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Original article

Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses

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Abstract

Objective:
For chronic pain treatment many health care authorities consider morphine to be the reference standard for strategic decisions in pain therapy. Although morphine's effectiveness is clear and its cost is low, it's unclear whether morphine should remain the first choice or reference treatment.

Research design and methods:
We performed a systematic review to evaluate the evidence available to support the position of morphine as the reference standard for step III opioids based on efficacy and tolerability outcomes.

Results:
The search yielded 5675 titles and 56 studies were included. Considerable heterogeneity precluded pair-wise meta-analysis on change of pain intensity and no difference between morphine and other opioids were found for tolerability outcomes. The network meta-analysis showed no statistically significant difference in change of pain intensity between morphine and oxycodone, methadone and oxymorphone. Compared to morphine, patients using buprenorphine are more likely to discontinue treatment due to lack of effect (OR 2.32, 95% CI 1.37 to 3.95). Patients using methadone are more likely to discontinue due to adverse events (OR 3.09, 95% CI 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR 0.29, 95% CI 0.17 to 0.50) or buprenorphine (OR 0.30, 95% CI 0.16 to 0.53). The most important limitation of this review is that the included studies are heterogeneous with regard to study population and intervention, which may affect the pooled effect estimates. The main strength is that we only included parallel RCTs, the strongest design for intervention studies.

Conclusions:
The current evidence is moderate, both in respect to the number of directly comparative studies and in the quality of reporting of these studies. No clear superiority in efficacy and tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.

Introduction

Step III (strong) opioids form the backbone of an effective treatment of severe chronic pain in cancer and non-cancer pain patients. According to Patt and Lang[1] the following medicines are considered step III opioids: morphine, diamorphine, oxymorphone, oxycodone, buprenorphine, fentanyl, sufentanil, hydromorphone, methadone, alfentanil, butorphanol, levorphanol, nalbuphine,

pethidine or meperidine, pentazocine. Some of these opioids may be used in combination with other medicines such as aspirin, paracetamol or ibuprofen (NSAIDs).

Morphine, first isolated by the German pharmacist Sertürner in 1806, is an alkaloid derived from the opium poppy, Papaver somniferum. By many it is considered the prototype mu-opioid receptor agonist as it is deemed the oldest and most studied potent opioid analgesic currently available in clinical practice. Morphine is metabolized to glucuronide compounds that can exert antinociceptive and ventilator effects and are renally cleared[2]. Just like most other opioid analgesics morphine's tolerability is determined by its side effect profile, which includes constipation, sedation, dysphoria, nausea and respiratory depression.

For many years morphine has been the strongest instrument for physicians managing severe chronic pain. In several countries this caused health care authorities to consider morphine as the reference or gold standard for strategic decisions in pain therapy (e.g. in guidelines or budgets)[3]. Although already shown to be effective, this position of morphine in the stage III opioid therapy as the first choice for severe or very severe pain became increasingly questioned, mainly because of serious side-effects[4–6]. Therefore the question was raised what evidence is available to support the position of morphine as the gold standard for step III opioids, in comparison to the use of other step III opioids.

No objective criteria have been used to put morphine forward as the reference standard. Possible criteria would be efficacy, tolerability, pharmacokinetics or costs. The most recent Cochrane review on morphine[7] concludes that morphine remains the gold standard for moderate to severe cancer pain. However, this is based on mainly qualitative evidence, showing that morphine is as effective as but not superior to other opioids. As other previous systematic reviews[8–12] also failed to provide clear evidence for an answer to this question we performed a new systematic review.

The main objective of this study was to evaluate efficacy (pain intensity, pain relief, Patient Global Impression of Change (PGIC), quality of sleep, quality of life) and tolerability (treatment discontinuations, serious adverse events) of morphine compared to placebo or other step III opioids in adult patients with chronic cancer or non-cancer pain, using parallel randomized controlled trials (RCTs).

Methods

Data sources and selection

In December 2010, we searched ten electronic databases (MEDLINE 1966 onwards, MEDLINE In-Process Citations 2007 onwards, Embase 1974 onwards, PsycINFO 1966 onwards, Cochrane Central Register of Controlled Trials [CENTRAL] and Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Database of Systematic Reviews [CDSR] in the Cochrane Library [Issue 4 2010], Health Technology Assessment Database [HTA] [2007 onwards], Latin American and Caribbean Health Sciences [LILACS] [2007 onwards], GIN International Guidelines Database [2007 onwards] for RCTs or systematic reviews evaluating the efficacy or safety of step III opioids. In addition, the following trial registers were sought: ClinicalTrials.gov, metaRegister of Controlled Trials and the WHO International Clinical Trials Registry Platform (ICTRP) (2007–2010). Table 1 presents the search strategy for PubMed. Search strategies were developed specifically for each database. References from retrieved articles and systematic reviews were checked and identified references were downloaded to Reference Manager Software for further assessment and handling.

We included randomized controlled trials (RCTs) that evaluated the efficacy or tolerability of step III opioids in patients above the age of 18 and suffering from cancer-related or non-cancer-related chronic pain. Studies had to compare an oral or transdermal step III opioid to placebo or to another step III opioid and report on at least one of our pre-specified outcomes of efficacy (pain intensity, pain relief, PCIG, quality of sleep, quality of life) or tolerability (treatment discontinuations, serious adverse events) after a minimum treatment duration of 24 hours. Crossover studies and *N*-of-1 studies were excluded as these studies are at higher risk of reporting and/or measurement bias, especially those comparing opioids to placebo. An *N*-of-1 study refers to trials that only include one patient. The patient receives the two (or more) treatments that are compared preferably in random order. The main focus of such trials is to determine objectively the optimal therapy for a single individual. Studies on breakthrough pain or acute flare-ups of chronic pain as well as studies examining intravenous opioids were excluded to increase homogeneity between the trials. Tapendatol was not included in the review because this drug is not commonly available. No language restriction was applied.

Two reviewers independently inspected the abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and the inclusion criteria were applied. Any disagreement was resolved through discussion or was checked by a third reviewer. Justifications for excluding studies from the review were documented for all titles found through database searches and reference tracking. Studies fulfilling all inclusion criteria were included in the review.

Table 1. Search strategy for Pubmed searching MEDLINE.

Original search Pubmed (searched December 2008)

1 randomized controlled trial.pt. (164211)
2 controlled clinical trial.pt. (32348)
3 random allocation.sh. (27399)
4 double blind method.sh. (53406)
5 single blind method.sh. (9687)
6 clinical trial.pt. (244882)
7 (clin$ adj25 trial$).ti,ab. (124376)
8 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (58811)
9 placebo$.ti,ab. (74158)
10 random$.ti,ab. (341859)
11 multicenter studies/ (82850)
12 research design.sh. (32322)
13 evaluation studies/ (108622)
14 drug evaluation/ (4240)
15 exp product surveillance, postmarketing/ (5606)
16 crossover.ti,ab. (19940)
17 or/1–16 (791214)
18 exp Analgesics, opioid/ (29095)
19 exp Narcotics/ (25660)
20 alfentanil.mp. (894)
21 buprenorphine.mp. (2053)
22 butorphanol.mp. (534)
23 codeine.mp. (1675)
24 dextromoramide.mp. (24)
25 dezocine.mp. (21)
26 diacetylmorphine.mp. (68)
27 diamorphine.mp. (191)
28 dihydrocodeine.mp. (180)
29 dihydromorphine.mp. (40)
30 diphenoxylate.mp. (48)
31 dipipanone.mp. (2)
32 desomorphine.mp. (0)
33 dextropropoxyphene.mp. (241)
34 fentanyl.mp. (6865)
35 hydrocodone.mp. (305)
36 hydromorphone.mp. (586)
37 hydromorphinol.mp. (0)
38 ketobemidone.mp. (57)
39 levomethorphan.mp. (3)
40 levorphanol.mp. (81)
41 meperidine.mp. (1292)
42 meptazinol.mp. (20)
43 methadone.mp. (4661)
44 morphine.mp.(15961)
45 nalbuphine.mp. (309)
46 oxycodone.mp. (913)
47 oxymorphone.mp. (169)
48 pabaveretum.mp. (0)
49 pentazocine.mp. (499)
50 pethidine.mp. (559)
51 phenazocine.mp. (77)
52 propoxyphene.mp. (172)
53 remifentanil.mp. (1921)
54 sufentanil.mp.(1093)
55 tramadol.mp. (1712)
56 or/18–55 (42641)
57 17 and 56 (11849)
58 exp neoplasms/ (845222)
59 (cancer or neoplasm).mp. [mp = title, original title, abstract, name of substance word, subject heading word] (560832)
60 ((neoplasms or (cancer or neoplasm)) adj3 pain).mp. (3266)
61 pain.mp. or exp Pain/ (229213)
62 chronic disease.mp. or exp Chronic Disease/ (82376)
63 (chronic adj3 pain).mp. (16911)
64 58 or 59 or 60 (974882)
65 61 and 64 (30627)
66 62 or 63 (92394)
67 61 and 66 (23465)
68 65 or 67 (52158)
69 57 and 68 (1159)

Updated Pubmed search (searched December 2010)

1 exp guideline/ (20518)
2 exp consensus development conference/ (7402)
3 exp consensus development conferences as topic/ (1745)
4 (consensus development conference or consensus development conference nih or guideline or practice guideline).pt. (26671)
5 Health Planning Guidelines/ (3436)
6 (clinical protocol$ or consensus$ or position paper$).ti,ab,ot. (78448)
7 (guideline$ or guidance or recommendation$ or clinical standard or clinical standards or clinical pathway$ or clinical path-way$).ti,ab,ot. (253880)
8 clinical trial phase i.pt. (11119)
9 (phase 1 adj4 (trial or trials or study or studies)).ti,ab,ot. (1897)
10 (phase I adj4 (trial or trials or study or studies)).ti,ab,ot. (17067)
11 randomized controlled trial.pt. (307057)
12 controlled clinical trial.pt. (83492)
13 randomized.ab. (211386)
14 placebo.ab. (124882)
15 randomly.ab. (154072)
16 trial.ab. (219385)
17 groups.ab. (1022464)
18 or/1–17 (1797759)
19 Animals/ not (animals/ and humans/) (3521849)
20 18 not 19 (1492739)
21 exp Analgesics, Opioid/ or exp Narcotics/ (88302)
22 (Subutex or Temgesic or Suboxone or Norspan or Butrans or Transtec or Buprenex or Buprex or NanoBUP).ti,ab,ot,hw. (147)
23 (Probuphine or Buprenex or Buprenorfina or Buprenorphinum or Buprenorphine or cl-112–302 or cl-112302 or cl112–302 or cl112302).ti,ab,ot,hw. (3548)
24 (finibron or lepetan or nih-8805 or nih8805 or rx-6029-m or rx-6029 m or rx6029m or um-952 or um952).ti,ab,ot,hw. (1)
25 (52485-79-7 or 53152-21-9).rn. (2935)
26 (Fentanyl or Actiq or Durogesic or Duragesic or Fentora or Onsolis or Instanyl).ti,ab,ot,hw. (15062)
27 (Fentanest or Fentanil or Fentanila or Fentanylum or Phentanyl or Propanamide or Propanamide or Propionanilide or Sentonil or Sublimaze).ti,ab,ot,hw. (414)
28 (r-4263 or r4263).ti,ab,ot,hw. (3)
29 or/21–28 (92598)
30 exp neoplasms/ (2198978)
31 (cancer$ or neoplas$ or malignan$ or tumo?r$).ti,ab. (1623393)
32 chronic disease/ (197423)
33 ((longterm or long term or sustained or long standing or permanent$ or intractable$ or persistent$ or unremitting or unrelenting or continual$ or continuous$ or constant$ or unending or unceasing) adj2 (disorder$ or condition$ or illness$ or illhealth$ or ill health$ or malad$ or sickness or disease$)).mp. (17759)
34 exp osteoarthritis/ or osteoarthrit$.mp. (44065)
35 Diabetic Neuropathies/ (10789)
36 ((diabetic adj2 neuropath$) or DPN).ti,ab. (6615)
37 (chronic$ adj2 (disorder$ or condition$ or illness$ or illhealth$ or ill health$ or malad$ or sickness or disease$)).mp. (285836)
38 or/30–37 (2827263)
39 failed back surgery syndrome/ (34)
40 low$ back pain$.mp. (17166)
41 exp neuralgia/ (10307)
42 pain, intractable/ (5068)
43 pain, referred/ (110)
44 pain/ (101672)
45 (pain or pains).ti,ab. (305971)
46 or/39–43 (31662)
47 or/44–45 (338455)
48 38 and 47 (87977)
49 46 or 48 (112301)
50 20 and 29 and 49 (1845)
51 limit 50 to yr = "2007–Current" (548)

Data extraction

Data extraction forms were piloted independently on a small selection of studies that varied in quality. For each study, data were extracted by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus.

For each included study, the following characteristics were extracted: timeframe and country of study, study design, duration of intervention, number of participants randomized and analysed, age, gender, setting, pain diagnosis, proportion of opioid-naïve patients, inclusion and exclusion criteria, intervention (dose, frequency, etc.), allowance of rescue medication. For continuous outcomes (e.g. pain intensity and pain relief), we extracted number of patients per arm, mean score and SD, SE or CI. For dichotomous outcomes (e.g. serious adverse events) we extracted the number of participants with an event and the total number in a group.

Studies reporting on different time points of measurement were categorized into three groups: from 1 day to 1 week, from 1 week to 1 month, and over 1 month. Outcomes measured within 24 hours were excluded, and within each time point, only the latest outcome was extracted.

Methodological quality

The Cochrane Collaboration quality assessment checklist was used to assess methodological quality[13]. Six domains (random sequence, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting and other potential threats to validity) were judged on study level relating to the risk of bias for that entry: 'yes' indicates low risk of bias, 'no' indicates high risk of bias and 'unclear' indicates unclear or unknown risk of bias. Quality assessment was carried out independently by two reviewers. Any disagreements were resolved by consensus. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design and conduct of future studies.

Data synthesis and analysis

Pair-wise meta-analysis

Pair-wise meta-analyses combine effect estimates of pair-wise comparisons such as opioid versus placebo, or opioid A versus opioid B. In this analysis, morphine was first compared to placebo and subsequently to 'any other step III opioid'. One study compared 30 mg morphine once daily versus 15 mg twice daily versus placebo and the morphine arms were pooled for morphine to be compared to placebo[14]. Another study compared both fentanyl and methadone to morphine[15]. Here, the two treatment arms were pooled and subsequently compared to morphine.

Dichotomous data were analysed by calculating the relative risk for each trial using the random effects model as proposed by DerSimonian and Laird[16] and the corresponding 95% confidence intervals.

Continuous data were analysed by calculating the weighted mean difference (WMD) between groups and the corresponding 95% confidence interval, after standardization of these outcomes to a 100-point scale provided that the scale was validated and measured the pain on a scale ranging from no or low pain to high pain. If the standard deviations were not reported, they were calculated from provided SE or CIs. If these were also not reported, the SD was estimated based on 'typical' values from other studies.

Because of heterogeneity the random-effects model was used for the calculation of overall relative risks or WMD. Heterogeneity was assessed by graphic inspection and by measuring the degree of inconsistency in the studies' results (I^2). We refrained from pooling if $I^2 \geq 76\%$, which corresponds with high heterogeneity[17]. We planned to formally investigate important heterogeneity whenever a particular outcome included more than 10 studies using meta-regression. However, none of the described outcomes with high heterogeneity included more than 10 studies.

Subgroup analyses were performed with respect to treatment duration (1 day to 1 week, 1 week to 1 month, and longer than 1 month) and to pain diagnosis (cancer pain, non-cancer pain), as pre-specified in the protocol.

Network meta-analysis

Network meta-analyses pool effect estimates of different treatments, even when there are no direct comparisons. Such analyses may include studies comparing opioid A versus opioid B, studies comparing opioid A versus placebo and studies comparing opioid C versus placebo to analyse the relative efficacy of opioid A compared to opioid B and to placebo. These analyses were performed on three outcomes: mean change of pain intensity, treatment discontinuation and serious adverse events. For dichotomous data, based on 2×2 tables (or 3×2 tables if there were three arms) from each study, we created as many data entries with respective coding for treatment and outcome (e.g. presence of serious adverse event) as there were patients in the respective cell[18]. We performed a logistic regression arm-level analysis with the dichotomous outcome (e.g. presence of serious adverse event) as dependent and the different treatment options as independent variables. Morphine was identified as the reference group to which the other treatments were compared. To preserve randomization within each trial, we included a dummy variable for each of the studies. This dummy variable also adjusted for differences in risk profiles and study

setup between trials. For the continuous outcome (mean change in pain intensity), all scales were standardized to a 100-p scale as described above. Mean change was calculated if baseline and final pain intensity score was reported. Studies were excluded from the analysis if they did not report a baseline measurement or did not present mean change data[19]. If a standard deviation was not reported or could not be calculated, it was imputed as described below.

For this analysis, we also created as many entries for a study as participants. For each participant we simulated the outcome by sampling from a normal distribution with mean and standard deviation of the concerning study and treatment arm. As the mean and standard deviation of a data set generated by sampling procedure gives slightly deviating values based on chance, these values were corrected. Finally, we performed a multiple regression analysis.

The following assumptions and imputations were made for the network meta-analysis. 1) When standard deviations (SD) were missing, these were imputed using a 'typical' SD for the studies. 2) We flagged studies using a 'reversed' (withdrawal) design. 'Standard' design studies randomized patients to the new medication or the comparison, with or without a preceding period where no pain medication was used. Reversed design studies randomized patients who already used an optimal dose of pain medication. The 'reversed design' studies were excluded for pain intensity but included for adverse events and treatment discontinuation. 3) In case a study compared several arms: an opioid vs an opioid with additional drug (i.e. paracetamol) vs placebo, the arm with the additional drug was omitted. 4) Finally, in case of dose finding studies (several doses of same drug vs placebo), the highest dose was included in the analysis. Sensitivity analyses were performed to assess the effect of our assumptions and imputations on the results. In addition, sensitivity analyses were performed excluding studies examining opioids for neuropathic pain.

We performed subgroup analyses by stratified analysis using treatment duration and pain diagnosis. We planned to formally assess effect modification using medication dose as co-variable, but this was not possible due to poor reporting of the dose. Statistical analyses were performed using the following software: Review Manager[20] and STATA[21]. The format to tabulate characteristics of included studies was derived from Review Manager.

Results

Number of studies found

Fifty-six studies were included in this systematic review[14,15,19,22–74] (Figure 1). Three compared morphine to placebo[14,19,70] and thirteen compared morphine to another opioid: four to transdermal fentanyl[22,50,55,73], three to methadone[24,38,51], four to oxycodone[40,41,45,71], one to hydromorphone[59] and one to transdermal buprenorphine[42]. One compared morphine both to fentanyl and methadone[15]. Four other studies directly compared oxycodone to another step III opioid: one compared it with hydromorphone[29] and three with oxymorphone[37,58,68]. Thirty-four studies compared an opioid to placebo[14,19,23,25,26,28,30–33,35–37,43,44,46–49,52,54,56,57,60–67,70,74,75].

Of all included studies, 16 examined cancer-related chronic pain, 36 examined non-cancer chronic pain and four studies investigated mixed or unclear samples of patients. In five studies, some[22] or all participants[19,28,60,74] had neuropathic pain. At least six studies included some participants with moderate pain[26,36,40,50,56,61]. Eleven studies did not provide data that could be used in the meta-analyses and were only described in the narrative[19,27,34,44,53,60,66,70,72–74]. Doses of opioids varied widely and were poorly reported. The dose of morphine in the included studies ranged from 30 mg/day[14] to 140 mg/day[22] for non-cancer pain and 45 mg/d[24] to 540 mg/d[60] for cancer pain. Table 2 presents the basic study characteristics while details of the study characteristics, including dose of opioids are provided in Supplemental Table 1.

Methodological quality of studies included in meta-analysis

Approximately 47% of the studies reported an adequate sequence generation and an adequate procedure for double blinding, 42% reported adequate allocation concealment, 64% of the studies addressed incomplete outcome adequately and 56% were free of selective reporting. None of the studies were free of other bias, mainly because we judged that studies that were sponsored by the manufacturer of the medicines were at risk of bias. Results of quality assessment for each individual study are presented in Supplemental Table 1.

Effects of morphine compared to other step III opioids: mean change of pain intensity

High heterogeneity ($I^2 = 87\%$) precluded pair-wise pooling of data on mean change of pain intensity. One study favoured other opioids, one favoured morphine and the remaining eight studies did not find any difference between the two medicines. In the subgroup of studies with a duration between 1 week and 1 month, morphine was more effective than other opioids (eight studies, $I^2 = 56\%$; WMD −5.8; 95% CI −9.5 to −2.1).

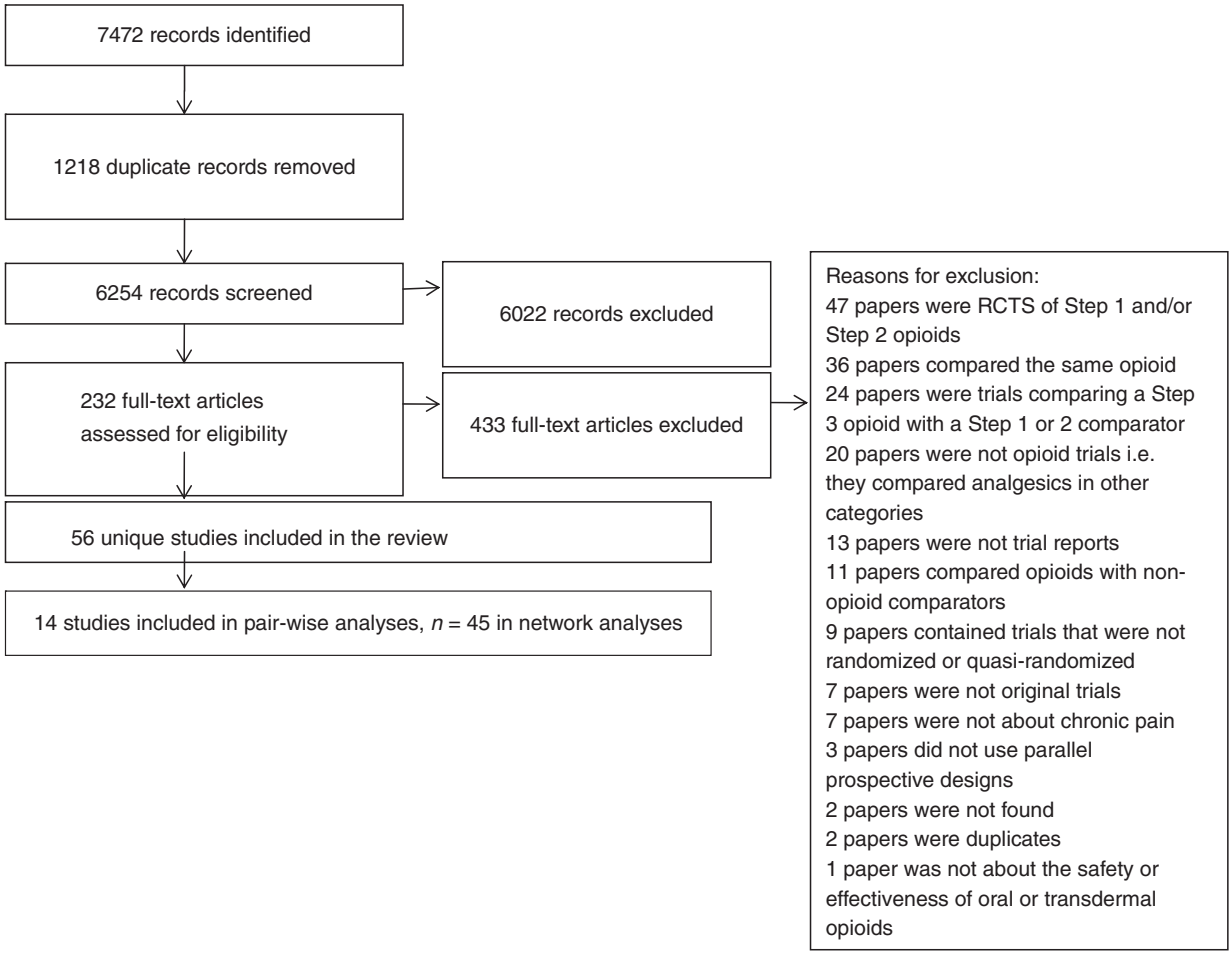

Figure 1. Flowchart of studies included in the systematic review.

Other differences were not significant. Results of subgroup analyses are presented in Table 3.

Network analyses showed that fentanyl (WMD 6.3; 95% CI 1.8 to 10.9) and hydromorphone (WMD 5.1; 95% CI 0.5 to 9.6) were less effective when compared to morphine. Also placebo was less effective (WMD 10.7; 95% CI 7.2 to 14.1). No differences with morphine were found for oxycodone (WMD 2.9; 95% CI −0.4 to 6.2), methadone (WMD 3.3; 95% CI −4.6 to 11.3), oxymorphone (WMD 0.4; −5.5 to 6.3) and buprenorphine (WMD 3.0; 95% CI −3.0 to 9.0). Results of subgroup analyses are presented in Table 4.

In sensitivity analyses where studies with imputed standard deviations were excluded, the differences between morphine and fentanyl and between morphine and hydromorphone were not significant (3.6; 95% CI −2.0 to 9.3 and 4.8; 95% CI −0.1 to 9.8). No differences were found when excluding studies examining opioids in neuropathic pain.

Tolerability of morphine compared to other step III opioids

Treatment discontinuation

No difference between morphine and 'other step III opioids' were found for risk of treatment discontinuation due to any reason (10 studies, $I^2 = 56\%$; RR 1.06; 95% CI 0.88 to 1.29), treatment discontinuation due to lack of efficacy (9 studies, $I^2 = 0\%$; RR 0.83; 95% CI 0.55 to 1.25) or treatment discontinuation due to adverse events (9 studies, $I^2 = 69\%$, RR 1.05; 95% CI 0.67 to 1.65). Results of subgroup analyses are presented in Table 5.

Network analyses showed no differences between morphine and any other step III opioid or placebo in treatment discontinuation when all reasons for discontinuation were pooled. Patients using buprenorphine and those using placebo are more likely to discontinue treatment due to lack of efficacy (OR 2.32, 95% CI 1.37 to 3.95, OR 4.12 95% CI 2.66 to 6.38, respectively) Patients using methadone are

Table 2. Basic characteristics of studies included in the systematic review.

Study	Population	Interventions	Study duration	Outcomes
Afilalo *et al.*, 2010[63,76]	Non-cancer pain Age range 40 to 91 Female 60.4%	Oxycodone CR 40 to 100 mg/day ($n=345$) Placebo ($n=339$)	3 to 5 months	PI, PR, PGIC, QoS, QoL, TD, SAE
Allan *et al.*, 2005[22]	Non-cancer pain Age range 21 to 90 Female 61%	Fentanyl 57 μg/h ($n=338$) Morphine 140 mg/day ($n=342$)	12 to 24 months	PR, QoL, TD, SAE
ALZA, 2006[67]	Non-cancer pain Age 21 yrs and over Female NR	Hydromorphone HCl 8 mg ($n=330$*) Hydromorphone HCl 16 mg ($n=330$*) Placebo ($n=330$*)	3 to 5 months	TD, SAE
Binsfeld *et al.*, 2010[68]	Non-cancer pain Age mean 57.5 Female 58%	Hydromorphone 8–32 mg/day ($n=254$) Oxycodone SR 20–80 mg/day ($n=250$)	6 to 11 months	PI, PR, QoS, QoL, TD, SAE
Bohme and Likar, 2003[23]	Chronic cancer or non-cancer pain Age range 26 to 83 Female 53.6%	Buprenorphine 35 μg/h ($n=35$), 52.5 μg/h ($n=41$) or 70 μg/h ($n=38$) Placebo ($n=37$)	7 days to 1 month	TD
Breivik *et al.*, 2010[65]	Non-cancer pain Age mean 62.9 Female 68%	Buprenorphine 5 μg/h, 10 μg/h, and 20 μg/h ($n=100$) Placebo ($n=99$)	6 to 11 months	PI, PGIC, TD, SAE
Bruera *et al.*, 2004[24]	Cancer pain Age range 26 to 87 Female 64%	Methadone 20 mg/day ($n=49$) Morphine 45 mg/day ($n=54$)	7 days to 1 month	PI, PR, PGIC, TD
Buynak *et al.*, 2010[62,77]	Non-cancer pain Age range 18 to 89 Female 57.9%	Oxycodone CR 40 to 100 mg/day ($n=334$) Placebo ($n=326$)	3 to 5 months	PI, PR, QoS, QoL, TD, SAE
Caldwell *et al.*, 1999[25]	Non-cancer pain Age range 32 to 82 Female 62.3%	Oxycodone 19.95 mg/day ($n=34$) Oxycodone + paracetamol 10.1 mg + 654.5 mg/day ($n=37$) Placebo ($n=36$)	7 days to 1 month	PI, QoS, TD
Caldwell *et al.*, 2002[14]	Non-cancer pain Age range NR Female 62.4%	Morphine 30 mg/day ($n=146$) Morphine 15 mg/twice day ($n=76$) Placebo $n=73$	7 days to 1 month	PI, QoS
Chindalore *et al.*, 2005[26]	Non-cancer pain Age mean 54.3 Female 69.2%	Oxycodone 10–40 mg/day (titrated) ($n=103$) Oxycodone + naltrexone 10–40 mg (titrated) + 0.002 mg/day ($n=103$) Oxycodone + naltrexone 10–40 mg (titrated) + 0.004 mg/day ($n=104$) Placebo ($n=52$)	7 days to 1 month	PI, PR, PGIC, TD
Fancourt *et al.*, 1984[66]	Non-cancer pain Age range 26 to 75 Female 74%	Meptazinol 200 mg orally every 3 to 6 hours as required ($n=30$*) Placebo ($n=30$*)	<7 days	PR
Ferrell *et al.*, 1989[27]	Cancer pain Age range 21 to 87 Female 57%	Short acting analgesics (maintained previous therapy) ($n=41$) Morphine dose NR ($n=22$)	1 to 2 months	PI
Gimbel *et al.*, 2003[28]	Neuropathic pain Age mean 58.9 (sd 11.3) Female 47.8%	Oxycodone 37 mg/day ($n=82$) Placebo ($n=77$)	1 to 2 months	PR, PI, PGIC, QoS, TD, SAE
Gladstein, 2007[57,78]	Non-cancer pain Age range 39 to 87 Female 62%	Oxycodone CR 20–40 mg/day ($n=169$) Placebo ($n=167$)	7 days to 1 month	PI, PGIC, QoS, QoL, TD, SAE
Hale *et al.*, 2005[58]	Non-cancer pain Age mean 46.5 Female 54.9%	Oxymorphone 79.4 mg/day ($n=80$) Oxymorphone 155 mg/day ($n=80$)	7 days to 1 month	TD
Hale *et al.*, 2007a[29]	Non-cancer pain Age range 38 to 91 Female 69.4%	Hydromorphone 15.8 mg/day ($n=71$) Oxycodone 24 mg/day ($n=69$)	1 to 2 months	PR, PI, PGIC, QoS, QoL, TD, SAE
Hale *et al.*, 2007b[30]	Non-cancer pain Age mean 47.1 Female 45.1%	Oxymorphone 43.6 mg ($n=70$) Placebo ($n=73$)	3 to 5 months	PI, PGIC, TD, SAE
Hale *et al.*, 2010[75]	Non-cancer pain Age mean 48.6 Female 50%	OROS Hydromorphone ER >12 mg and <64 mg/d ($n=134$) Placebo ($n=134$)	3 to 5 months	PR, TD, SAE
Hanna and Thipphawong, 2008[59]	Cancer pain Age mean 59.8 Female 51%	Hydromorphone 12–108 mg/day ($n=99$) Morphine sulphate 60–540 mg/day ($n=101$)	3 to 5 months	PI, PR, PGIC, TD, SAE
Hanna *et al.*, 2008[60]	Non-cancer pain Age range 24 to 81 Female 36%	Oxycodone dose NR ($n=169$) Placebo ($n=169$)	3 to 5 months	PI, PGIC, TD, SAE

(*continued*)

Table 2. Continued.

Study	Population	Interventions	Study duration	Outcomes
Harke *et al.*, 2001[19]	Non-cancer pain Age range 24 to 81 Female 51.2%	Morphine 1–1.25 mg/kg/day ($n=21$) Placebo ($n=17$)	7 days to 1 month	PR, PI, TD, SAE
Hartrick *et al.*, 2009[61,79]	Non-cancer pain Age range 20 to 79 Female 49%	Oxycodone IR 33 mg/day ($n=172$) Placebo ($n=172$)	1 to 2 months	PI, PR, PGIC, QoS, TD, SAE
Jamison *et al.*, 1998[72]	Non-cancer pain Age range 30 to 60 Female 57.1%	Oxycodone up to 20 mg/day ($n=13$) Oxycodone + morphine SR (individually titrated) ($n=11$)	12 to 24 months	PI, QoS, QoL
Katz *et al.*, 2007[31]	Non-cancer pain Age mean 49.7 Female 53.1%	Oxymorphone 40.05 mg/day ($n=105$) Placebo ($n=100$)	3 to 5 months	PI, TD, SAE
Katz *et al.*, 2010[70]	Non-cancer pain Age mean 54.5 Female 58%	Morphine + naltrexone hydrochloride (MSsNT) 40–160 mg/day ($n=171$) Placebo ($n=173$)	3 to 5 months	PI, QoS, TD, SAE
Kivitz *et al.*, 2006[32]	Non-cancer pain Age mean 61.8 Female 60.5%	Oxymorphone 10 mg/day ($n=95$) Oxymorphone 20–40 mg/day ($n=93$) Oxymorphone 20–50 mg/day ($n=91$) Placebo ($n=91$)	7 days to 1 month	PI, QoL, QoS, TD, SAE
Kongsgaard and Poulain, 1998[33]	Cancer pain Age range 24 to 83 Female 35.8%	Fentanyl 65 μg/h ($n=47$) Placebo ($n=48$)	7 days to 1 month	PI, TD, SAE
Kress *et al.*, 2008[34]	Cancer pain Age mean 62, sd 11 Female 40%	Fentanyl dose NR ($n=117$) Standard opioids (oral or transdermal) dose NR ($n=103$)	7 days to 1 month	PI, TD, SAE
Langford *et al.*, 2006[36]	Non-cancer pain Age range 40 to 90 Female 67%	Fentanyl 42.5 μg/h ($n=202$) Placebo ($n=197$)	1 to 2 months	PI, QoL, TD, SAE
Landau *et al.*, 2007[35]	Non-cancer pain Age range 23 to 87 Female 62.5%	Buprenorphine 5 to 20 μg/h ($n=129$) Placebo ($n=138$)	7 days to 1 month	PI, TD, SAE
Matsumoto *et al.*, 2005[37]	Non-cancer pain Age mean 62.3 Female 60.7%	Oxymorphone 40 mg/day ($n=121$) Oxymorphone 20 mg/day ($n=121$) Oxycodone 20 mg/day ($n=125$) Placebo ($n=124$)	7 days to 1 month	PI, PGIC, QoS, QoL, TD
Mercadante *et al.*, 1998[38]	Cancer pain Age range 35 to 82 Female 52.5%	Morphine 109.5 mg/day ($n=20$) Methadone 25.2 mg/day ($n=20$)	1 to 2 months	PI
Mercadante *et al.*, 2004[39]	Cancer pain Age range 44 to 73 Female 35.7%	Fentanyl 1.8 mg/day ($n=2$) Methadone 13.3 mg/day ($n=3$)	1 to 2 months	PI, TD
Mercadante *et al.*, 2008[15]	Cancer pain Age range 18 to 78 Female 48.6%	Morphine 82.7 mg/day ($n=36$) Fentanyl 1.18 mg/day ($n=36$) Methadone 17.7 mg/day ($n=36$)	7 days to 1 month	PI, QoL, TD
Mercadante *et al.*, 2010[71]	Cancer pain Age mean 63.2 Female 59%	Oxycodone SR 20 mg/d, increased as needed ($n=30$) Morphine SR 30 mg/d, increased as needed ($n=30$)	1 to 2 months	PI, TD
Mucci-LoRusso *et al.*, 1998[40]	Cancer pain Age range 30 to 83 Female 45%	Oxycodone 101 mg/day ($n=48$) Morphine 140 mg/day ($n=52$)	7 days to 1 month	PI, PGIC, TD
Munera *et al.*, 2010[64]	Non-cancer pain Age range NR Female 67%	Buprenorphine 5–20 μg/h ($n=152$) Placebo ($n=163$)	7 days to 1 month	PI, PR, PGIC, TD, SAE
Nicholson *et al.*, 2006[41]	Non-cancer pain Age range 20 to 83 Female 50.5%	Oxycodone 34 to 84.7 mg/day ($n=54$) Morphine 30 to 78.7 mg/day ($n=43$)	6 to 11 months	PI, PGIC, QoS, QoL, TD, SAE
Öztürk *et al.*, 2008[73]	Cancer pain Age mean 55 yrs Female NR	Fentany 25–100 μg/h ($n=25$) SR Morphine 20, 60, 120, 200 μg/day ($n=25$)	7 days to 1 month	PI
Pace *et al.*, 2007[42]	Cancer pain Age mean 54.5 Female 48.1%	Buprenorphine 35 to 52.5 μg/h ($n=26$) Morphine 60 to 90 mg/day ($n=26$)	1 to 2 months	PI, PGIC, QoL, QoS
Poulain *et al.*, 2008[43]	Cancer pain Age range 33 to 85 Female 41.3%	Buprenorphine dose NR ($n=94$) Placebo ($n=94$)	7 days to 1 month	PI, TD

(*continued*)

Table 2. Continued.

Study	Population	Interventions	Study duration	Outcomes
Price and Latham, 1982[44]	Chronic pain Age range 18 to 65 Female NR	Meptazinol 1200 mg/day ($n=101$) Placebo ($n=86$)	7 days to 1 month	PI
Rauck *et al.*, 2006[45]	Non-cancer pain Age range 28 to 73 Female 61%	Oxycodone 53.3 mg/day ($n=189$) Morphine 63.7 mg/day ($n=203$)	1 to 2 months	PI, PR, QoL, TD, SAE
Richards *et al.*, 2002[46]	Non-cancer pain Age range 19 to 80 Female 55.5%	Oxycodone dose NR ($n=$NR) Placebo ($n=$NR)	3 to 5 months	PI, PR
Roth *et al.*, 2000[47]	Non-cancer pain Age range 32 to 90 Female 73.7%	Oxycodone 20 mg/day ($n=44$) Oxycodone 40 mg/day ($n=44$) Placebo ($n=45$)	7 days to 1 month	PI, TD
Sittl *et al.*, 2003[48]	Cancer and non-cancer pain Age range 28 to 86 Female 54.8%	Buprenorphine 35 μg/h ($n=41$) Buprenorphine 52.5 μg/h ($n=41$) Buprenorphine 70 μg/h ($n=37$) Placebo ($n=38$)	7 days to 1 month	PI, PR, PGIC, QoS, TD
Sorge and Sittl, 2004[49]	Cancer and non-cancer pain Age mean 55.9 Female NR	Buprenorphine 0.8 mg/day ($n=90$) Placebo ($n=47$)	7 days to 1 month	PR, QoS, TD
van Seventer *et al.*, 2003[50]	Cancer pain Age range 26 to 91 Female 35.1%	Morphine 105 mg/day ($n=64$) Fentanyl 67 μg/h ($n=67$)	7 days to 1 month	PI, PR, PGIC, QoS, TD, SAE
Ventafridda *et al.*, 1986[51]	Cancer pain Age mean 55.3 Female 42.6%	Morphine 119.4 mg/day ($n=30$) Methadone 18 mg/day ($n=36$)	7 days to 1 month	PI, TD
Vondrackova *et al.*, 2008[52]	Non-cancer pain Age mean 56.3, sd 10.98 Female 61.6%	Oxycodone + naloxone 10 mg + 10 or 40 mg/day ($n=154$) Oxycodone 20 or 40 mg/day ($n=151$) Placebo ($n=158$)	3 to 5 months	TD, SAE
Ward, 1981[53]	Non-cancer pain Age range 15 to 60 Female 46.6%	Meptazinol 400 mg/day ($n=52$) Pentazocine 100 mg/day ($n=53$)	Less than 7 days	PI, PGIC, TD
Webster *et al.*, 2006[54]	Non-cancer pain Age mean 48 Female 61.5%	Oxycodone 39 mg/day ($n=206$) Oxycodone + naltrexone 35 mg + 4 μg/day ($n=206$) Oxycodone + naltrexone 69 mg + 4 μg/day ($n=206$) Placebo ($n=101$)	3 to 5 months	PI, TD
Wong *et al.*, 1997[55]	Cancer pain Age range 30 to 79 Female 27.5%	Morphine 174 mg/day ($n=20$) Fentanyl 61.3 μg/h ($n=20$)	7 days to 1 month	PI, QoS, QoL
Zautra and Smith, 2005[56,80]	Non-cancer pain Age mean 62 Female 73%	Oxycodone up to 120 mg/day ($n=56$) Placebo ($n=51$)	1 to 2 months	PI, TD, SAE
Zin *et al.*, 2010[74]	Non-cancer pain (neuropathic) Age range 45 to 91 Female 43.5%	Oxycodone + pregabalin (10 mg + 75 to 300 mg bd ($n=29$) Placebo + pregabalin ($n=33$)	1 to 2 months	PI, PR, PGIC, QoS, QoL, TD, SAE

PR: pain relief, PI: pain intensity, SAE: serious adverse events, TD: treatment discontinuations, PGIC: Patient Global Impression of Change, QoL: quality of life, QoS: quality of sleep, sd: standard deviation, h: hour, bd: twice daily.
*Estimated numbers based on overall sample and statement that groups were randomized equally.

more likely to discontinue due to adverse events (OR 3.09, 95% CI 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR 0.29, 95% CI 0.17 to 0.50), buprenorphine (OR 0.30, 95% CI 0.16 to 0.53) and placebo (OR 0.12, 95% CI 0.08 to 0.18). Results of subgroup analyses are presented in Table 6.

The sensitivity analysis showed that the results for treatment discontinuation were robust to the exclusion of studies with a reversed design. One different result emerged: after excluding the reversed design studies, oxymorphone showed increased risk for treatment discontinuation for any reason (OR 2.32, 95% CI 1.49 to 3.63) whereas this was non-significant in the overall analysis (OR 1.00, 95% CI 0.70 to 1.44). No differences were found when excluding studies examining opioids in neuropathic pain.

Serious adverse events

Three studies comparing morphine to another step III opioid reported serious adverse events. No difference in risk was found in the pair-wise meta-analysis ($I^2 = 0\%$, RR 1.15; 95% CI 0.79 to 1.67).

Table 3. Results of pairwise meta-analysis on pain intensity comparing morphine to any other step III opioid.

Subgroup (*n* studies in subgroup)	WMD (95% CI)	I^2
Treatment duration 1 day – 1 week (5 studies, $n = 834$)	−2.3 (−5.2 to 0.6)	0%
Treatment duration 1 week – 1 month (8 studies, $n = 1198$)	−5.8 (−9.5 to −2.1)*	56%
Treatment duration > 1 month (3 studies, $n = 541$)	2.9 (−12.1 to 17.8)	94%
Studies on cancer pain (8 studies, $n = 912$)	−1.7 (−10.3 to 6.9)	89%
Studies on non-cancer pain (2 studies, $n = 489$)	−4.0 (−8.9 to 0.9)	0%

*Statistically significant results.
Presented values are WMD (95% confidence interval); values >0 indicate that morphine is less effective than the comparative opioid.

The network analysis also found no difference in risk of serious adverse events for patients using morphine compared to those using oxycodone, fentanyl, placebo, buprenorphine, oxymorphone and hydromorphone.

Results of other outcomes (pain relief, PGIC, quality of sleep, quality of life) are presented in Supplemental Table 2.

Discussion

This systematic review showed no clear differences in efficacy and tolerability between morphine and other opioids in pair-wise and network meta-analyses. We evaluated these outcomes of step III opioids in the context of using morphine as reference standard in the treatment of severe chronic pain for strategic decisions. One reason for the placement of morphine as the reference standard would be tradition; because morphine has been used for so long, dosing equivalents of all opioids are expressed as morphine equivalents. Although morphine might still be used as a reference drug for dosing, this review found no evidence to support morphine as reference standard on the basis of superiority in efficacy or tolerability. Based on the current evidence, justification for the placement of morphine as 'the' reference standard for the treatment of severe chronic pain would include: 1) wide availability, 2) low cost, 3) equal efficacy to newer drugs. In resource-poor countries, these may be taken as reasons to introduce only morphine to the local essential medicine lists. However, the pharmacokinetics of morphine is less than ideal due to the possibility of the accumulation of active metabolites in patients with reduced renal function[2], and two new opioids may have better tolerability (transdermal fentanyl and buprenorphine). These results indicate that considering effects and tolerability other opioids may have to be considered as relevant for chronic pain treatment as well.

One of the main strengths of this review is that we only included studies using a parallel randomized design. Although many crossover trials have been performed to evaluate opioids, parallel studies are to be preferred when

Table 4. Results of subgroup analyses of the network meta-analysis on pain intensity comparing morphine to other step III opioids and placebo.

Intervention	Treatment duration 1 day – 1 week	Treatment duration 1 week – 1 month	Treatment duration >1 month	Studies on cancer pain (9 studies, $n = 696$)	Studies on non-cancer pain (19 studies, $n = 4963$)
Oxycodone	3.3 (−1.2 to 7.8)	3.4 (−0.4 to 7.2)	3.9 (−1.4 to 9.2)	2.3 (−5.4 to 10.1)	4.6 (0.1 to 9.1)*
Fentanyl	5.8 (−0.7 to 12.4)	8.8 (4.2 to 13.4)*	1.0 (−32.6 to 34.6)	8.7 (2.7 to 14.7)*	6.7 (−0.1 to 13.6)
Methadone	−1.6 (−9.0 to 5.8)	12.2 (−0.04 to 24.5)	–	3.9 (−3.4 to 11.3)	–
Buprenorphine	–	9.6 (3.6 to 15.6)*	−16.4 (−30.3 to −2.5)*	−16.4 (−29.0 to −3.8)*	8.0 (0.6 to 15.4)*
Oxymorphone	–	3.5 (−2.5 to 9.6)	–	–	2.2 (−4.6 to 8.9)
Hydromorphone	–	3.0 (−4.4 to 10.4)	6.7 (−0.1 to 13.5)	3.0 (−4.2 to 10.2)	7.4 (1.1 to 13.6)*
Placebo	9.4 (3.4 to 15.3)*	13.8 (9.8 to 17.8)*	11.1 (5.4 to 16.8)*	–	12.4 (7.8 to 17.1)*

*Statistically significant results.
Presented values are WMD (95%CI); values >0 indicate that morphine is more effective than the comparative opioid.

evaluating subjective outcomes such as pain. This is especially the case when an opioid is compared to placebo, since the difference in efficacy and side effects is so obvious that at least a proportion of participants will be unblinded after the first period, and this is likely to affect the way patients experience and report their pain (reporting and/or measurement bias). Other problems with cross-over studies are the unstable nature of chronic pain and the risk of carry-over effects, even when washout periods are included in the design. Systematic reviews that include both parallel trials and crossover trials evaluating opioids in chronic pain should perform sensitivity analyses to examine the influence of including crossover trials on the overall estimates.

Table 5. Results of pairwise meta-analysis on treatment discontinuation comparing morphine to any other step III opioid.

Subgroup (*n* studies in subgroup)	RR (95% CI)	I^2
Due to any reason		
Studies on cancer pain (7 studies, $n=754$)	1.05 (0.67 to 1.63)	70%
Studies on non-cancer pain (3 studies, $n=1181$)	1.05 (0.94 to 1.18)	0%
Due to lack of efficacy		
Studies on cancer pain (6 studies, $n=708$)	0.71 (0.37 to 1.34)	0%
Studies on non-cancer pain (3 studies, $n=1181$)	0.93 (0.50 to 1.73)	15%
Due to adverse events		
Studies on cancer pain (6 studies, $n=708$)	1.00 (0.34 to 2.89)	77%
Studies on non-cancer pain (3 studies, $n=1181$)	1.04 (0.72 to 1.48)	56%

Table 6. Results of subgroup analyses of the network meta-analysis on treatment discontinuation comparing morphine to other step III opioids and placebo.

Intervention	Studies on cancer pain (10 studies, $n=1047$) OR (95% CI)	Studies on non-cancer pain (27 studies, $n=8177$) OR (95% CI)
Due to any reason		
Oxycodone	0.86 (0.32 to 2.30)	1.11 (0.85 to 1.44)
Fentanyl	0.43 (0.24 to 0.75)*	1.01 (0.83 to 1.23)
Methadone	1.17 (0.69 to 1.98)	–
Buprenorphine	0.11 (0.03 to 0.46)*	1.01 (0.68 to 1.49)
Oxymorphone	–	0.95 (0.65 to 1.40)
Hydromorphone	1.69 (0.94 to 3.07)	0.80 (0.56 to 1.16)
Placebo	0.46 (0.16 to 1.39)	0.87 (0.66 to 1.13)
Due to lack of efficacy		
Oxycodone	1.09 (0.07 to 17.8)	0.71 (0.43 to 1.16)
Fentanyl	1.20 (0.39 to 3.65)	0.82 (0.48 to 1.40)
Methadone	0.89 (0.31 to 2.54)	–
Buprenorphine	0.48 (0.07 to 3.14)	2.37 (1.32 to 4.28)*
Oxymorphone	–	0.73 (0.39 to 1.39)
Hydromorphone	3.03 (0.93 to 9.87)	0.94 (0.51 to 1.74)
Placebo	1.88 (0.43 to 8.20)	3.71 (2.27 to 6.08)*
Due to adverse events		
Oxycodone	0.51 (0.12 to 2.17)	0.92 (0.58 to 1.49)
Fentanyl	0.12 (0.04 to 0.36)*	0.41 (0.19 to 0.87)*
Methadone	3.00 (1.11 to 8.11)*	–
Buprenorphine	–	0.49 (0.24 to 0.99)*
Oxymorphone	–	0.78 (0.40 to 1.51)
Hydromorphone	1.46 (0.64 to 3.36)	0.77 (0.44 to 1.35)
Placebo	6.27 (0.74 to 53.12)	0.13 (0.08 to 0.21)*

*Statistically significant results.

This systematic review is the first to employ both a pair-wise meta-analysis and a network meta-analysis on step III opioids for severe chronic pain. A network analysis allows a comparison between more than two interventions using both direct and indirect comparisons. Such analyses are especially relevant when the multiple interventions are evaluated, such as in this review, as it estimates relative effects of the different medicines. An important assumption for network analysis is that studies should be similar in all ways except the intervention. This assumption may be compromised in this review, as we included both patients with cancer and non-cancer pain, and both oral and transdermal opioids. In addition, some studies included patients with moderate pain, which are not indicated for step III opioids. Including non-similar trials in a network analysis is a potential source of bias. The finding that the results from the two approaches were very similar, showing no clear differences in efficacy between morphine and other step III opioids, concur with the use of network analyses supporting the pair-wise analysis in this review.

Two other limitations related to the topic and design should be discussed. First, only RCTs were included. This design provides best evidence on effectiveness of interventions but is less suitable for evaluating its adverse events. Especially rare, long-term or previously unrecognized adverse events may not be identified[81]. In this review we evaluated treatment discontinuations, which may be less sensitive to the problems stated above but the argument is still valid for the outcome serious adverse events. Second, the majority of included studies were industry funded. Recent studies showed that when two competing drugs in a head-to-head comparison are funded by a sponsor, these are more likely to favour the sponsor's drug[82,83] for example due to using inadequate dosing of the comparator. Although industry funds the majority of RCTs on drugs and thus provides an important source of information, there is a risk of bias. A widespread use of trial registries may improve transparency and increase trust in industry-sponsored RCTs. In this review we were not able to incorporate dose as co-variable in the analyses due to poor reporting but in some results it may be relevant. For example, regarding discontinuations due to adverse events, network analysis showed patients treated with methadone were more likely to discontinue due to adverse events (OR 3.09, 95% CI 1.14 to 8.36) whereas the risk was decreased for patients taking fentanyl (OR 0.29, 95% CI 0.17 to 0.50) and buprenorphine (OR 0.30,

95% CI 0.16 to 0.53). These results might be dose-related as the dose of fentanyl was typically about 1/20 of that of morphine while for methadone the dose was at least twice as high (based on 10 mg morphine = 0.1 mg fentanyl = 1 mg methadone).

The poor reporting of the methodological quality of the included studies hampered our quality assessment. About half of the studies did not report the methods of randomization in sufficient detail to judge the corresponding risk of bias. Whether the trial was adequately blinded was not clear in about 25% of the trials. When discussing methodological quality, it is important to distinguish actual study quality from reported study quality. In a systematic review it is only possible to evaluate reported quality with the assumption that this reflects the actual study quality. A list of important study quality items of randomized studies that should be reported is known as the CONSORT statement[84]. Future studies should comply with that list to enhance quality assessment of such studies in systematic reviews. The number of studies and the methodological quality of studies included in a systematic review bear on the strength of the conclusion as they reflect the confidence in the study results. Although we included 56 studies in this review, the actual numbers of studies that contributed to a certain comparison were sometimes limited. When pooling a limited number of studies in a meta-analysis, this results in decreased precision of the pooled estimate which is illustrated by wide confidence intervals.

As the methodological quality of the studies included in this review was at best moderate, the evidence base for this review should be interpreted with some caution. This concerns both the evidence that morphine is not clearly superior to any other step III opioid and also the evidence that any of the other step III opioids is not clearly superior to morphine. There are no differences in analgesia and only limited differences in adverse events. These results seem to indicate that the effects/side-effects ratio does not differ much across opioids, although based on the network meta-analysis it appeared that two of the newer opioids lead to fewer discontinuations due to adverse effects. This may indicate that there has been progress on tolerability beyond morphine, and morphine may actually be worse than a gold standard.

Important details about the characteristics of the population included in the primary studies or intervention were infrequently reported, such as proportion of opioid-naive participants, use of rescue medication, length of follow-up, details on diagnosis (e.g. patients with neuropathic pain), and release type of medicine. Also dose was poorly reported, which hampered the assessment of whether dose has an impact on study results but also whether studies that compared two different opioids used an equi-analgesic dose. Dose is likely to be an important factor and future studies should report more details of the intervention and population in order to assess influence of dose on results and results of certain subgroups.

The implications of our findings may be different for policy makers and for clinical practice. Fourth hurdle (reimbursement) agencies usually take what is current practice as the reference standard. This review shows no clear differences between any step III opioids and morphine. If any other opioid in current practice is widely used, this would implicate that other opioids should be an acceptable comparator for a new drug. Regarding clinical practice, our conclusion implicates that doctor/patient preferences, anticipated adverse effects, convenience, and other factors such as costs would determine the choice of the drug, because analgesic effects are similar. In either situation, our conclusion suggests that morphine would not be 'the' reference standard, but 'one of several possible' reference drugs.

Conclusion

This is the first review on the efficacy and tolerability of step III opioids that also employed network meta-analysis. The current evidence is moderate, both in respect to the number of direct comparative studies as in the quality of reporting of these studies. No clear superiority in efficacy or tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.

Future studies would benefit by improved reporting of study methods as required by the CONSORT statement. Improved reporting of study population would enhance investigation of potential differences in results between subgroups of patients.

Transparency

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