORPHINE NEAR "EXTENDED RELEASE")
#15 (MORPHINE NEAR EXTENDED-RELEASE)
#16 (MORPHINE and ((((((MST or SRM) or IRM) or MSS) or MSC) or MOS) or MHIR))
#17 (MORPHINE and CONTIN)
#18 (MORPHINE near (ORAL next SOLUTION))
#19 KADIAN
#20 KAPANOL
#21 ((((((((((((((#1 or #2) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13) or #14) or #15) or #16) or #17) or #18) or #19) or #20)
#22 ADMINISTRATION-ORAL:ME
#23 (ORAL-ADMINISTRATION or (ORAL next ADMINISTRATION))
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#24 (ORAL next ROUTE)
#25 (ORAL near MORPHINE)
#26 ORAL-MORPHINE
#27 (((#22 or #23) or #24) or #25) or #26)
#28 (#21 and #27)
#29 NEOPLASMS*:ME
#30 CANCER*
#31 NEOPLASM*
#32 ((#29 or #30) or #31)
#33 PAIN*:ME
#34 PAIN-MEASUREMENT:ME
#35 PAIN-THRESHOLD:ME
#36 PAIN*
#37 (((#33 or #34) or #35) or #36)
#38 ((#28 and #32) and #37)

Appendix 2. EMBASE search strategy

#1 morphine/
#2 exp delayed release formulation/
#3 enteric coated tablet/
#4 2 or 3
#5 2 AND 4
#6 (MST or SRM or IRM or MSS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
#7 (MSC or MOS or MHIR).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
#8 (MORPHINE and CONTIN).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
#9 (KADIAN or KAPENOL).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
#10 5 or 6 or 7 or 8 or 9
#11 exp oral drug administration/
#12 10 AND 11
#13 CANCER.mp. or neoplasm/
#14 pain/
#15 pain assessment/
#16 14 OR 15
#17 12 AND 13 AND 16

Appendix 3. CENTRAL search strategy

#1 "morphine":ti,ab,kw (Word variations have been searched)
#2 Neoplasms
#3 Pain OR pain assessment
#4 #1 AND #2 AND #3

FEEDBACK

Feedback submitted, July 2016

Summary

Name: Alison MacRobbie

Email Address: alison.macrobbie@nhs.net

Affiliation: NHS Highland

Role: Pharmacist

Comment: "The term 'modified release' replaces the term 'sustained release' used in the first version of this review".

This follows SPCPA guidance developed alongside the Scottish guidelines which aimed to reduce confusion, mirrors the BNF guidance etc (as for example some people abbreviating 'sustained release' to SR when others use the same SR abbreviation to mean 'standard release' although the letters SR are still contained within the names of some branded formulation).

The review article continues by using the abbreviations Mm/r and MIR to distinguish modified release from Immediate release formulations.

- there are close similarities between the symbol ' / ' and the letter 'l' and if prescribers now start to use these abbreviations in prescriptions this could lead to errors when dispensing.
- there is also potential for people to start to use the terms and write as MMR (abbreviation for measles mumps and rubella vaccine) or MIR potentially causing further confusion.

This has potential patient safety implications.

Reply

Response prepared by the author Professor Philip Wiffen.

Thank you for your feedback. We made a decision to move away from sustained release as some of the newer products are described as modified release. We decided to use the BNF notation of m/r so Mm/r referred to Morphine modified release. I accept that there may be potential for confusion with MIR but most readers would see that in the context of the evidence. Having said that, we are happy to amend the review if you can recommend an internationally acceptable shorthand for Mm/r and MIR bearing in mind that Cochrane reviews are used worldwide.

Contributors

Feedback Editor Kate Seers, Managing Editor Anna Erskine, and Co-ordinating Editor Christopher Eccleston.

WHAT'S NEW

Date	Event	Description
24 March 2021	Review declared as stable	See updated Published notes .

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 4, 2003

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest .
29 May 2019	Amended	Contact details updated.

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Date	Event	Description
31 August 2016	Feedback has been incorporated	See Feedback.
20 April 2016	Review declared as stable	See Published notes .
27 November 2015	New citation required but conclusions have not changed	We did not add any new studies to this review and the conclusions have not changed.
5 October 2015	New search has been performed	We updated the searches on 7 October 2015. We identified seven studies: we excluded six; one study is ongoing.
25 April 2014	Amended	Spelling errors corrected.
27 November 2013	Amended	Information added to Published notes .
10 May 2013	New search has been performed	New searches carried out; 'Risk of bias' tables updated.
10 May 2013	New citation required and conclusions have changed	Updated to include 10 new studies; conclusions strengthened.
14 June 2010	Amended	Contact details amended.
9 November 2009	Amended	Contact details updated.
7 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

PW initiated the review, carried out the searches, agreed on included and excluded trials, extracted the data, and wrote the text. RAM worked on the updated review for 2013 by extracting data, performing some analyses, and helped re-write the text. BW provided clinical oversight. PW undertook the 2015 update. The review will be stabilised for five years as it is unlikely that new evidence with the potential to change the conclusions will be available in the near future.

DECLARATIONS OF INTEREST

PW none known.

RAM has received institutional grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attended 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).

BW is a specialist palliative care practitioner and manages patients with cancer pain.

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 Research funds, UK

External sources

- Department of Health, UK

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

For the 2015 update: 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

This review has developed considerably since the protocol was first published in 2002. Since that date the requirements for Cochrane reviews have changed significantly. For this update and the previous version we have added an outcome of no worse than mild pain and 'Risk of bias' tables and graphs.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely 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 necessitate major revisions.

Assessed for updating in 2021

In February 2021 we did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised for five years following discussion with the authors and editors. 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 necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics, Opioid [*administration & dosage]; Morphine [*administration & dosage]; Neoplasms [*complications]; Pain [*drug therapy] [radiotherapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans