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Hydromorphone for cancer pain (Review)

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[Intervention Review]

Hydromorphone for cancer pain

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ABSTRACT

Background

Cancer pain is an important and distressing symptom that tends to increase in frequency and intensity as the cancer advances. For people with advanced cancer, the prevalence of pain can be as high as 90%. It has been estimated that 30% to 50% of people with cancer categorise their pain as moderate to severe, with between 75% and 90% of people with cancer experiencing pain that they describe as having a major impact on their daily life. Epidemiological studies suggest that approximately 15% of people with cancer pain fail to experience acceptable pain relief with conventional management. Uncontrolled pain can lead to physical and psychological distress and can, consequently, have a drastic effect on people's quality of life.

Objectives

To determine the analgesic efficacy of hydromorphone in relieving cancer pain, as well as the incidence and severity of any adverse events.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase and clinical trials registers up to April 2016. There were no language, document type or publication status limitations applied in the search.

Selection criteria

We included randomised controlled trials (RCTs) that compared hydromorphone with placebo or other active pain medication for cancer pain in both adults and children. The four main outcomes selected have previously been identified as important to people with cancer; pain no worse than mild pain, and the impact of the treatment on consciousness, appetite and thirst. We did not consider physician-, nurse- or carer-reported measures of pain.

Data collection and analysis

Two review authors independently extracted data. For binary outcomes, we calculated risk ratio (RR) and its 95% confidence interval (CI), on an intention-to-treat basis. For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. We used a random-effects model and assessed the risk of bias for all included studies. A meta-analysis was not completed on any of the primary outcomes in this review due to the lack of data. We assessed the evidence using GRADE and created two 'Summary of findings' tables.

Main results

We included four studies (604 adult participants), which compared hydromorphone to oxycodone (two studies) or morphine (two studies). Overall, the included studies were at low or unclear risk of bias, rated unclear due to unknown status of blinding of outcome assessment; we rated three studies at high risk of bias for potential conflict of interest. Data for 504 participants were available for analysis. We collected data on endpoint participant-reported pain intensity measured with a visual analogue scale (VAS) (mean ± standard deviation (SD): hydromorphone 28.86 ± 17.08, n = 19; oxycodone 30.30 ± 25.33, n = 12; scale from 0 to 100 with higher score indicating worse pain), and Brief Pain Inventory (BPI) 24 hours worst pain subscale (mean ± SD: hydromorphone 3.5 ± 2.9, n = 99; morphine 4.3 ± 3.0, n = 101, scale from 0 to 10 with higher score indicating worse pain). The data demonstrated a similar effect between groups with both comparisons. The pain intensity data showed that participants in all four trials achieved no worse than mild pain. There were several adverse events: some were the expected opioid adverse effects such as nausea, constipation and vomiting; others were not typical opioid adverse effects (for example, decreased appetite, dizziness and pyrexia, as shown in Table 1 in the main review), but generally showed no difference between groups. There were three deaths in the morphine group during the trial period, considered to be due to disease progression and unrelated to the drug. Three trials had over 10% dropout, but the reason and proportion of dropout was balanced between groups. The overall quality of evidence was very low mainly due to high risk of bias, imprecision of effect estimates and publication bias. There were no data available for children or for several participant-important outcomes, including participant-reported pain relief and treatment impact on consciousness, appetite or thirst.

Authors' conclusions

This review indicated little difference between hydromorphone and other opioids in terms of analgesic efficacy. Data gathered in this review showed that hydromorphone had a similar effect on participant-reported pain intensity as reported for oxycodone and morphine. Participants generally achieved no worse than mild pain after taking hydromorphone, which is comparable with the other drugs. It produced a consistent analgesic effect through the night and could be considered for use in people with cancer pain experiencing sleep disturbance. However, the overall quality of evidence was very low mainly due to risk of bias, imprecision of effect estimates and publication bias. This review only included four studies with limited sample size and a range of study designs. Data for some important outcomes, such as impact of the treatment on consciousness, appetite or thirst, were not available. Therefore, we were unable to demonstrate superiority or inferiority of hydromorphone in comparison with other analgesics for these outcomes. We recommend that further research with larger sample sizes and more comprehensive outcome data collection is required.

PLAIN LANGUAGE SUMMARY

Hydromorphone for the treatment of cancer pain

Background

Over 75% of people with cancer experience pain. Around 30% to 50% of these people have moderate to severe pain, which can have a negative impact on daily life. Cancer pain is a distressing symptom that tends to worsen as the disease progresses. Hydromorphone may help relieve these symptoms.

Cancer-related pain is usually treated with medicines such as morphine, oxycodone, fentanyl or hydromorphone. This review looked at how effective hydromorphone was in relieving symptoms of moderate to severe cancer pain.

Results

In April 2016, we searched for clinical trials looking at hydromorphone in people with moderate to severe cancer pain. We found four small, but well conducted, studies with 604 adults (none of the studies included children) comparing hydromorphone with oxycodone or morphine.

Based on very low quality evidence, we found no differences between the treatment groups relating to pain intensity and most people had good pain relief. Hydromorphone seemed to work as well as morphine and oxycodone. There were some side effects, such as confusion, constipation and diarrhoea, but generally there was no difference between people taking hydromorphone and people taking morphine or oxycodone.

Conclusions

The studies did not provide enough high quality evidence to draw conclusions from; however, based on very low quality evidence, hydromorphone seemed to work as well as morphine and oxycodone and had similar side effects. Hydromorphone provided consistent pain relief through the night and could be considered for use in people with cancer who find it difficult to sleep due to the pain.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Hydromorphone compared to oxycodone for cancer pain

Patient or population: people with cancer pain
Setting: unclear if these are inpatients or community patients
Intervention: hydromorphone
Comparison: oxycodone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oxycodone	Hydromorphone				
Participant-reported pain intensity	**Pain intensity scores:** 1 study (n = 31) using VAS (0 to 100, higher = worse outcome): mean (± SD) endpoint score for hydromorphone 28.86 ± 17.08 (n = 19); oxycodone 30.30 ± 25.33 (n = 12). SD of the oxycodone group was much more widespread than for the hydromorphone group 1 study (n = 81) using BPI (0 to 10; higher = worse outcome): mean change score of 'pain at its worst in the past 24 hours' for hydromorphone -1.8 ± 3.29 (n = 40); oxycodone -1.7 ± 3.91 (n = 41) **No worse than mild pain:** 1 study (n = 31) using 5-point categorical pain intensity scale (0 to 4; higher = worse outcome): mean (± SD) score across all days for hydromorphone 1.5 ± 0.1; oxycodone 1.4 ± 0.1. Both groups achieved no worse than mild pain 1 study (n = 81) using BPI (0 to 10; higher = worse outcome): 'average pain in the past 24 hours' for hydromorphone 2.9; oxycodone 3.3, SD not reported. Both groups achieved no worse than mild pain (defined as score of ≤ 4)				⊕◯◯◯ **Very low**[1,2,3]	For pain intensity, the results were similar in hydromorphone and oxycodone groups, although data were skewed Both oxycodone and hydromorphone groups had mean pain levels of 'no worse than mild pain'
Adverse events - nausea Follow-up: 28 days	See comment	See comment	Not estimable	254 (1 study)	⊕◯◯◯ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Adverse events - constipation Follow-up: 28 days	See comment	See comment	Not estimable	254 (1 study)	⊕◯◯◯ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions

Adverse events - vomiting Follow-up: 28 days	See comment	See comment	Not estimable	254 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Leaving the study early Follow-up: 14-28 days	**Study population**		**RR 0.61** (0.2 to 1.87)	304 (2 studies)	⊕○○○ **Very low**[1,2,4]	-
	480 per 1000	**293 per 1000** (96 to 898)				
	Moderate					
	470 per 1000	**287 per 1000** (94 to 879)				
Death Follow-up: 28 days	See comment	See comment	Not estimable	260 (1 study)	⊕○○○ **very low**[1,2,3]	We are uncertain if there is any difference between interventions

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BPI: Brief Pain Inventory; **CI:** confidence interval; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded once: risk of bias: sample size of < 200 per treatment arm.
[2] Downgraded once: imprecision: sample size was smaller than optimal information size; CI around estimate of effect was wide and included no effect and appreciable benefit/harm.
[3] Downgraded once: publication bias: only 1 small trial was identified for this comparison, thus publication bias was highly suspected.
[4] Downgraded once: inconsistency: unexplained heterogeneity was high between included studies.

BACKGROUND

This review updates and replaces the previously published 'Hydromorphone for acute and chronic pain' review which was withdrawn as the original author team were unavailable to update the review (Quigley 2013). The scope of the current review is limited to cancer pain.

Description of the condition

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 2011).

Cancer pain is an important and distressing symptom of the disease, which tends to increase in frequency and intensity as the cancer advances. For people with cancer, pain can arise from the progression of the cancer itself as well as from treatments designed to alleviate the condition such as radiotherapy, chemotherapy and surgery. Cancer-related pain can be classified as acute or chronic, though it is sometimes thought to be an ongoing acute pain. Acute pain is defined as having "a temporal pattern of onset... generally associated with subjective and objective physical signs" (Meier 2010), whereas chronic pain is more continuous, lasting six months or longer (Meier 2010).

One previous systematic review indicated the prevalence of pain to be more than 50% in all cancer types (Van den Beuken-van Everdingen 2007). For people with advanced cancer, the prevalence of pain can be as high as 90% (Laird 2008). It has been estimated that 30% to 50% of people with cancer categorise their pain as moderate to severe and that between 75% and 90% of people with cancer experience pain which has a major impact on their daily life (Portenoy 1999). Epidemiological studies suggest that approximately 15% of people with cancer who experience pain fail to experience acceptable pain relief with conventional management (Running 2011; Yakovlev 2008). Uncontrolled pain can lead to physical and psychological distress and can have a drastic effect on people's quality of life.

Description of the intervention

The options available for managing cancer-related pain include pharmacological treatments (e.g. opioid analgesics), psychological therapy (e.g. cognitive behavioural therapy) and alternative treatments (e.g. acupuncture or massage). Opioid pharmacotherapy (such as morphine, oxycodone, fentanyl, hydromorphone and methadone) are the most effective of these therapies (Portenoy 2011).

The World Health Organization (WHO) has recommended oral morphine as the first choice for the management of moderate to severe cancer-related pain (WHO 1986). This recommendation is largely due to its cost and availability rather than proven superiority (Caraceni 2012), with a previous review suggesting that a significant proportion of people do not achieve sufficient pain relief by taking morphine due to unmanageable adverse events, including nausea, delirium or myoclonus (muscle spasm) (Murray 2005). However, evidence from one Cochrane Review on oral morphine for cancer pain suggested that only around 5% of participants stopped taking morphine due to lack of pain relief or unacceptable adverse events (Wiffen 2013). Morphine has also been associated with toxicity in people with renal impairment (King 2011a).

Hydromorphone (also known as dihydromorphinone) is a semi-synthetic derivative of morphine, and is marketed in various countries under a range of brand names. Since its clinical introduction in 1926, it has been used as an alternative opioid analgesic to morphine, as it has a similar chemical structure but is more lipid soluble (Urquhart 1988) and potent (Twycross 1994). Hydromorphone hydrochloride has high aqueous solubility and is beneficial for people who require higher doses (Portenoy 2011), and OROS (osmotic-controlled release oral delivery system) hydromorphone extended-release (ER) is five times as potent as morphine, and has 8.5 times the equianalgesic effect when administered intravenously (Binsfeld 2010; Sarhill 2001). This also allows a smaller dose of hydromorphone to be used for an equianalgesic effect. Hydromorphone is administered through several routes (e.g. oral, intravenous, subcutaneous, epidural and intrathecal) (Murray 2005).

Hydromorphone is represented in several international guidelines for the treatment of pain. For the management of chronic cancer pain, including break-through pain, the WHO uses a model of a three-step ladder, in which step-one therapy consists of non-opioid analgesics with or without adjuvant therapy. For persistent or increasing pain, an opioid for mild to moderate pain (e.g. tramadol, codeine) might be added. If this combination fails to relieve the pain or if the pain increases, an opioid for moderate to severe pain (e.g. morphine, methadone, hydromorphone, oxycodone or fentanyl) should be substituted (Ambrosio 2003). Recommendations issued by the European Association for Palliative Care in 2012 agree with the three-step process and additionally suggest that hydromorphone be included as a step-two opioid when used at low doses (e.g. 4 mg/day) (Caraceni 2012). Consensus-based guidelines for the intrathecal treatment of cancer pain propose using intrathecal morphine as first-, second- or third-line therapy for people with moderate to severe intractable cancer pain (Deer 2011). For chronic non-cancer pain, the American Society of Interventional Pain Physicians includes hydromorphone in their guidelines for the use of opioids (Trescot 2006).

How the intervention might work

Like morphine, hydromorphone is primarily an agonist at μ-opioid receptors, displaying weak affinity for κ-opioid receptors. μ-Opioid receptors mediate pain-relieving properties but they can also result in adverse events such as nausea, constipation and respiratory depression (Murray 2005). One systematic review showed

that hydromorphone has similar analgesic and adverse effects to morphine (Miller 1999), while a more recent review concluded that no study has yet clearly demonstrated whether hydromorphone is better than oral morphine (Pigni 2011).

Hydromorphone, in common with other opioid analgesics, has the potential to produce adverse events that include respiratory depression, nausea, vomiting, constipation and itching. Tolerance may develop during chronic opioid therapy such that larger doses may be required to sustain the analgesic effect. In addition, people can be at risk of physiological dependence and experience opioid withdrawal syndrome upon sudden cessation of the opioid or administration of an antagonist. When used for the relief of pain in malignant disease, the actions of relieving anxiety, producing drowsiness and allowing sleep may be welcome (Grahame-Smith 2002).

Why it is important to do this review

This is one of a suite of reviews investigating analgesics for cancer pain. Although WHO recommends oral morphine as a first-line analgesia for cancer-related pain, the use of hydromorphone remains a consideration in some circumstances (Wiffen 2013). Previous systematic reviews have compared the efficacy and adverse effects of hydromorphone with other medications, but the inconsistency of their conclusions and the limited (low to moderate) methodological quality of the studies that were included suggested that further research is needed (Pigni 2011). This review updates the evidence by evaluating the effectiveness of hydromorphone for cancer-related pain and examines the incidence and severity of its adverse effects.

OBJECTIVES

To determine the analgesic efficacy of hydromorphone in relieving cancer pain, as well as the incidence and severity of any adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that focused on hydromorphone for the treatment of cancer pain and assessed pain as an outcome measure in this review. The RCTs included parallel or cross-over studies of any duration. We excluded studies which did not state that participants were allocated at random.

Types of participants

We intended to include studies of both adults and children with moderate to severe cancer pain (as defined in each study) who were clinically assessed as requiring treatment with opioid analgesia.

Types of interventions

We included studies in which hydromorphone (any dose and route of administration) was the active intervention. Comparison treatments included placebo, an alternative opioid or another active control.

Types of outcome measures

We assessed participant-reported pain intensity and pain relief through the use of validated pain scales, including visual analogue scales (VAS) and categorical scales. Where possible, we collected data on the four main outcomes previously highlighted as important to people with cancer (Moore 2013); pain no worse than mild, and the impact of the treatment on consciousness, appetite and thirst (Wiffen 2014).

Primary outcomes

- Participant-reported pain intensity levels as measured using a validated VAS or categorical pain scale. We were particularly interested in, but not limited to, numbers of participants who achieve 'no worse than mild pain' (Moore 2013). "No or mild pain" has been previously considered as: 3/10 on a numerical rating scale, or 30/100 mm on a VAS (Wiffen 2013). We did not consider physician, nurse or carer-reported measures of pain.
- Participant-reported pain relief measured using a validated scale.

Secondary outcomes

- Adverse events, for example, drowsiness/sedation, nausea and constipation, impact of the treatment on consciousness, appetite and thirst (incidence and severity, as defined and measured in each study).
- Improvement in participants' quality of life measured using the EuroQol EQ-5D, the World Health Organization Quality of Life Assessment or a similar validated quality of life instrument.
- Leaving the study early or discontinuation of treatment for any reason.
- Death.

Search methods for identification of studies

Electronic searches

To identify potentially relevant studies to be assessed for inclusion in this review, we searched the databases listed below. See Appendix 1 for search strategies.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3) in the Cochrane Library.
- MEDLINE (Ovid) 1946 to April 2016.
- Embase (Ovid) 1974 to April 2016.

Searching other resources

In an attempt to identify any relevant published or unpublished reports not found in the electronic searches, we manually checked the references of each included paper. We contacted the authors of each included paper and of publications which were only available in abstract format. Where possible, we contacted representatives from the pharmaceutical companies marketing hydromorphone to ask for any relevant published or unpublished studies, or missing data.

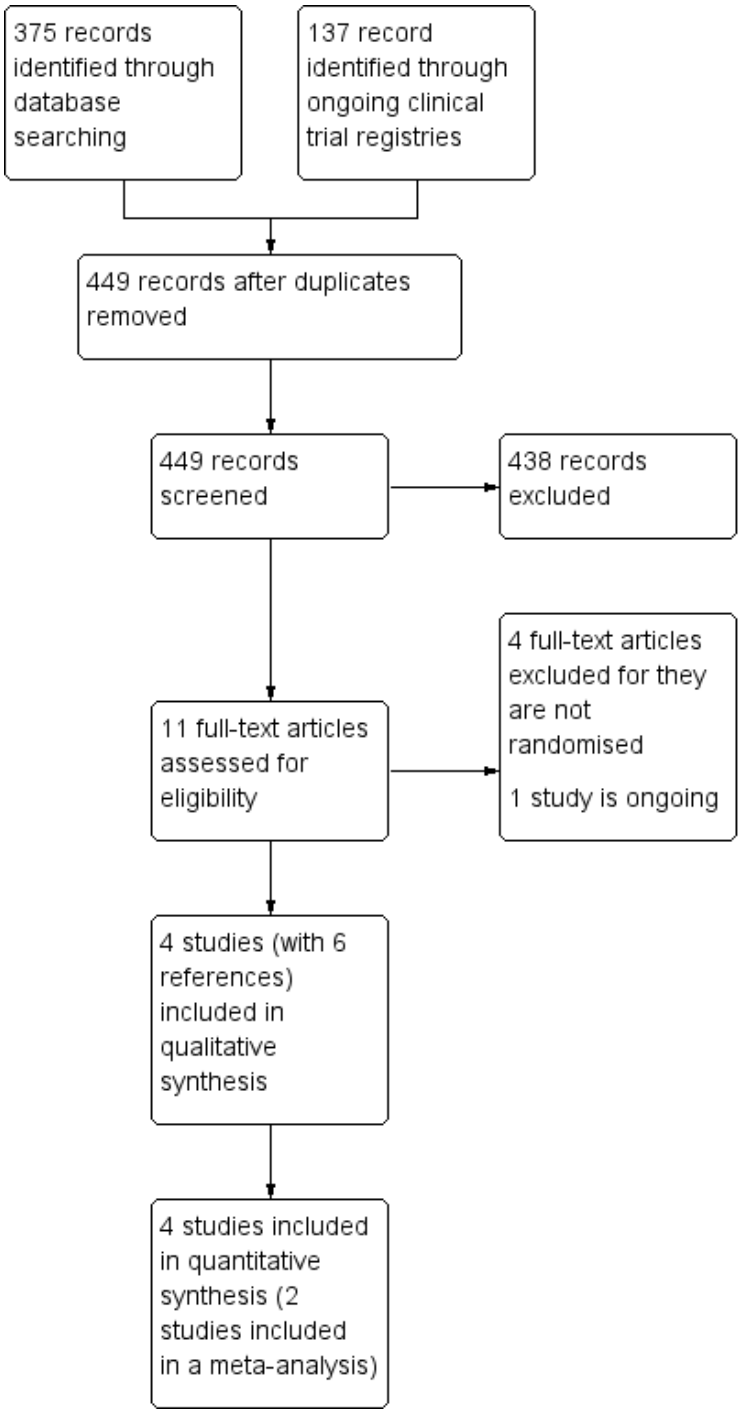
There was no limitation on publication date or on language. Had there been any non-English papers, we would have translated as necessary. We also searched for ongoing trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). We intended to search metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), however, the website was unavailable.

Data collection and analysis

Selection of studies

Two review authors (YJB and BJH) assessed the titles and abstracts of all studies identified by the searches and independently considered the full records of all potentially relevant studies for inclusion by applying the selection criteria outlined in the Criteria for considering studies for this review section. We resolved disagreements by discussion. We did not restrict the inclusion criteria by date or language. To promote transparency of the search and systematic review process, we produced a PRISMA flow diagram (Figure 1), as per the PRISMA statement (Moher 2009).

Figure 1. Study flow diagram.



Data extraction and management

We extracted data using the Cochrane Pain, Palliative and Supportive Care Group's recommended data extraction form and recorded baseline data on participants, details of interventions, outcomes and results relevant to our review. Had we identified any study that included a subset of participants who received hydromorphone, we would have extracted data from this group. We resolved any disputes by discussion.

Assessment of risk of bias in included studies

Two review authors (YJB and BJH) independently assessed the methodological quality of each included study using the 'Risk of bias' assessment method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included the following risk of bias domains: allocation and randomisation methods; blinding and methods of maintaining blinding; selective reporting of outcome measures; incomplete outcome data and 'other' sources of bias (e.g. sources of funding). We rated the domains as 'low risk', 'high risk' or 'unclear risk' of bias. We completed a 'Risk of bias' table for each included study. We resolved any disagreements between the assessors by discussion. Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Moore 2012; Nüesch 2010); therefore, we considered studies to be at low risk of bias if they had 200 or more participants per treatment arm, at unclear risk if they had between 50 and 200 participants per treatment arm, and at high risk if they had fewer than 50 participants per treatment arm (Wiffen 2013).

Measures of treatment effect

For dichotomous outcomes, we calculated the risk ratio (RR) and the corresponding 95% confidence interval (CI) and P value. For continuous outcomes, we calculated the mean difference (MD) and its corresponding 95% CI when means and standard deviations (SD) were available. If such information was unavailable, we would have use the methods described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* to calculate standardised mean differences (SMD) from, for example, F ratios, t values, Chi^2 values and correlation coefficients (Higgins 2011). In cases where continuous measures were used to assess the same outcomes using different scales, we would have pooled these data using Hedges' g to estimate the SMD. When effect sizes could not be pooled, we would have reported study-level effects narratively. We would also have calculated numbers needed to treat for an additional outcome (NNTB) and additional harmful outcomes (NNTH).

Unit of analysis issues

We only included studies that randomised the individual participant.

Dealing with missing data

We assessed missing data in the included studies. Where possible, we investigated and reported the reasons and numbers of those dropping out of each included study. Where studies were identified as having missing data, we initially attempted to contact the study authors to obtain this information. For dichotomous outcomes, we performed an intention-to-treat (ITT) analysis. If there was missing participant information, we recorded this and commented in the individual study's 'Risk of bias' table. We assigned participants with missing data to a 'zero improvement' category, and we performed a sensitivity analysis comparing the resulting effect sizes with those obtained using completer-only data. For continuous outcomes, we intended to use baseline observation carried forward (BOCF), where rating scales were employed. However, this was not done as data of the few continuous outcomes were skewed. Where data are missing for substantial numbers of participants (greater than 10%), we rated the study as a high risk of bias.

Assessment of heterogeneity

We intended to assess for heterogeneity among primary outcome studies using the I^2 statistic along with its corresponding P and Chi ^{2} values (Higgins 2011), and discuss any observed heterogeneity and its magnitude. Had we identified heterogeneity, we would have investigated possible sources using subgroup analyses and sensitivity analyses.

Assessment of reporting biases

We looked for the original trial protocols of the included studies and compared the results to these when they were found. When no protocol was available, we compared the reported outcomes against the methods section of the paper to look for selective reporting of outcomes.

Data synthesis

We entered all extracted data into Review Manager 5 software for analysis (RevMan 2014). In order to take into account differences between studies, we synthesised data using a random-effects model. We used a fixed-effect model in a sensitivity analysis in order to investigate any differences in the estimate of effect. We

meta-analysed the data where possible. Where this was not feasible, we summarised data narratively in the results and discussion sections and the relevant tables.

Grading of evidence

This section is taken from the Cochrane Drugs and Alcohol Group recommended text. We assessed the overall quality of the evidence for each outcome using the GRADE system (Guyatt 2011), and presented it in the 'Summary of findings' tables, to present the main findings of a review in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes. The GRADE system uses the following criteria for assigning grade of evidence:

- high = further research is very unlikely to change our confidence in the estimate of effect;
- moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- very low = any estimate of effect is very uncertain.

We decreased grade if there was:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1).

'Summary of findings' table

We included two 'Summary of findings' tables to present the main findings in a transparent and simple tabular format. In particular, we include key information concerning the quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the outcomes participant-reported pain intensity, adverse events, leaving the study early and death.

Subgroup analysis and investigation of heterogeneity

Had there been data available, we would have carried out the following subgroup analyses:

- method of administration (long-acting versus short-acting);
- single dose versus multiple dose;
- type of cancer;
- age (adults versus children).

Sensitivity analysis

Had there been sufficient data available, we would have examined the robustness of meta-analyses by conducting a sensitivity analysis. In future updates of this review, we plan to exclude studies are at 'high risk of bias' across any one of the risk of bias domains in order to assess any differences in the estimate of treatment effect. We further plan to conduct a sensitivity analysis for high levels of attrition (greater than 10%) in individual studies, comparing completer-only data with our assumptions of ITT and to assess any differences when synthesising data using a fixed-effect rather than a random-effects model.

RESULTS

Description of studies

Results of the search

Details of the search results are illustrated in the PRISMA table (Figure 1).

In the original search, we found 512 (375 through databases and 137 through international ongoing clinical trial registries) records that were potentially relevant. After removing duplicate records, we screened 449 abstracts, of which we were able to exclude 438 records that were clearly irrelevant. We eventually identified 11 full-text articles as potentially eligible for inclusion. Upon close inspection of these papers, we were able to include four studies (with six references) in this review. There was one ongoing study and there are no studies awaiting assessment.

Included studies

We found four RCTs in adults (604 participants) that satisfied the inclusion criteria of this review; see Characteristics of included studies for a full description. The search found no studies including children.

Design and setting

Three of the included studies were conducted in high-income countries. Hagen 1997 was conducted in Canada; Hanna 2008 was a multicentre trial involving 37 centres in Belgium, Canada, France, Germany, the Netherlands, Spain, Sweden and the UK. This study reported that it included inpatients, outpatients and day patients. Moriarty 1999 was conducted in the UK. The remaining study was conducted in China (Yu 2014).

Two studies had a cross-over study design (Hagen 1997; Moriarty 1999), and two had a two-stage, parallel design that included an initial titration stage followed by a slow release (SR) or maintenance phase (Hanna 2008; Yu 2014).

Sample sizes

Hagen 1997 was the smaller trial of the four with 44 participants randomised, but only 31 people completed the trial. Hanna 2008 had a sample size of 200. Moriarty 1999 randomised 100 participants, but only 89 completed the trial. Yu 2014 randomised 260 people, but only 137 completed the trial through to the end of maintenance phase.

Participants

All four studies included adults with chronic cancer pain. The mean age in Hagen 1997, Hanna 2008, and Yu 2014 was about 56 to 59 years with evenly distributed gender; the age of Moriarty 1999 was over 18 years but no age range was given. We found no studies including children. The proportion of men in the study ranged from 42% (Hagen 1997) to 66% (Yu 2014).

The severity of cancer pain was unclear in Hagen 1997, but participants required stable analgesics. Participants in Hanna 2008 had moderate to severe pain and required 60 mg to 540 mg of oral morphine every 24 hours at baseline. Moriarty 1999 and Yu 2014 also involved people with moderate to severe cancer pain. The locations of the primary tumour were mainly breast, colorectal, lung, prostate, gastrointestinal and central nervous system. A smaller proportion of participants had cancer in the oral cavity, lymphoma, leukaemia and bone cancer.

Interventions

Interventions included hydromorphone versus oxycodone (Hagen 1997; Yu 2014), and hydromorphone versus morphine (Hanna 2008; Moriarty 1999).

Hagen 1997 compared controlled release (CR) hydromorphone versus CR oxycodone given every 12 hours for seven days. The mean (± SD) daily doses were given as 24 ± 4 mg for hydromorphone and 120 ± 22 mg for oxycodone. Cross-over was completed without a washout period.

In the two-stage Yu 2014 trial, the eight-day titration phase was followed by a 28-day maintenance phase. Both phases used CR formulations; OROS hydromorphone or oxycodone CR and the maximum daily doses were 32 mg for OROS hydromorphone and 80 mg for oxycodone CR.

The titration stage for Hanna 2008 used instant release (IR) formulations of either hydromorphone or morphine given every four hours (six times daily) for two to nine days. The titrated dosage of hydromorphone during this phase was 12 mg/day to 108 mg/day and for morphine was 62 mg/day to 540 mg/day. This was followed by a 10- to 15-day SR stage, when the same drugs were given but in a CR formulation; OROS hydromorphone once daily or morphine CR twice daily. The starting dose was the same level as dose-stable pain achieved in IR phase, adjusted as required every two days at most.

Moriarty 1999 used tablet formulation of hydromorphone CR 4 mg and morphine CR 30 mg.

Outcomes

We were able to collect data on pain intensity, but the data were skewed. Other outcomes reported by the studies included adverse events, death and leaving the study early.

Excluded studies

We excluded four studies. Although all of them had relevant participants and interventions, they were not RCTs. See Characteristics of excluded studies for further details (Han 2014; Lee 2012; Wirz 2008; Wirz 2009).

Studies awaiting assessment

There are no studies awaiting assessment.

Ongoing studies

The search found one ongoing RCT eligible for inclusion, which compared hydromorphone with oxycodone and fentanyl patch in adults with moderate to severe cancer pain (NCT02084355). The total sample size of this study was unclear. Expected completion date was January 2016.

Risk of bias in included studies

The general risk of bias in respect of study design and conduct was low. However, two trials were industry funded (Hagen 1997; Hanna 2008), which raised some concern over potential conflicts of interest. Furthermore, Hagen 1997 had a high dropout rate and those dropping out were excluded from their final analysis. See Figure 2 and Figure 3 for graphic representation of the risk of bias assessment.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

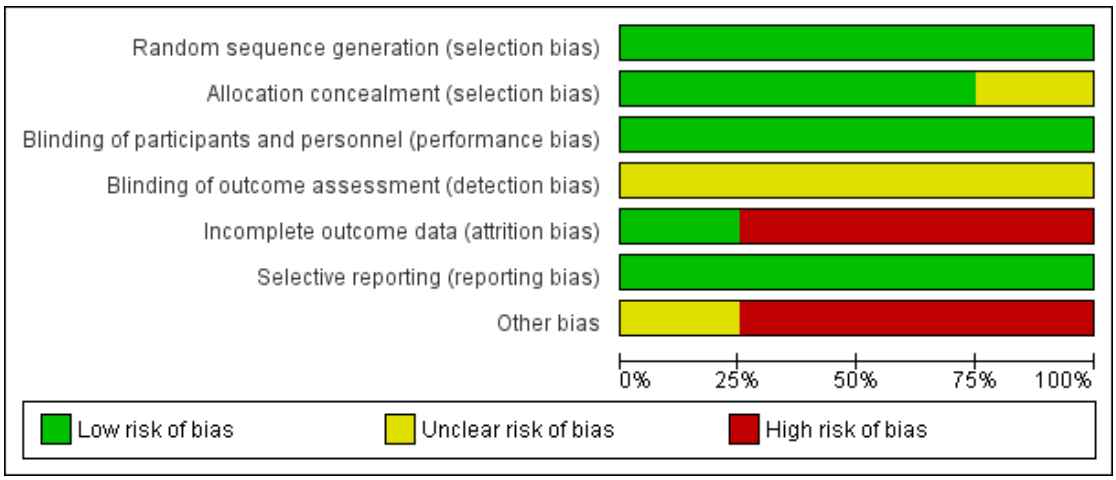
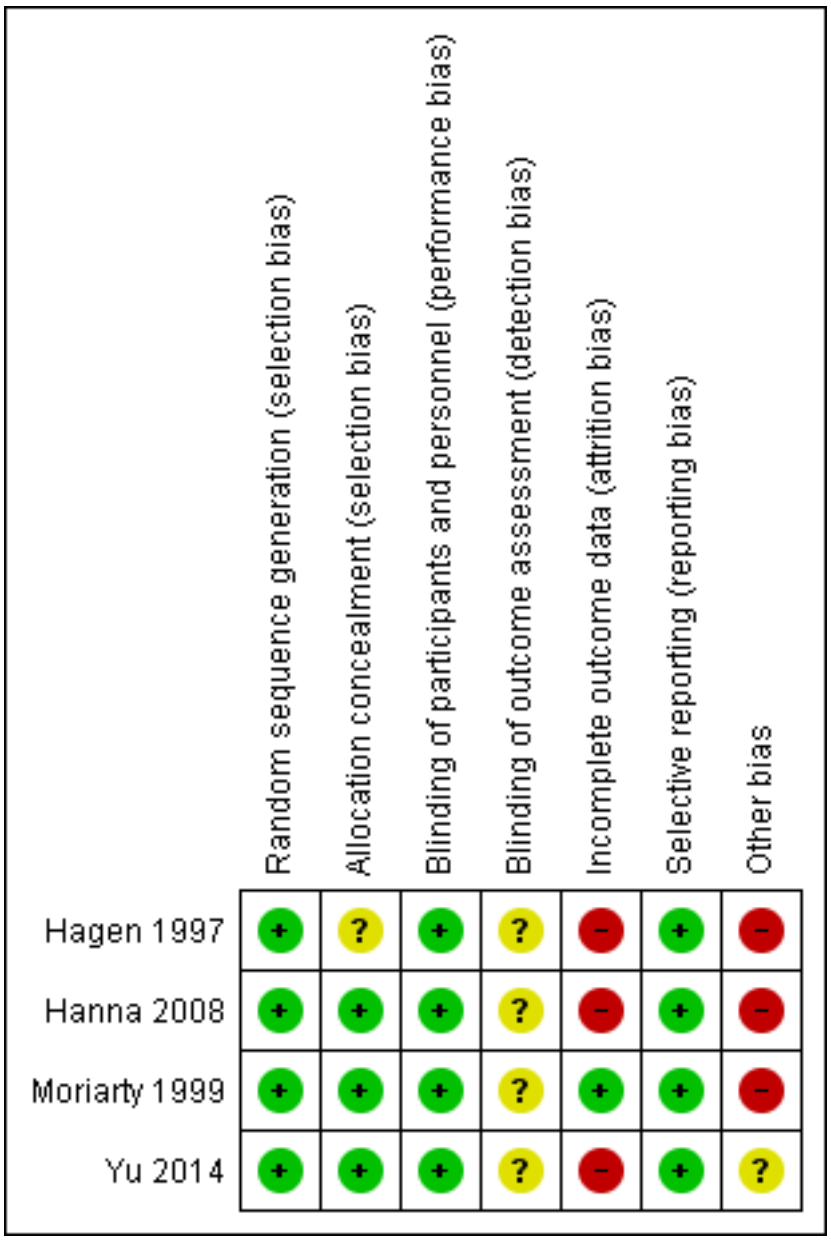


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

We assigned all four included studies low risk of bias for random sequence generation. Hanna 2008 randomised participants on a 1:1 ratio via a central computer-generated randomisation list. Similarly, Yu 2014 also used central randomisation (1:1) using an online dynamic minimisation allocation program. Hagen 1997 did not describe randomisation procedure in detail, but it was a double-blind trial, thus it was likely to have had adequate randomisation. Moriarty 1999 employed a third-party randomisation method.

Allocation concealment

None of the studies provided explicit detail on allocation concealment. We considered Hanna 2008 was more likely to have used concealment since the randomisation was done via a central list, and so we judged this study at low risk of bias. We also judged Moriarty 1999 and Yu 2014 at low risk of bias because they used third-party randomisation, which typically conceals allocation. We judged Hagen 1997 at unclear risk of bias because there was no detail reported in the paper, thus review authors were unable to make any conclusive judgement.

Blinding

Blinding of participants and personnel

Three of the four studies were described as double-blind (Hagen 1997; Hanna 2008; Moriarty 1999). Hanna 2008 was reported as double blind, but without further description of the blinding method; in this case, we accepted the author's reporting as true and accurate, thus rated it at low risk of bias. Hagen 1997 and Moriarty 1999 used double-blind and double-dummy to protect the blinding. Yu 2014 did not offer an explicit description on blinding; however, review authors felt that double-blinding was likely to have been used, as the study employed over-encapsulated tablet and placebo to mask blinding, hence we rated it at low risk of bias.

Blinding of outcome assessment

It was unclear in any of the studies if the outcome assessment was blinded, because none of the included studies provided an explicit description of this risk domain. Therefore, we rated this risk domain at unclear risk for all of the four studies.

Incomplete outcome data

Dropout was common and the proportion of dropout exceeded 10% in all four studies, thus the general risk of bias in this domain was high. Hanna 2008 had applied ITT analysis and the reasons and proportion for dropout was similar between groups, however, the dropout rate was greater than 10%, thus it was rated as high risk. Hagen 1997 was rated as high risk as it had over 10% dropout and these were excluded from final analysis, which further compromised the already weakened evidence. Moriarty 1999 had 11 (11%) participants drop out with reasons given and were included in the final analysis. The dropout rate was over 10%, but only marginally so. We felt the drop-out was unlikely to have caused significant bias, as reasons and proportion of dropout were comparable between groups. We therefore judged this study to be at a low risk of bias for this domain. Sixty (46%) people dropped out of the hydromorphone group and 63 (48%) people dropped out of the oxycodone group in Yu 2014, but the proportion and reasons were balanced between groups. Nevertheless, we judged it as high risk because the dropout rate was greater than 10%.

Selective reporting

Two of the four trials had protocols (Hanna 2008; Yu 2014), and we did not identify any differences between the planned outcome measures in the protocol and the reported outcome measures in the full report. Two trials had no available protocols (Hagen 1997; Moriarty 1999). We compared the reported outcomes with the paper's methodology section and did not find any evidence of selective reporting. Therefore, we judged all four included studies as being at low risk of reporting bias.

Other potential sources of bias

We judged three included studies to be at a high risk of bias for this domain (Hagen 1997; Hanna 2008; Moriarty 1999). There were two major concerns of other bias regarding sample size and sponsorship. Two studies were funded by pharmaceutical companies (Hagen 1997; Hanna 2008). One of the authors of Moriarty 1999 was an employee of a pharmaceutical company, which raised concern over conflict of interest. Three of the four studies had a small sample size (fewer than 200 participants per treatment arm), which raised potential risk of bias (Hagen 1997; Hanna 2008; Moriarty 1999). Yu 2014 had between 50 and 199 participants per treatment arm, and so we judged this study at unclear risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Hydromorphone compared to oxycodone for cancer pain;

Summary of findings 2 Hydromorphone compared to morphine for cancer pain

We were able to extract numerical data from three of the four included studies.

Comparison 1: hydromorphone versus oxycodone

This particular comparison had very low quality evidence from Hagen 1997 (n = 44) and Yu 2014 (n = 260) (Summary of findings for the main comparison), downgraded three times due to risk of bias, imprecision, publication bias or inconsistency.

1.1 Participant-reported pain intensity

Data were presented in separate data tables because they were skewed. Hagen 1997 reported VAS score (0 to 100 with higher score indicating worse outcome). The mean VAS endpoint pain intensity scores at seven days were similar between groups (mean (± SD): hydromorphone 28.86 ± 17.08, n = 19; oxycodone 30.30 ± 25.33, n = 12), although the SD of the oxycodone group was larger than for the hydromorphone group indicating a wider spread of the data. Both groups achieved no worse than mild pain on the categorical pain intensity as measured on a four-point VAS (higher = worse outcome) (hydromorphone 1.5 ± 0.1 points; oxycodone 1.4 ± 0.1 points).

Yu 2014 reported Brief Pain Inventory (BPI) score (0 to 10 with higher score indicating worse outcome). The BPI change score of 'pain at its worst in the past 24 hours' from baseline was similar between groups at 28 days (hydromorphone -1.8 ± 3.29, n = 40; oxycodone -1.7 ± 3.91, n = 41). BPI score for 'mean pain in the past 24 hours' of the same study showed that both groups achieved no worse than mild pain (hydromorphone 2.9; oxycodone 3.3, SDs not reported, n = 81) (Analysis 1.1).

Neither study reported 'no worse than mild pain'.

1.2 Participant-reported pain relief

Neither study reported participant-reported pain relief.

1.3 Adverse events

Hagen 1997 presented data measured using VAS at seven days in separate data tables because the continuous data for this outcome were skewed. The mean endpoint nausea scores were comparable between groups (hydromorphone 16.05 ± 17.51, n = 19; oxycodone 16.68 ± 21.53, n = 12). However, the oxycodone group had a higher mean endpoint sedation score than the hydromorphone group (hydromorphone 19.92 ± 20.62, n = 19; oxycodone 24.81 ± 25.73, n = 12), although we were not certain if the difference was statistically significant.

The above findings were consistent with Yu 2014, which indicated no significant differences between groups at 28 days on the following adverse events: nausea (RR 0.94, 95% CI 0.67 to 1.32); constipation (RR 0.94, 95% CI 0.67 to 1.32) and vomiting (RR 0.90, 95% CI 0.65 to 1.26). Other adverse events identified in this study showed no significant differences between groups. See Table 1 for further details.

Neither study reported impact on consciousness, appetite or thirst.

1.4 Quality of life

Neither study reported quality of life.

1.5 Leaving the study early

Two studies involving 304 participants reported on participants leaving the study early (Hagen 1997; Yu 2014). We found no evidence of difference between hydromorphone and oxycodone (RR 0.61, 95% CI 0.20 to 1.87) (Analysis 1.4).

1.6 Death

One study reported death (n = 260) (Yu 2014). This was claimed to be a consequence of disease progression, and there was no statistically significant difference between groups (RR 0.50, 95% CI 0.22 to 1.13) (Analysis 1.5).

Comparison 2: hydromorphone versus morphine

In this comparison, there was very low quality evidence from a single study (Hanna 2008, n = 200). The other study which investigated these interventions did not report any usable numerical data for analysis (Moriarty 1999) (Summary of findings 2, downgraded three times due to risk of bias, imprecision and publication bias).

2.1 Participant-reported pain intensity: BPI endpoint (SR phase) subscale score (high = more pain; data skewed)

The continuous data from one RCT were too skewed to report in a graph. Therefore, we have presented them in a data table (Analysis 2.1). Subscale data derived from the BPI scale showed that the morphine group appeared to have a higher endpoint mean score on 'worst pain' (mean ± SD: hydromorphone 3.5 ± 2.9, n = 99; morphine 4.3 ± 3.0, n = 101), nevertheless, mean scores on 'least pain' and 'mean pain' were almost identical. The 'mean pain' subscale data showed that both groups achieved no worse than mild pain (see Analysis 2.1).

Although it was not possible to extract and analyse data by groups from Moriarty 1999, the study gave a clear indication that participants in both groups achieved no worse than mild pain as measured by VAS. The mean score of both groups was below 20 on the 0- to 100-mm VAS.

We found no studies reporting the number of participants who achieved 'no worse than mild pain'

2.2 Participant-reported pain relief

Neither study reported participant-reported pain relief.

2.3 Adverse events

One study reported adverse events (Hanna 2008). There was no difference between groups for the following adverse events:

- anaemia (hydromorphone 25/77; morphine 21/86; RR 1.21, 95% CI 0.73 to 2.02);
- anorexia (hydromorphone 24/77; morphine 20/86; RR 1.22, 95% CI 0.72 to 2.07);
- anxiety (hydromorphone 27/77; morphine 16/86; RR 1.72, 95% CI 0.99 to 2.99);
- asthenia (hydromorphone 28/77; morphine 19/86; RR 1.50, 95% CI 0.9 to 2.51);
- dizziness (hydromorphone 26/77; morphine 23/86; RR 1.15, 95% CI 0.71 to 1.88);
- fatigue (hydromorphone 26/77; morphine 21/86; RR 1.26, 95% CI 0.76 to 2.09);
- headache (hydromorphone 25/77; morphine 17/86; RR 1.50, 95% CI 0.87 to 2.60);
- insomnia (hydromorphone 27/77; morphine 19/86; RR 1.45, 95% CI 0.86 to 2.43);
- nausea (hydromorphone 37/77; morphine 40/86; RR 0.94, 95% CI 0.66 to 1.34);
- peripheral oedema (hydromorphone 23/77; morphine 23/86; RR 1.02, 95% CI 0.61 to 1.69);
- pruritus (hydromorphone 25/77; morphine 20/86; RR 1.28, 95% CI 0.76 to 2.14);
- pyrexia (hydromorphone 26/77; morphine 17/86; RR 1.56, 95% CI 0.9 to 2.69);
- somnolence (hydromorphone 30/77; morphine 27/86; RR 1.13, 95% CI 0.73 to 1.76);
- vomiting (hydromorphone 29/77; morphine 34/86; RR 0.87, 95% CI 0.58 to 1.31).

There was a statistically significant difference favouring the morphine group on the following outcomes. However, the stability of these analysis results is compromised by missing data, and two of the outcomes (confusion and diarrhoea) were no longer statistically significant once we had taken into account the missing data in a sensitivity analysis. See 'Comparison 2: sensitivity analysis for hydromorphone versus morphine' for further details.

- Confusion (hydromorphone 29/77; morphine 17/86; RR 1.74, 95% CI 1.02 to 2.96).
- Constipation (hydromorphone 52/77; morphine 34/86; RR 1.56, 95% CI 1.12 to 2.17).
- Diarrhoea (hydromorphone 29/77; morphine 17/86; RR 1.74, 95% CI 1.02 to 2.96).

The Hanna 2008 study did not report impact on consciousness, appetite or thirst.

Moriarty 1999 observed similar adverse events, but did not report the number of participants, thus preventing pooling of the results. The type and number of adverse events appeared to be balanced between groups without any obvious differences. See Table 2 for a detailed account.

2.4 Quality of life

We found no studies reporting quality of life.

2.5 Leaving the study early

2.5.1 Overall

One study (with 200 participants) reported leaving study early (Hanna 2008) (Analysis 2.3). For this subgroup, we found no evidence of a clear difference between OROS hydromorphone and morphine sulphate (RR 1.42, 95% CI 0.95 to 2.12).

2.5.2 Due to adverse events

One study (with 200 people) reported leaving the study early due to adverse events (Hanna 2008) (Analysis 2.3). For this subgroup, we found no evidence of a clear difference between the two treatments (RR 1.39, 95% CI 0.67 to 2.88).

2.5.3 Due to lack of efficacy

One study (with 200 people) reported leaving the study early due to lack of efficacy (Hanna 2008) (Analysis 2.3). However, we found no evidence of a clear difference between the two treatments (RR 2.81, 95% CI 0.92 to 8.52).

2.6 Death

One trial (with 200 participants) reported death (Hanna 2008) (Analysis 2.4). There was no clear difference between hydromorphone and morphine (RR 0.15, 95% CI 0.01 to 2.78).

Comparison 2: sensitivity analysis for hydromorphone versus morphine

In accordance with our protocol, we performed a sensitivity analysis for the adverse events data reported by Hanna 2008 comparing the effect size with and without drop-outs. When we included dropouts in the analysis, we found a statistically significant difference favouring the morphine group for the following outcomes: confusion (RR 1.74, 95% CI 1.02 to 2.96), constipation (RR 1.56, 95% CI 1.12 to 2.17) and diarrhoea (RR 1.74, 95% CI 1.02 to 2.96). However, when we analysed completers data, only constipation remained statistically different (RR 1.76, 95% CI 1.09, 2.87).

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Hydromorphone compared to morphine for cancer pain

Patient or population: people with cancer pain
Setting: inpatients, outpatients and day patients
Intervention: hydromorphone
Comparison: morphine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Morphine	Hydromorphone				
Participant-reported pain intensity	**Pain intensity scores:** 1 study (n = 200) using subscale data derived from BPI scale (0 to 10; higher = worse outcome): mean (± SD) endpoint score for 'worst pain' hydromorphone 3.5 ± 2.9 (n = 99); morphine 4.3 ± 3.0 (n = 101) Mean scores on 'least pain' and 'average pain' were almost identical **No worse than mild pain:** 1 study (n = 200) using subscale data derived from BPI scale (0 to 10; higher = worse outcome): the 'average pain' subscale data showed that both groups achieved no worse than mild pain				⊕○○○ **Very low**[1,2,3]	Higher mean endpoint scores for 'worst pain' in morphine group Similar scores for 'average' and 'least' pain in hydromorphone and morphine groups Both morphine and hydromorphone groups had mean pain levels of 'no worse than mild pain'
Adverse events - confusion Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Adverse events - headache Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions

Adverse events - insomnia Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Adverse events - nausea Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Adverse events - pyrexia Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Death Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions
Leaving the study early - overall Follow-up: 24 days	See comment	See comment	Not estimable	200 (1 study)	⊕○○○ **Very low**[1,2,3]	We are uncertain if there is any difference between interventions

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BPI: Brief Pain Inventory; **CI:** confidence interval; **SD:** standard deviation

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded once: risk of bias: sample size < 200 per treatment arm.
[2] Downgraded once: imprecision: sample size was smaller than optimal information size; CI around estimate of effect was wide and included no effect and appreciable benefit/harm.
[3] Downgraded once: publication bias: only 1 small trial was identified for this comparison, thus publication bias was highly suspected.

DISCUSSION

Summary of main results

We were only able to include four studies in this review, with a total sample size of 604 participants (data for 504 participants available for analysis). Two studies compared hydromorphone to oxycodone and two studies compared hydromorphone to morphine. Overall, there was no evident difference in treatment efficacy between groups, and participants achieved no worse than mild pain in all included studies (Hagen 1997; Hanna 2008; Moriarty 1999; Yu 2014). Data on pain intensity demonstrated a similar effect between groups. There were several adverse events, but most showed no difference between groups except for confusion, constipation and diarrhoea, which favoured the morphine group. However, the clinical significance of the observed differences are questionable due to the instability of analysis caused by missing data from the trial. Hanna 2008 reported three deaths in the morphine group during the trial period, but trialists claimed that they were not related to the drug but were the consequences of cancer. Yu 2014 also reported death (8 in the hydromorphone group and 16 in the oxycodone group), but the most common reason was disease progression. The two studies that contributed the most data in this review had over 10% dropout rates, but the reasons and proportion of dropouts were balanced between groups (Hagen 1997; Hanna 2008). We hoped to observe effects on consciousness, thirst and appetite, but the included studies did not report these data.

Prevalence of sleep disturbance in people with cancer ranges from 24% to 95% (Graci 2005; Mercadante 2004), and is more common among females with cancer, older people, and people with depression or anxiety (Akechi 2007; Graci 2005). Therefore, we suggest that more attention is given to pain control for increasing quality of sleep (Graci 2005; Kvale 2006). Opioids are useful for the initial restoration of night-time sleep (Graci 2005; Kvale 2006); however, long-term opioid use can cause sedation and daytime sleeping, as well as disturbed sleep patterns and circadian rhythms (Graci 2005; Hearson 2008). Unlike opioids and short-acting hydromorphone, OROS hydromorphone is gradually absorbed over 24 hours without causing fluctuations in blood concentration (Nalamachu 2012). Hanna 2008 demonstrated that pain levels in the evening were significantly lower after OROS hydromorphone compared with CR morphine. Therefore, OROS hydromorphone could be considered for people with cancer pain with sleep disturbance.

Opioids are the mainstay of pain treatment. Knowledge regarding the use of opioids can improve the care provided to people with cancer. Opioid rotation is a common practice for the improvement of pain control or drug tolerability, or both (Quigley 2004). When these appropriate interventions have been exhausted or when adverse effects are rapid and severe (or both), rotation to an alternative opioid may help, but there is a lack of evidence to support rotation.

Overall completeness and applicability of evidence

There is a lack of data on children and younger adults. The mean age of participants included in this review was approximately 56 years. We were able to collect data on the primary outcome of no worse than mild pain and most of the secondary outcomes that we intended to measure, with the exception of quality of life. There was a lack of data on other participant-important outcomes, such as the impact of the treatments on consciousness, appetite and thirst. Applicability of the evidence is further limited by the fact that only oxycodone and morphine were compared to hydromorphone in the included studies. Included studies were conducted in high-income countries, which may have limited generalisability in some lower-income countries.

There was a heterogeneity within the included trials with respects to their study design, formulations used and duration of follow-up. Two studies were cross-over design and two used a parallel design using two phases. All of the studies used CR or ER opioids, yet one study included an initial phase which used an IR formulation (Hanna 2008). The duration of follow-up between the trials ranged from 7 to 28 days. These factors increased the difficulty of drawing specific conclusions from the studies.

It is worth noting that two of the trials in this review used the OROS formulation of hydromorphone which has some unique properties that differ from other formulations of hydromorphone (Hanna 2008, n = 200; Yu 2014, n = 260). It is a unique long-acting opioid formulation that utilises Push-Pull active osmotic technology and maintains consistent hydromorphone plasma concentrations throughout the 24-hour dosing interval, providing long-lasting analgesia (Angst 2001; Drover 2002; Palangio 2002). The dosage form controls the drug release into the body, almost independently from factors such as the surrounding pH or gastric motility (Bass 2002; Verma 2002). There is a minimal effect of food on the rate and extent of absorption of hydromorphone from OROS hydromorphone (Sathyan 2007). It has been reported that the pharmacokinetics of OROS hydromorphone are also minimally affected by alcohol. These unique features of OROS may further limit the generalisability of evidence. Similarly, we are aware of other formulations of hydromorphone (and other opioids) which may have potential benefits for specific groups of people with cancer but we found no evidence for these as part of this review.

Quality of the evidence

The four included studies (n = 604) were of low or unclear risk of bias overall as they adopted appropriate study design, adequate randomisation, and blinded participants and investigators. The two most prominent risks of bias concerned sample size and sponsorship. One of the studies only had 44 participants (Hagen 1997), and three studies were either funded or conducted by industry (Hagen 1997; Hanna 2008; Moriarty 1999). The quality of the

body of evidence was very low, mainly due to risk of bias caused by small sample size and sponsorship with potential conflict of interest, as well as imprecision around effect estimates and publication bias. See Summary of findings for the main comparison; Summary of findings 2 for detailed assessment results of each individual outcome. The current body of evidence identified does not allow a robust conclusion, as the majority of the data for the outcomes were either skewed or had wide CIs around the estimated effect size.

Potential biases in the review process

Although we searched mainstream biomedical databases and clinical trials registries, searches beyond these resources to include other non-English literature may improve the comprehensiveness of the search results. Two review authors independently performed screening and data extraction, but we were unable to extract any data from Moriarty 1999, which may have had some influence on the results.

Agreements and disagreements with other studies or reviews

The current review indicated little difference between hydromorphone and two other opioids, oxycodone and morphine, in terms of analgesic efficacy. This finding is consistent with the 2012 European Association for Palliative Care (EAPC) guidelines (Caraceni 2012), which included a series of systematic reviews reviewing the evidence for opioids in people with moderate to severe cancer pain (Caraceni 2011; King 2011a; King 2011b; Pigni 2011). The reviews concluded that there is a lack of evidence to demonstrate superiority or inferiority of hydromorphone in comparison with other analgesics and EAPC makes a weak recommendation that hydromorphone, morphine or oxycodone could be used as the first choice for step three of the WHO analgesic ladder. The results of this review do not differ from the results of the previous Cochrane Review (Quigley 2003).

AUTHORS' CONCLUSIONS

Implications for practice

For people with cancer pain

Based on data gathered from the four included trials, it appears that hydromorphone has a similar effect on participant-reported pain intensity as oxycodone and morphine for adults with moderate to severe cancer pain. There was no evident comparative difference in analgesic effect between hydromorphone and other opioids investigated in this review and, on average, participants achieved no worse than mild pain on all investigated treatments. There were several adverse events, but generally there was no difference between groups. In summary, the evidence suggests that hydromorphone has a similar therapeutic effect and adverse effects to oxycodone and morphine in adults with moderate to severe chronic cancer pain. However, this finding should be applied with caution for it only included four studies with different designs and limited sample size. There were no data available for children or for some important outcomes such as impact of the treatment on consciousness, appetite and thirst.

For clinicians

Based on four included trials with different designs and limited number of participants, we found a lack of evidence to support a preference for hydromorphone over other opioid analgesics such as morphine and oxycodone. The treatment effect of hydromorphone appeared to be similar to that of the comparator drugs for adults with moderate to severe cancer pain. There were minor adverse events in all treatment groups and generally no significant difference between groups. However, most of the outcome data were based on single randomised controlled trials with small sample size, thus the findings of the current review should be interpreted and applied with caution. We found no data for children. The insufficient evidence requires clinicians to balance potential benefits against potential adverse events on the merit of each individual case when recommending treatment in clinical practice.

For policy makers

This review identified little evidence to support hydromorphone as the first-, second- or third-line treatment for cancer pain. However, evidence collated in the current review suggests hydromorphone has a similar analgesic effect as morphine and oxycodone, it can be considered as an alternative when other opioids result in excessive adverse events such as sedation and respiratory depression, and when people with cancer pain experience renal failure. We found no data for children. Included studies were conducted in high-income countries, which may compromise the external validity of the review as some of the drugs investigated may have limited accessibility in some lower-income countries. Finally, it is worth noting that findings from the current review are mainly based on small trials with different designs and limited sample size and some risk of bias, therefore, should be applied with caution.

Implications for research

This review reveals a general lack of research in this subject area. Future trials with significant numbers of participants (e.g. over 200 per treatment arm) are needed to evaluate the safety and effectiveness of hydromorphone for the management of moderate to severe cancer pain in adults. Future research is encouraged to involve children and young adults to provide direct evidence in this

population. Further adequately powered randomised controlled trials should use standardised tools or scales to measure pain as a primary outcome. More data on other secondary outcomes, as well as the comparative effect of a more comprehensive range of medications, would also be useful to enable the review to draw a more reliable and conclusive effect. Longer-term toxicity data should be collected if possible.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Hagen 1997

Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: pre-cross-over phase: 7 days in each phase. Total study duration 14 days Funding: 'Purdue Frederick', since renamed 'Purdue Pharma' Setting: Canada. Unclear if these were inpatients or community patients Design: cross-over
Participants	Diagnosis: people with chronic cancer pain and stable analgesic requirements n = 44 (31 analysed) Age (mean ± SD): 56 ± 3 years Sex: men 13; women 18 History: of the 31 participants who completed the study, location of primary tumour was breast (7), colorectal (5), lung (1), urological/prostate (5), central nervous system (4), unknown primary site (2) and other (7) Included: people with chronic cancer pain and stable analgesic requirements Exclusion: known hypersensitivity to opioid analgesics; intolerance of oxycodone or hydromorphone; presence of a medical or surgical condition likely to interfere with drug absorption in the gastrointestinal tract; concurrent use of other opioid analgesics during the study period; presence of intractable nausea or vomiting; people who had undergone or were expected to undergo therapeutic procedures likely to influence their pain during study period Consent: "The study protocol and informed consent form received scientific and ethical approval, and patients gave written informed consent before participating in the study" (p. 1429)
Interventions	• Hydromorphone CR, dose unknown (mean (± SD) daily dose reported as 24 ± 4 mg); n = 22 (19 completed study) • Oxycodone CR, dose unknown (mean (± SD) daily dose reported as 120 ± 22 mg); n = 22 (12 completed study) Each intervention was administered every 12 hours for 7 days pre-cross-over. No other opioids permitted. Non-opioid analgesics that had been part of the person's treatment before the study were permitted. Incident and non-incident breakthrough pain was treated with IR oxycodone and hydromorphone matching the active opioid analgesic at a dosage of approximately 10% of the daily scheduled opioid dose
Outcomes	Pain intensity VAS* Pain intensity ordinal* Sedation VAS* Nausea VAS* Dropouts* Unable to use Frequency of rescue analgesic use was not reported as there was no pre-cross-over data
Notes	* Unpublished data obtained from Purdue Pharma

Hagen 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Data only analysed for 31/44 participants. Dropout rate > 10%
Selective reporting (reporting bias)	Low risk	None obvious
Other bias	High risk	Drug company-funded. Sample size small, < 50 people per treatment arm

Hanna 2008

Methods	Allocation: randomised Blindness: double-blind Duration: up to 24 days Funding: Johnson & Johnson (previously ALZA Corporation) Setting: multicentre (37 centres in Belgium, Canada, France, Germany, the Netherlands, Spain, Sweden and the UK); inpatients, outpatients and day patients Design: parallel
Participants	Diagnosis: people with moderate to severe chronic cancer pain requiring 60 mg to 540 mg of oral morphine (or equivalent) every 24 hours n = 200 Age (mean): 59.8 years Sex: 98 men (49%); 102 women (51%) History: cancer type: breast (56), lung (39), genitourinary (30), gastrointestinal (32), oral cavity (6), lymphoma (3), leukaemia (3), bone (2) and other (29) Included: inpatients, outpatients and day patients ≥ 18 years of age; moderate to severe chronic cancer pain; currently receiving strong oral or transdermal opioid analgesics (60 mg to 540 mg of oral morphine or equivalent every 24 hours); appropriate candidate for strong oral or transdermal analgesics (anticipated requirement, 60 mg to 540 mg of oral morphine or equivalent every 24 hours); pain suitable for treatment with a once-daily formulation

	Exclusion: pain not considered potentially responsive to opioids; pain present only upon movement; need for other opioid analgesics (except study medication and breakthrough pain medication) after randomisation; current or recent (within 6 months) history of drug or alcohol abuse (or both); pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions; intolerance of, or hypersensitivity to, hydromorphone or other opioids; presence of gastrointestinal disease of sufficient severity to likely interfere with oral analgesia (e.g. dysphagia, vomiting, no bowel movement or bowel obstruction due to impaction within 5 days of study entry, severe gut narrowing that may affect analgesic absorption or transit); use of monoamine oxidase inhibitors within 2 weeks prior to study entry; investigational drug use within 4 weeks of study entry; presence of conditions for which risks of opioid use outweigh potential benefits (e.g. raised intracranial pressure, hypotension, hypothyroidism, asthma, reduced respiratory reserve, prostatic hypertrophy, hepatic impairment, renal impairment, older and debilitated people, convulsive disorders, Addison's disease) Consent: "All patients who entered the trial were informed of the nature of the study, and provided written informed consent for participation. The study was conducted in accordance with the principles of the Declaration of Helsinki."
Interventions	• Hydromorphone IR 12 mg/day to 108 mg/day; dose titrated to next higher dose level if participant had > 3 breakthrough pain episodes requiring pain medication within the previous 24 hours, maximum once a day, dose titration continued until dose-stable pain* control achieved; n = 99 • Morphine IR 62 mg/day to 540 mg/day, dose titrated to next higher dose level if participant had > 3 breakthrough pain episodes requiring pain medication within the previous 24 hours, maximum once a day, dose titration continued until dose-stable pain* control achieved; n = 101 Initial IR phase and subsequent SR phase • IR phase: formulations of either hydromorphone (Dilaudid, Abbott Laboratories) or morphine (morphine sulphate IR (Sevredol, Napp Laboratories)) every 4 hours (6 times daily) for 2 to 9 days. Individual dose levels based on participant characteristics and selected according to available tablet strength and a working conversion ratio of 1: 5 (1 hydromorphone: 5 morphine equivalence). Concomitant chemotherapy or radiotherapy was permitted. • SR phase: duration 10 to 15 days: same drugs received but in SR formulation (OROS hydromorphone, once daily, or CR morphine (morphine sulphate SR (MST Continus, Napp Laboratories)), twice daily. Same starting dose level as dose-stable pain achieved in IR phase, adjusted as required every 2 days at most. * dose-stable pain control: defined as participants who experience 2 consecutive days with $\leq$ 3 breakthrough pain episodes requiring rescue medication - they could then begin SR phase of the study. Participants not achieving dose-stable pain control by day 9 were withdrawn from the study
Outcomes	Pain ('worst pain in the past 24 hours' item of the BPI) Adverse events
Notes	
Risk of bias	

Hanna 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised 1:1, with a central computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	There was no explicit description on allocation concealment, but we considered concealment is likely to have been used since the randomisation was done via a central list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals from study were addressed Quote: "All efficacy variables were analyzed using the intent-to-treat (ITT) population, which included all patients who took at least one dose of study medication and had at least one assessment from each study phase" The proportion of dropout appeared to be higher in hydromorphone group; however, the reasons for dropout were comparable between groups, thus review authors consider the proportional difference between groups is unlikely to have had an effect on effect estimate. However, because the dropout rate was > 10%, we rated this domain as high risk
Selective reporting (reporting bias)	Low risk	Detailed data of the following 2 scales were not given: Mini-Mental State Examination and Eastern Cooperative Oncology Group performance status was administered, but authors did comment that the assessment scores were similar between groups
Other bias	High risk	Drug company-funded One of writers was employed by Johnson & Johnson (study sponsor) Study size small, < 200 participants per treatment arm

Moriarty 1999

Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: 6 days (with run-in period of 1 to 3 days) Funding: not stated Setting: not stated. Unclear if these were inpatients or community patients Design: cross-over
Participants	Diagnosis: people with cancer pain n = 100 Age: not stated Sex: men 53; women 47 History: most common of primary malignancies presented by participants were lung, breast, gastrointestinal and genitourinary Included: people aged ≥ 18 years, with cancer and achieving pain control with CR morphine sulphate Exclusion: people with significant respiratory depression; severe renal or hepatic impairment; people taking strong opioid analgesics other than 12-hourly morphine sulphate, and people taking monoamine oxidase inhibitors currently or within the previous 2 weeks; pregnant (or not adequately protected from becoming pregnant) or lactating women Consent: no details
Interventions	• Hydromorphone CR 4 mg • Morphine CR 30 mg
Outcomes	Pain VAS Adverse events Treatment preference Use of rescue medication
Notes	No pre-cross-over data available. No contact details available to request necessary information We are also unclear about the intensity of people's cancer pain. This review only intended to include people with moderate to severe cancer pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...according to a randomisation schedule previously prepared by the clinical supplies department at Napp Laboratories Limited..." Comment: third-party randomisation was used and is likely to be low risk of bias
Allocation concealment (selection bias)	Low risk	Third-party randomisation was used, thus we considered allocation concealment is likely to have been done

Moriarty 1999 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Marched placebos were taken throughout to maintain the blinding of the study (double-dummy technique)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 people left the study early and were not included in the final analysis. Although the dropout rate was marginally > 10%, it is unlikely to have had a biased effect on the results, as reasons and proportion for dropout were given and comparable between groups
Selective reporting (reporting bias)	Low risk	None obvious
Other bias	High risk	1 of the study authors is an employee of Napp Laboratories Ltd, a pharmaceutical company that produces analgesics Sample size small, 100 participants in total in the 2 arms

Yu 2014

Methods	Allocation: randomised Blindness: double-blind Duration: 3-phase study: screening period up to 14 days prior to randomisation; dose titration phase up to 8 days, and a 28-day dose maintenance phase Funding: not stated Setting: China. Unclear if these are inpatients or community patients Design: parallel
Participants	Diagnosis: Chinese people with moderate to severe cancer pain n = 260 Age: 18 to 70 years Sex: men and women History: most common of primary malignancies presented by people were lung, breast, gastrointestinal and genitourinary Included: people who required or were expected to require between 40 mg and 184 mg of oral morphine or morphine equivalents every 24 hours for chronic management of cancer pain and people who were reasonably expected to achieve a stable dose of opioid study medication during the study Exclusion: people with pure neuropathic pain or pain of unknown origin (where a mechanism or physical cause could not be identified), only had pain on movement or acute pain, required other opioid analgesics (apart from the morphine hydrochloride, in IR formulation, allowed as rescue medication for break through pain), had any significant central nervous system disorder, risk of treatment with study medication could outweigh

	the potential benefits, women of childbearing potential who were pregnant or lactating Consent: written informed consent was obtained before entering the study
Interventions	• Hydromorphone ER (OROS hydromorphone) 8 mg to 32 mg. n = 130 • Oxycodone CR 10 mg to 40 mg. n = 130 Study completed a dose titration phase (up to 8 days), and a 28-day dose maintenance phase Dose titration phase: randomised participants were converted from their prior opioids to their morphine equivalents and titrated to adequate effect (as determined by the pain assessments and supplementary analgesic requirements), and dosage adjustments were made no more frequently than every 2 days. Upward and downward dose titrations were allowed, but the maximum total daily dose was not to exceed hydromorphone ER 32 mg or oxycodone CR 80 mg Participants had to achieve a stable dose providing pain control at least in the last 2 days of the titration phase (2 to 8 days) to be eligible to enter the maintenance phase Maintenance phase: the titrated dose was continued for 28 consecutive days. Upward and downward dose titrations were not to exceed a total daily dose of hydromorphone ER 32 mg or oxycodone CR 80 mg
Outcomes	BPI pain intensity Participant assessment of pain at its worst in the past 24 hours (assessed with BPI) Pain at its least in the past 24 hours Pain relief in the past 24 hours Adverse events, assessed with treatment-emergent adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation (1:1) by an online dynamic minimization allocation programme as the stratification factors was implemented" Comment: third-party central randomisation was used, thus is likely to be low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "Interactive web based response system designated a unique patient number and treatment code, which dictated the treatment assignment for each patient" Comment: judging from the above description, allocation was concealed by the third party who conducted randomisation

Yu 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Hydromorphone ER, oxycodone CR and placebo were provided in the form of over-encapsulated tablets. Dosing had to start in the morning and the study drug was administrated twice daily, with placebo tablet substitute for 1 dose of hydromorphone ER to maintain blinding. The blinding was broken only if specific emergency treatment dictated knowing the treatment status" Comment: placebo was employed to mask blinding where necessary, thus is likely to be low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	137/260 participants completed the study, loss to follow-up > 10%
Selective reporting (reporting bias)	Low risk	It appears all measured outcomes were reported
Other bias	Unclear risk	50 to 199 participants per treatment arm

BPI: Brief pain inventory; CR: controlled release; ER: extended release; IR: instant release; n: number of participants; OROS: osmotic-controlled release oral delivery system; SD: standard deviation; SR: slow release; VAS: visual analogue scale.

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

Study	Reason for exclusion
Han 2014	Not a randomised controlled study.
Lee 2012	Not a randomised controlled study.
Wirz 2008	Not a randomised controlled study. Participants who were already taking the experimental and control medication were randomly selected to be consented to take part in the study
Wirz 2009	Not a randomised controlled study. Participants who were already taking the experimental and control medication were randomly selected to be consented to take part in the study

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

NCT02084355

Trial name or title	Study Efficacy and Safety of Opioid Rotation Compared with Opioid Dose Escalation in Patients with Moderate to Severe Cancer Pain - Open Label, Randomized, Prospective Study
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: supportive care
Participants	People with cancer pain **Inclusion criteria:** aged > 18 years; being treated with 1 strong opioid including oral oxycodone, oral hydromorphone or fentanyl patch with range from 60 mg to 200 mg of oral morphine equivalent daily dose; moderate to severe cancer pain (numeric rating scale > 3) at screening; uncontrolled adverse effects associated with currently applied opioid **Exclusion criteria:** previous opioid rotation; unable to take oral medication; life expectancy < 1 month; newly started chemotherapy or radiotherapy (or both) within past 2 weeks of screening; serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 2.5 times of upper normal limit; serum total bilirubin or creatinine > 1.5 times of upper normal limit
Interventions	Oral oxycodone Oral hydromorphone Fentanyl patch
Outcomes	Not described in the registration record.
Starting date	April 2014
Contact information	Se-Il Go; Tel: +82 55 750 9454 ext 9454; Email: gose1@hanmail.net
Notes	Estimated completion date: January 2016

DATA AND ANALYSES

Comparison 1. Hydromorphone versus oxycodone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported pain intensity (skewed data)			Other data	No numeric data
1.1 Visual analogue scale (VAS) endpoint pain intensity score (high score = poor outcome)			Other data	No numeric data
1.2 Brief Pain Inventory worst pain in past 24 hours (change score)			Other data	No numeric data
2 Adverse event: measured with VAS (high score = poor outcome, skewed data)			Other data	No numeric data
2.1 Nausea			Other data	No numeric data
2.2 Sedation			Other data	No numeric data
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Constipation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Leaving the study early	2	304	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.20, 1.87]
5 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Hydromorphone versus morphine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant-reported pain intensity: Brief Pain Inventory endpoint (slow-release phase) subscale score (high = more pain; data skewed)			Other data	No numeric data
1.1 Worst pain subscale score			Other data	No numeric data
1.2 Least pain subscale score			Other data	No numeric data
1.3 Mean pain			Other data	No numeric data
2 Adverse events	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Confusion	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Headache	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Insomnia	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Nausea	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Pyrexia	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

3 Leaving the study early	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Overall	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Due to adverse events	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Due to lack of efficacy	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Death	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. Comparison 1: hydromorphone versus oxycodone (adverse events)

Adverse event	Hydromorphone		Morphine	
	No of reports	Total (n)	No of reports	Total (n)
Abdominal discomfort	4	128	7	126
Abdominal distension	7	128	7	126
Anaemia	14	128	14	126
Asthenia	11	128	9	126
Bone marrow failure	9	128	9	126
Chest discomfort	9	128	6	126
Decreased appetite	20	128	21	126
Diarrhoea	12	128	9	126
Dizziness	21	128	22	126
Hyperhidrosis	3	128	8	126
Hypoproteinaemia	9	128	5	126
Neutrophil count decreased	7	128	5	126
Oedema peripheral	11	128	6	126
Platelet count decreased	8	128	7	126
Pyrexia	24	128	27	126
Rash	7	128	4	126
Urinary tract infection	4	128	7	126

Table 1. Comparison 1: hydromorphone versus oxycodone (adverse events) (*Continued*)

White blood cell count decreased	13	128	17	126

n: number of participants

Table 2. Comparison 2: hydromorphone versus morphine (adverse events)

Adverse event	Hydromorphone		Morphine	
	No of reports	Treatment related	No of reports	Treatment related
Abdominal discomfort/ pain	2	1	5	1
Confusion	1	1	1	0
Constipation	1	1	2	1
Dizziness	2	2	2	2
Drowsiness	0	0	2	2
Fatigue	0	0	1	1
Nausea	3	2	2	0
Vomiting	3	1	2	0
Others	22	0	38	0
TOTAL	33	8	55	7

CONTRIBUTIONS OF AUTHORS

Protocol development: all authors contributed equally.

Study screening: YJB, BJH.

Data extraction: YJB, BJH.

Data analysis: WH, XYK, LPY.

Report writing: YJB, BJH, JX, RK.

Future update: all authors in the existing team will be responsible for future updates.

DECLARATIONS OF INTEREST

YJB: none known; YJB is a specialist oncology physician and manages patients with cancer pain.

WH: none known; WH is a specialist oncology physician and manages patients with cancer pain.

XYK: none known; XYK is a pharmacologist.

LPY: none known; LPY is a specialist nephropathy physician and manages patients with nephropathy.

JX: none known; JX is a methodologist and does not have a clinical connection.

BJH: none known; BJH is a specialist oncology physician and manages patients with cancer pain.

RK: none known; RK is a pharmacist and manages patients with pain.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In accordance with the new Cochrane guidelines, we have used GRADE to assess the quality of evidence and added the method for using GRADE to the review. We expanded the 'Description of the intervention' section.

NOTES

This review replaces the original review 'Hydromorphone for acute and chronic pain' as the original author team were unavailable to complete the update (Quigley 2013). The new review focuses on cancer pain only and adheres to current Cochrane standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects; *therapeutic use]; Hydromorphone [adverse effects; *therapeutic use]; Morphine [adverse effects; therapeutic use]; Neoplasms [*complications]; Oxycodone [adverse effects; therapeutic use]; Pain [*drug therapy; etiology]; Pain Measurement; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male