Systematic Review

Efficacy and Safety of Opioid Analgesics for the Management of Chronic Low Back Pain: An Evidence from Bayesian Network Meta-Analysis

Chandrasekhar Boya, PhD[1], Dipika Bansal, MD[1], Shailaja Kanakagiri, MPharm[1], and Babita Ghai, MD[2]

From: [1]Clinical Research Unit, Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, SAS Nagar, India; [2]Department of Anaesthesia, Post Graduate Institute of Medical Education and Research, Chandigarh- India

Address Correspondence:
Dipika Bansal, MD
Clinical Research Unit,
Department of Pharmacy Practice
National Institute of Pharmaceutical Education and Research
SAS Nagar, Punjab, India-160062
Email: dipikabansal079@gmail.com

Disclaimer: Funding was received from The Indian Council of Medical Research (ICMR), New Delhi, India for the conduction of this network meta-analysis.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-29-2019
Revised manuscript received: 07-15-2020
Accepted for publication: 07-27-2020

Free full manuscript: www.painphysicianjournal.com

Background: Chronic low back pain (CLBP) incurs huge costs owing to increased healthcare expenditure, disability, insurance, and work absenteeism. Opioid analgesics are commonly used for the management of CLBP.

Objective: To compare and rank the opioids used in the management of CLBP, in terms of efficacy and safety.

Study Design: Systematic review and network meta-analyses (NMA).

Method: The search was conducted in Embase, PubMed, Cochrane databases for randomized controlled trials (RCTs) that had evaluated the efficacy and safety of opioids in CLBP. Two authors independently performed data extraction and quality assessment. The proportion of patients reporting either 30% or 50% reduction in pain from baseline to follow-up on the numeric rating scale, was measured as efficacy outcome. Pairwise meta-analyses and Bayesian NMA, within the random-effects model, were used to synthesize data. Effect estimates from Bayesian NMA were presented as odds ratio (OR) with 95% credible intervals (CrI). Heterogeneity and convergence were assessed by using I 2 and deviation information criteria.

Results: Twenty-three RCTs with a total of 8,420 patients, evaluating 13 different opioids were included in this NMA. For 30% pain reduction, oxymorphone (OR: 5.36; 95% CrI: 1.02-30.3), tramadol with acetaminophen (OR: 2.37; 95% CrI: 1.08-5.17), and buprenorphine (OR: 2.29; 95% CrI: 1.05-5.07) shown statistically significant more effective than placebo. For 50% pain reduction, the statistically significant difference is observed with buprenorphine (OR: 2.38 95% CrI: 1.08-5.24), oxymorphone (OR: 5.10; 95% CrI: 1.31-20.41), and tramadol with acetaminophen (OR: 2.11; 95% CrI: 1.07-4.21). Hydrocodone (OR: 0.33; 95% CrI: 0.14-0.77) was found statistically safer compared to the other opioids.

Limitations: Only 5 trials had more than a 12-week study duration. We need clinical trials with longer follow-up as CLBP management requires a longer duration, and long-term prescribing of opioids associated with severe adverse event profile, development of tolerance, and dependence.

Conclusions: Oxymorphone has an advantage over other opioids to reduce pain by 30% and 50% in patients with CLBP.

Key words: Chronic low back pain, opioids, Bayesian analyses, network meta-analyses, systematic review

Pain Physician 2021: 24:73-82

Low back pain (LBP) is a ubiquitous, disabling musculoskeletal disorder confronted frequently in the clinical practice. A global burden of disease study promulgated LBP amongst the top 5 leading causes of years lived with a disability (1). LBP is defined as pain or discomfort in the lumbar region,

below the costal margin and above the gluteal fold, that may or may not radiate to the leg (2). Chronic LBP (CLBP) is characterized as persistence of symptoms for a period greater than 12 weeks (3). From the societal perspective, CLBP incurs huge costs owing to increased healthcare expenditure, disability, insurance, and work absenteeism (4).

The management of CLBP is challenging because of its heterogeneous aetiologies and underlying mechanisms. Patients are managed depending on the type and source of the pain. Many noninvasive treatment options, including pharmacologic (e.g., skeletal muscle relaxants, antidepressants, and opioids) and nonpharmacologic interventions (e.g., yoga, exercise, etc.), are available for the management of CLBP (5). Most of the management guidelines recommend paracetamol or nonsteroidal anti-inflammatory drugs as first line therapy (6). The American College of Physicians recommended tramadol or duloxetine as a second line therapy (5, 6). However, if the pain becomes nonresponsive to the first- or second-line therapy, opioids are recommended. Furthermore, 50 to 60% of global LBP cases are being regularly prescribed opioids, around 20% being long time users (7,8). Meanwhile, there is still a large group of physicians opposing chronic opioid use because of their side effect profile, the risk of abuse, and physical dependence.

In randomized, controlled trials (RCTs), opioids have demonstrated their superior efficacy over placebo (9,10). However, relative efficacy of opioids is unknown due to paucity of trial on head-to-head comparisons between various opioids or their combinations. Therefore, this network meta-analysis (NMA) of RCTs was performed to compare opioids with either another opioid or placebo to provide relative efficacy and ranking of opioids based on their efficacy and safety for the management of CLBP.

Methods

The manuscript adheres to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for NMA (11).

Eligibility Criteria

The RCTs were included in this NMA if they had recruited adult patients of with either CLBP, with or without radiating symptoms in the lower limbs, and evaluated the efficacy and safety of opioids for a period of at least 4 weeks or longer as compared to any other opioid or placebo. We included RCTs with opioids given by oral or transdermal route.

Types of Outcomes

The RCTs must have reported on at least one of the following outcomes: proportion of patients reporting either 30% or 50% pain reduction on the numeric rating scale (NRS-11) or visual analog scale (VAS) from baseline to follow-up (efficacy outcomes), and total withdrawal, due to any reason from the trial (safety outcome).

Exclusion Criteria

Studies were excluded if they had recruited patients with acute LBP, sub-acute LBP, failed back surgery pain, postoperative surgical pain, and osteoarthritis and if the opioids were administered by intravenous route. The RCTs comparing an opioid with another nonpharmacological therapy were excluded. Case series, reviews, observational studies, editorials, and letters to editor are also excluded.

Search Strategy

The search strategy was developed and conducted in PubMed, Cochrane database, clinical trial registries, and EMBASE databases separately, retrieving relevant RCTs using keywords by a skilled medical librarian, with inputs from investigators. The reference section of relevant systematic reviews for the retrieval of additional eligible trials were also examined (Supplemental Tables 1-3).

Selection of Studies

Two authors (BC and KS) independently screened titles and abstracts of the studies retrieved during the initial search for their potential eligibility. The RCTs having divergent opinion were selected according to a consensus reached between the 2 authors. In the absence of a consensus, a third investigator (BG) evaluated the potential eligibility of the study and resolved any disagreements through discussion.

Data Extraction

Two authors (BC and KS) independently extracted the following data from included RCTs using predesigned data collection forms. 1) study details; 2) disease details; 3) intervention details; and 4) outcome details. If patients were randomized to different dosages of the active intervention, then only data for the most effective dosage of the medication was considered.

Risk of Bias

Two authors (BC and KS) independently performed the rating for the risk of bias in the included RCTs using 11-item PEDro scale (12). Each item in the PEDro scale (excluding the item for external validity) was scored as either present (1) or absent (0) to give a total score out of 10. Trials with a score greater than 7 were to be considered at high risk of bias; those scoring less than or equal to 7 were to be considered at low risk of bias.

Statistical Analysis

For binary outcome variables, the outcome measure calculated was the odds ratio (OR) along with the 95% credible interval (CrI). Pairwise meta-analysis (PMA) was performed between 2 similar interventions, which have more than 2 trials by using a random effects model. Network meta-analysis (NMA) is a statistical technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of RCTs. NMA produces estimates of the relative effects between any pair of interventions in the network and yields more precise estimates than a single direct or indirect estimate. It also allows an estimation of the ranking and hierarchy of interventions. For indirect comparisons of opioids, NMA for all treatments to the given outcome was performed within a Bayesian framework using the Winbugs (13).

A random effects model was used to perform NMA of different opioids as significant heterogeneity was expected. Noninformative priors with vague normal (mean 0, variance 0.0001) and uniform (0-2) prior distributions for efficacy and safety outcomes used to estimate the posterior distribution of these outcomes. These posterior distributions are used to make inference about clinical parameters. Posterior distributions of clinical outcome parameters are estimated by using Markov Chain Monte Carlo (MCMC) simulation. MCMC provides algorithms for systematic, random sampling from probability distributions. Three markov chains (MC) with different initial values of efficacy and safety outcomes are used to generate MCMC simulations. A total of 50,000 simulations for each chain were generated and the first 50,000 initial values of clinical outcomes were discarded to avoid potential impact of initial values (called burn in process) on the arbitrary value of outcomes. The inference of final summary statistics are based on simulation of an additional 1,000,000 iterations. The goodness of fit are compared with the posterior mean of the total residual deviance and the deviance information criterion (DIC). Convergence was assessed by inspection of trace plots, quintile plots, and MC error of monitored efficacy and safety parameters.

A network graph was created to show relationships among different interventions compared for specific outcome by using netmeta package in R programming language (14). The relative efficacy and safety of opioids are reported as netleage tables. The ranking of opioids for the efficacy and safety outcomes were also evaluated by using posterior estimates. The opioid with a larger *P*-value was considered as more effective than others. Therefore, *P*-values are used to evaluate the ranking probabilities of each opioid for specific outcome.

Additional Analyses

Heterogeneity Assessment

To test the heterogeneity of each PMA, trial variation (σ) and tau statistic were used. The effective number of parameters (pD) were also used to assess the heterogeneity. Inconsistency was evaluated only when a loop exists in the evidence network.

Scenario Analyses

Reformulated Opana ER (oxymorphone hydrochloride) by Endo Pharmaceuticals received the Food and Drug Administration (FDA) withdrawal in 2017 due to shift in the pattern of Opana ER abuse from the nasal to the injection route after it was reformulated. Hence, we performed separate scenario analyses by removing the Opana ER NMA.

Results

Study Selection

The initial search, from inception to July 14, 2018, retrieved 3,835 reports from different databases. After removing the duplicates, the remaining (n = 2046) were screened by reading the title and abstract for relevant studies. A total of 1,896 articles were further excluded due to various reasons. Full texts were retrieved for the remaining 150 articles and were read thoroughly. After this, 127 articles were excluded. Finally, 23 eligible studies were included in the present NMA (Fig. 1).

Study Characteristics

Twenty-three RCTs with a total of 8,420 patients,

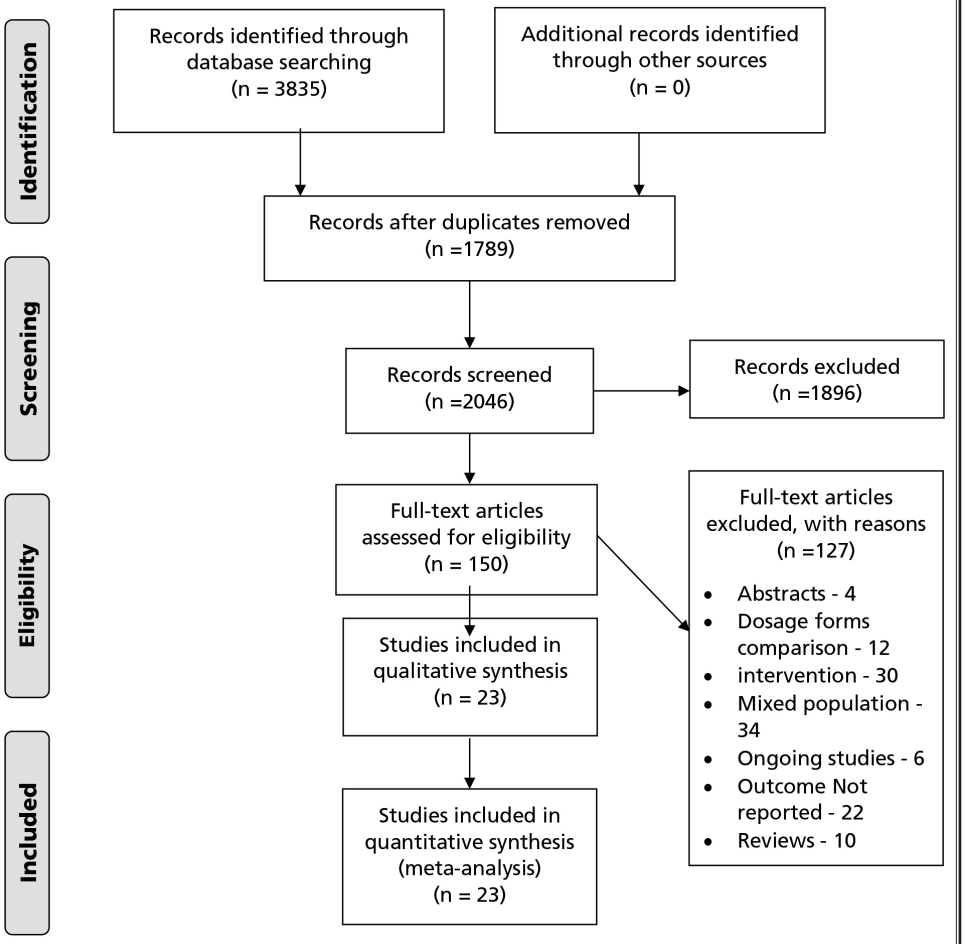

Fig. 1. *PRISMA flow chart.*

evaluating 13 different opioids, were included in this NMA (9,10,15-34). These studies were published from 2003 to 2017. A majority of the patients were female (57%; n = 4827) and mean (SD) age of patients was 52.30 (5.4) years. Two-thirds of the trials (n = 18) were conducted in the United States, 2 in Germany (15,25), and one each in Seoul (20) and Canada (16), and the United States (10). The NRS-11 (n = 13) and VAS (n = 10) were used to assess the pain intensity. The median (IQR) number of patients in the included studies were 370 (52-981) (Supplemental Tables 4 and 5).

Forty percent (n = 8) of the studies had evaluated tramadol with placebo or active comparator, of which 5 had compared tramadol alone (21,25,26,30). While 3 studies had compared its combination with acetaminophen (AP) (10,20,22). The remaining 60% (n = 12) of studies had evaluated hydrocodone (n = 3), morphine (n = 2), oxymorphone (n = 2), buprenorphine (n = 3), oxycodone (n = 3), hydromorphone (n = 1) (9), and tapendatol (n = 1) (15).

Sixty-five percent (n = 15) of the RCTs were parallel group, 26% (n = 6) were enriched design (23,24,26,31-33), and 9% (n = 2) were crossover studies (16,19). The median (IQR) trial duration was 12 (8-16) weeks. All the RCTs were conducted in a double-blind (DB) manner and the median (IQR) length of DB phase was 11 (2-13) weeks.

Rescue medications like AP, oxymorphone, oxycodone, hydrocodone/AP, and diclofenac were permitted to use in 80% (n = 16) of the RCTs to manage severe pain. The mean dropout rates were found similar in the intervention (34.5%) and control (37.9%) groups, respectively. Mean (SD) PEDro score of the included studies was 8.6 (1.5), which indicates that most of the included studies associated with high quality and low risk of bias (Supplemental Table 6).

Network Meta-Analysis

Model Fit

The random effect model for 30% pain reduction, 50% pain reduction and withdrawal outcomes, were used as this model contains lower DIC and total residual deviance values compared to the fixed effect model (Supplemental Table 7).

30% Pain Reduction

The thirty percent pain reduction network consisted of 6,099 subjects from 16 studies with 11 interventions (Fig. 2). Each lined joining 2 treatments, in Fig. 2, represents direct head-to-head comparison. The pair of interventions without direct connection were compared indirectly through a NMA approach. Two loops were formed between oxycodone-placebo-tapendatol and morphine-placebo-morphine with nortriptyline (NT) in this network.

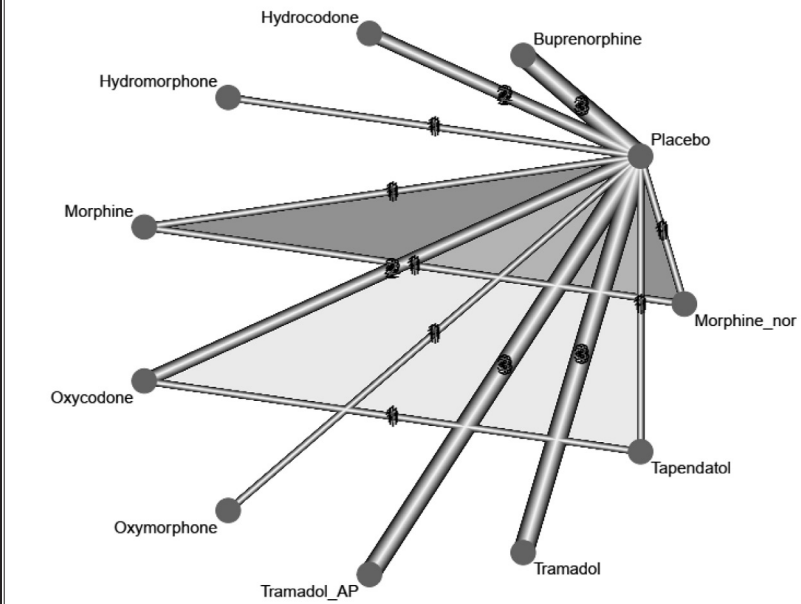

Fig. 2. *Network of opioids with 30% pain reduction.*

All interventions show numerical superiority in terms of relative efficacy over the placebo, except tramadol. However, a statistically significant difference was observed with oxymorphone (OR: 5.36; 95% CrI: 1.02 - 30.3), and tramadol + AP (OR: 2.37; 95% CrI: 1.08-5.17), buprenorphine (OR: 2.29; 95% CrI:1.05-5.07) (Table 1). This shows that oxymorphone, tramadol + AP, and buprenorphine showed a higher efficacy in pain reduction than other opioids when compared to placebo.

Figure 3 shows the ranking probability of opioids for 30% pain reduction. Oxymorphone (48.3%) has the highest probability, followed by morphine + NT (27.2%), to be the best treatment. Hydrocodone and the placebo were < 1% probability to be the best treatment (Supplemental Table 8).

50% Pain Reduction

The fifty percent pain reduction network consisted of 4,380 patients from 12 studies with 9 interventions. In this network, one loop is formed between oxycodone-placebo-tapendatol (Supplemental Fig. 1). Relative efficacy of all interventions shows numerical superiority over the placebo. However, a statistically significant difference is observed with oxymorphone (OR: 5.10; 95% CrI: 1.31-20.41), buprenorphine (OR: 2.38; 95% CrI: 1.08-5.24), and tramadol + AP (OR: 2.11; 95% CrI: 1.07-4.21) (Supplemental Table 9). This shows that oxymorphone, tramadol + AP, and buprenorphine shown a higher efficacy in pain reduction than other opioids when compared to placebo.

For a 50% pain reduction outcome, oxymorphone has the highest probability (64.42%) to be the best treatment (Supplemental Table 10 and Supplemental Fig. 2).

Total Withdrawal from Clinical Trial

The safety network consisted of 7,886 patients from 22 studies with 13 interventions. In this network, 3 loops were formed: 1) oxycodone-placebo-oxytrex; 2) tapendatol-placebo-oxycodone and other between morphine–placebo–morphine + NT (Supplemental Fig. 3).

The relative safety of opioids is shown in the Supplemental Table 11. Among these, opioids like buprenorphine (OR: 0.73; 95% CrI: 0.31-1.71), hydromorphone (OR: 0.50; 95% CrI: 0.11-2.09), tapendatol (OR: 0.67; 95% CrI: 0.18-2.40), tapendatol + pregabalin (OR: 0.76; 95% CrI: 0.10-5.34), oxycodone (OR: 0.82; 95% CrI: 0.34-1.95), and tramadol + AP (OR: 0.90; 95% CrI: 0.39-2.08) showed more safety than the placebo. However, a statistically significant difference was observed with hydrocodone (OR: 0.33; 95% CrI: 0.14-0.77).

For the safety outcome, hydrocodone (43.8% probability) was found to be a safer opioid, followed by hydromorphone (22.3 % probability) (Supplemental Table 12 and Supplemental Fig. 4 in).

Heterogeneity and Inconsistency

A moderate heterogeneity, between studies regarding treatment effects, was observed for 30% pain reduction (SD: 0.62; 95% CrI: 0.38-0.79), 50% pain reduction (SD:0.39; 95% CrI: 0.09-0.72), and withdrawal (SD: 0.69; 95% CrI: 0.53-0.75) outcomes.

Table 1. *League tables showing relative efficacy opioids based on the number of patients who achieved thirty percent pain reduction from baseline to follow up*

	Placebo	Buprenorphine	Hydrocodone	Hydromorphone	Morphine	Oxycodone	Oxymorphone	Tramadol_AP	Tramadol	Tapendatol
Placebo										
Buprenorphine	**2.29 (1.05-5.07)**									
Hydrocodone	1.60 (0.63-4.11)	0.69 (0.20-2.36)								
Hydromorphone	2.27 (0.58-8.98)	0.98 (0.20-4.77)	1.41 (0.26-7.38)							
Morphine	1.37 (0.27-6.97)	0.6 (0.09-3.62)	0.85 (0.13-5.54)	0.60 (0.07-5.05)						
Oxycodone	1.88 (0.69-5.41)	0.81 (0.22-3.07)	1.17 (0.29-4.79)	0.82 (0.15-4.72)	1.36 (0.20-9.46)					
Oxymorphone	**5.36 (1.02-30.35)**	2.33 (0.37-15.46)	3.34 (0.49-23.59)	2.37 (0.27-21.32)	3.90 (0.38-41.35)	2.85 (0.39-20.89)				
Tramadol_AP	**2.37 (1.08-5.17)**	1.03 (0.33-3.11)	1.481 (0.43-4.89)	1.043 (0.21-5.02)	1.72 (0.28-10.27)	1.26 (0.33-4.47)	0.44 (0.06-2.76)			
Tramadol	0.71 (0.33-1.53)	**0.31 (0.10-0.92)**	0.44 (0.13-1.47)	0.31 (0.06-1.50)	0.51 (0.08-3.09)	0.38 (0.10-1.33)	**0.13 (0.02-0.82)**	**0.30 (0.10-0.89)**		
Tapendatol	2.24 (0.66-7.87)	0.97 (0.23-4.23)	1.39 (0.30-6.62)	0.98 (0.15-6.29)	1.63 (0.21-12.56)	1.19 (0.34-4.03)	0.41 (0.05-3.35)	0.94 (0.22-4.13)	3.12 (0.74-13.54)	
Morphine_nor	3.76 (0.73-19.94)	1.63 (0.26-10.27)	2.34 (0.35-15.67)	1.65 (0.19-14.23)	2.72 (0.53-14.22)	1.99 (0.28-13.83)	0.70 (0.06-7.27)	1.58 (0.25-9.99)	5.25 (0.86-32.76)	1.67 (0.21-13.13)

A high degree of convergence was observed in trace plots and history plots. The MC error of odds ratios of opioids, compared to each other and placebo, were < 5% of the posterior SD, which indicates good convergence.

Pairwise Meta-Analyses

The PMA showed tramadol + AP was better than placebo regarding a 30% and 50% pain reduction from baseline to follow-up. Whereas for safety outcome, there was no statistically significant difference regarding withdrawal from RCTs, compared to placebo. There was no data available to compare between opioids. A moderate heterogeneity was observed in PMA. The results from PMA were consistent with the NMAs for both efficacy and safety outcomes (Table 2).

Scenario Analyses

Two RCTs assessed the Opana ER in CLBP patients. The scenario analysis results of NMA, after excluding Opana ER, RCTs from efficacy and safety networks, showed that relative efficacy estimates did not change from the main analyses. However, the probability of morphine + NT to become more effective was increased from 27.2% to 44.25% for a 30% pain reduction outcome.

Discussion

Although, RCTs provide the best evidence for the treatment effect of drugs, but they do not include all available comparative interventions for making a clinical decision. To the best of our knowledge, this is the first attempt to perform Bayesian NMA to obtain the relative efficacy and safety of opioids in patients with CLBP, which enabled an indirect com-

parison of multiple treatments from studies that either lacked or contained insufficient direct head-to-head comparisons.

Regarding efficacy, this NMA suggested that oxymorphone showed the highest probability to become first for both a 30% and 50% pain reduction among all opioids compared for CLBP patients, with no significant differences in efficacies among opioids. Oxymorphone is a semi-synthetic, highly specific mu-opioid receptor agonist. It is about 3 times as potent as morphine. It also showed effective in treating various chronic pain condition like osteoarthritis and cancer (35). Even though oxymorphone showed the highest probability to become more efficacy as intended by physician, recently it got FDA withdrawal from the United States market due to its misuse. The injection abuse of reformulated Opana ER has been associated with a serious outbreak of human immunodeficiency virus (HIV) and hepatitis C, as well as cases of a serious blood disorder (thrombotic microangiopathy), that is why prescribing this medication needs careful attention (36).

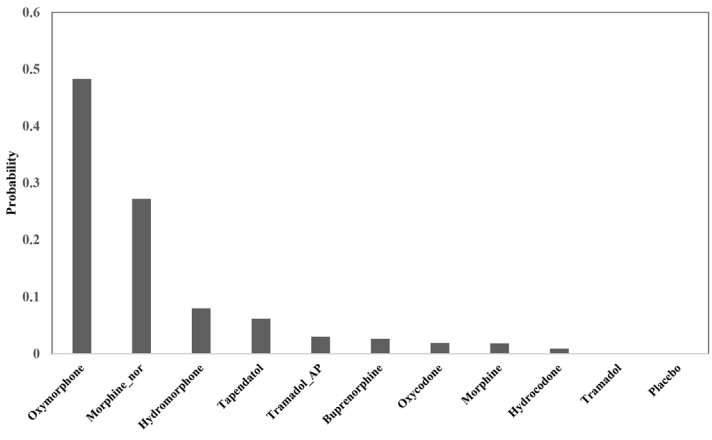

Fig. 3. *Ranking probabilities*

Table 2. *Pairwise meta-analysis of opioids compared to control.*

Opioid	NOS	OR	LCI	UCI	Q	tau2	I2	Total in CG	Total in IG
30% Pain Reduction									
Buprenorphine	3	**2.267**	**1.1615**	**4.4255**	11.54	0.2758	82.70%	587	558
Hydrocodone	2	1.655	0.2261	12.1190	46.03	2.0187	97.80%	447	443
Oxycodone	2	1.990	0.5643	7.0225	4.42	0.6645	77.40%	343	352
Tramadol_AP	3	**2.367**	**1.5262**	**3.6735**	4.54	0.0841	56.00%	416	413
Tramadol	3	**0.680**	**0.5141**	**0.9009**	3.95	0.0299	49.40%	908	892
50% Pain Reduction									
Buprenorphine	2	2.387	0.8355	6.8217	17.22	0.5406	94.20%	540	511
Hydrocodone	2	2.035	0.9862	4.2016	5.99	0.2287	83.30%	443	447
Oxycodone	2	1.703	0.7654	3.7899	2.04	0.2009	50.90%	343	352
Tramadol_AP	3	**2.097**	**1.4151**	**3.1098**	3.16	0.0446	36.60%	416	413
Withdrawal from Clinical Trial									
Buprenorphine	3	0.748	0.2747	2.0409	26.17	0.7072	92.40%	613	588
Hydrocodone	3	0.332	0.1085	1.0216	26.15	0.8959	92.40%	505	514
Morphine	2	1.231	0.6640	2.2844	0.29	0	0.00%	102	101
Oxycodone	3	0.885	0.5013	1.5653	6.57	0.1625	69.50%	453	566
Oxymorphone	2	1.941	0.0963	39.179	39.94	4.5823	97.50%	173	175
Tramadol	4	1.548	0.7845	3.0559	26.7	0.4167	88.80%	1037	1023
Tramadol_AP	3	0.896	0.4086	1.9667	14.65	0.4125	86.30%	446	453

Abbreviations: NOS: number of studies; OR: odds ratio; LCI: lower confidence interval; UCI: upper confidence interval; CG: control group; IG: intervention group Bold numbers present the comparison is statistically significant compared with control.

The evidence shows that tramadol alone is less effective compared to placebo in both PMA (OR: 0.68; 95% CI: 0.51-0.90) and NMA (OR: 0.71; 95% CrI: 0.33-1.54). In contrast to this, a combination of tramadol + AP showed to be more effective in both PMA (OR: 2.36; 95% CI: 1.52-3.67) and NMA (OR: 2.37; 95% CrI: 1.09-5.18) for a 30% pain reduction. A similar pattern was observed with a combination of tramadol + AP for a 50% pain reduction (PMA; OR: 2.09; 95% CI 1.41-3.10) (NMA; OR: 2.11; 95% CrI: 1.15 - 3.88). The results from the NMAs and PMA were consistent. The evidence shows that by combining medications that have multiple mechanisms of action within the central nervous system produces synergistic analgesic action, which reduces more pain. Tramadol acts by mu-opioid receptor agonism and norepinephrine/serotonin reuptake inhibition, whereas AP potential have centrally mediated mechanisms of action, including inhibition of N-methyl-D-aspartate or substance-P mediated nitric oxide synthesis and inhibition of prostaglandin-E2 release in the spinal cord (37).

In terms of safety based on total number of patients' withdrawal from clinical trial, no significant difference was observed in the withdrawal rate among the opioids compared to placebo, suggesting comparable safety among the opioids and placebo. Within the opioids, oxymorphone (OR: 5.51; 95% CrI: 1.28-23.6) and tramadol (OR: 4.71; 95% CrI: 1.37-16.0) have a higher withdrawal compared to hydrocodone. Our NMA suggests hydrocodone to be the safest among all opioids included in this study.

A systematic review by Chung et al (38) reported that oxycodone, oxymorphone, and buprenorphine showed a statistically significant effective pain relief compared to placebo in pain relief . The Cochrane systematic review reported that strong opioids (OR: 1.91; 95% CI: 1.41- 2.58) and buprenorphine (OR: 1.49; 95% CI; 1.08-2.06) were found to be better than placebo for a 30% pain reduction. Whereas tramadol (OR: 0.82: 95% CI: 0.76 - 0.90) was less effective than placebo (39). An indirect comparison of duloxetine with scheduled and nonscheduled opioids showed that scheduled opioids were found to be more effective than duloxetine (40). The results from our NMA are comparable to these existing studies.

The results generated from this NMA study is useful to clinicians for effective decision making for the management of patients with CLBP by providing the most effective intervention for a specific outcome. Inputs from the present study is also useful to perform a cost-effective analysis of opioids. The present NMA provides up-to-date evidence regarding opioid efficacy and safety in CLBP. This evidence is useful for the development of clinical guidelines in CLBP.

Limitations

Only 5 RCTs had more than a 12 week study duration. It indicates that trials included in this NMA assessed the 'short-term' efficacy and safety, and no trial assessed the long-term period. We need additional RCTs with a longer duration of follow-up, as CLBP management requires longer duration. Careful prescribing of opioids is required for long-term management of CLBP, as long term prescribing of opioids is associated with severe adverse event profile, development of tolerance, and dependence. We recommend that future studies should compare opioids to other analgesics, with the goal of obtaining long-term data on relative effectiveness and safety.

Even though the included studies reported baseline demographic data, many RCTs did not report the duration of CLBP, previous use of opioid analgesics, or response to previous interventions used for management of CLBP, which may affect treatment outcomes.

When multi-arm trials are included in the network, identification of inconsistency becomes more complex as multi-arm trials provide evidence on all edges of loop, which cannot be inconsistent with itself. In the present study, loops are formed by 3 arm trials, hence no inconsistency was observed. The use of an enrichment strategy in RCTs, can lead to biased results by including only those patients who responded to the treatment. In this NMA, 6 studies with enrichment strategy are included, thus, patients who are poor responders to opioids are generally discontinued from the studies, which may have compromised the blinding to treatment condition.

Given the complex nature of the CLBP and narrowly defined inclusion criteria in the included clinical trials, limits the generalization of these results to other CLBP conditions like pain outside this area, such as CLBP occurring due to failed back surgery syndrome and postoperative surgical pain.

Conclusions

Oxymorphone has an advantage over other opioids to reduce pain by 30% and 50% from baseline to follow-up in CLBP. Whereas hydrocodone has the highest safety profile among all opioids. This study

also recommends the clinical trials with long-term follow-up to assess the long-term efficacy and safety of opioids.

Funding status: Funding was received from The Indian Council of Medical Research (ICMR), New Delhi, India for the conduction of this network meta-analysis.

Supplemental material available at www.painphysicianjournal.com

References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390:1211-1259.
2. Chou R. Low back pain (chronic). *BMJ Clin Evid* 2010; 2010:1116.
3. Dionne CE, Dunn KM, Croft PR, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine* 2008; 33:95-103.
4. Hoy D, March L, Brooks P, et al. The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73:968-974.
5. Varrassi G, Muller-Schwefe G, Pergolizzi J, et al. Pharmacological treatment of chronic pain - the need for CHANGE. *Curr Med Res Opin* 2010; 26:1231-1245.
6. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2017; 166:514-530.
7. Deyo RA, Smith DH, Johnson ES, et al. Opioids for back pain patients: Primary care prescribing patterns and use of services. *J Am Board Fam Med* 2011; 24:717-727.
8. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: A systematic review and meta-analysis. *JAMA Intern Med* 2016; 176:958-968.
9. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin* 2010; 26:1505-1518.
10. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: A multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 2003; 25:1123-1141.
11. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015; 162:777-784.
12. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Aust J Physiother* 2009; 55:129-133.
13. Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. *Stat Med* 2009; 28:3049-3067.
14. Rucker G, Krahn U, Konig J, Efthimiou O, Schwarzer G. Network meta-analysis using frequentist methods. CRAN 2019. https://cran.r-project.org/web/packages/netmeta/netmeta.pdf. Asessed on 15-07-2019. Accessed 07/15/2019.
15. Baron R, Martin-Mola E, Muller M, Dubois C, Falke D, Steigerwald I. Effectiveness and safety of tapentadol prolonged release (PR) versus a combination of tapentadol pr and pregabalin for the management of severe, chronic low back pain with a neuropathic component: A randomized, double-blind, phase 3b study. *Pain Pract* 2015; 15:455-470.
16. Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: A randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther* 2010; 32:844-860.
17. Hale ME, Ahdieh H, Ma T, Rauck R, Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *J Pain* 2007; 8:175-184.
18. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin* 2007; 23:117-128.
19. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 2007; 130:66-75.
20. Lee JH, Lee CS, Ultracet ER Study Group. A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. *Clin Ther* 2013; 35:1830-1840.
21. O'Donnell JB, Ekman EF, Spalding WM, Bhadra P, McCabe D, Berger MF. The effectiveness of a weak opioid medication versus a cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug in treating flare-up of chronic low-back pain: Results from two randomized, double-blind, 6-week studies. *J Intern Med Res* 2009; 37:1789-1802.
22. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N, Protocol TRP-CAN-1 Study Group. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in

treatment of chronic low back pain: A multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol* 2004; 31:2454-2463.

23. Rauck RL, Nalamachu S, Wild JE, et al. Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: A randomized double-blind, placebo-controlled study. *Pain Med* 2014; 15:975-985.
24. Steiner DJ, Sitar S, Wen W, et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: An enriched, randomized, double-blind, placebo-controlled study. *J Pain Symptom Manage* 2011; 42:903-917.
25. Uberall MA, Mueller-Schwefe GH, Terhaag B. Efficacy and safety of flupirtine modified release for the management of moderate to severe chronic low back pain: Results of SUPREME, a prospective randomized, double-blind, placebo- and active-controlled parallel-group phase IV study. *Curr Med Res Opin* 2012; 28:1617-1634.
26. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *J Opioid Manag* 2008; 4:87-97.
27. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain* 2006; 7:937-946.
28. Wen W, Sitar S, Lynch SY, He E, Ripa SR. A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of single-entity, once-daily hydrocodone tablets in patients with uncontrolled moderate to severe chronic low back pain. *Expert Opin Pharmacother* 2015; 16:1593-1606.
29. Chu LF, D'Arcy N, Brady C, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: A double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain* 2012; 153:1583-1592.
30. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol* 2000; 27:772-778.
31. Gimbel J, Spierings EL, Katz N, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: Results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016; 157:2517-2526.
32. Kopecky EA, Vaughn B, Lagasse S, O'Connor M. Tolerability, safety, and effectiveness of oxycodone DETERx in elderly patients >/=65 years of age with chronic low back pain: A randomized controlled trial. *Drugs Aging* 2017; 34:603-613.
33. Bartoli A, Michna E, He E, Wen W. Efficacy and safety of once-daily, extended-release hydrocodone in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain. *Postgrad Med* 2015; 127:5-12.
34. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: Results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother* 2010; 11:1787-1804.
35. McIlwain H, Ahdieh H. Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain: A one-year study. *Am J Ther* 2005; 12:106-112.

Food and drug administration. FDA requests removal of Opana ER for risks related to abuse. 2017. Available from: www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/oxymorphone-marketed-opana-er-information. Accessed 07/15/2019.

36. Bjorkman R, Hallman KM, Hedner J, Hedner T, Henning M. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance *P. Pain* 1994; 57:259-264.
37. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: Systematic review and meta-analysis. *Pain Physician* 2013; 16:E685-E704.
38. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: An update of the Cochrane Review. *Spine* 2014; 39:556-563.
39. Cawston H, Davie A, Paget MA, Skljarevski V, Happich M. Efficacy of duloxetine versus alternative oral therapies: An indirect comparison of randomised clinical trials in chronic low back pain. *Eur Spine J* 2013; 22:1996-2009.

Supplemental Table 1. *Search strategy in PubMed.*

S.no	Search Strategy	Number of hits
1	(("Back Pain"[Mesh] OR "Sciatic Neuropathy"[Mesh] OR "Spondylosis"[Mesh] OR dorsalgia[tiab] OR back pain*[tiab] OR backache*[tiab] OR back ache*[tiab] OR lumbar pain[tiab] OR coccyx[tiab] OR coccydynia[tiab] OR sciatic*[tiab] OR Vertebrogenic pain*[tiab] OR spondylosis[tiab] OR lumbago[tiab] OR "disc degeneration"[tiab] OR "disc prolapse"[tiab] OR "disc herniation"[tiab] OR "failed back"[tiab])) OR (((chronic low back pain) OR "Low Back Pain"[Mesh]) OR CLBP)	98484
2	"Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Research Design"[Mesh] OR "Comparative Study" [Publication Type] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Drug Therapy"[Mesh] OR "drug therapy"[Subheading] OR "Follow-Up Studies"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Clinical Study" [Publication Type] OR "Controlled Before-After Studies"[Mesh] OR "Multicenter Studies as Topic"[Mesh] OR "Multicenter Study" [Publication Type] OR "Placebos"[Mesh] OR Random*[tiab] OR "latin square"[tiab] OR pragmatic trial*[tiab] OR clinical article*[tiab] OR placebo*[tiab] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR RCT*[tiab] OR ((comparative[tiab] OR control*[tiab] OR clinical[tiab] OR prospectiv*[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR volunteer*[tiab] OR "Cross-Over"[tiab] OR crossover[tiab] OR allocat*[tiab] OR assign*[tiab] OR factorial[tiab]	8638250
3	((("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid" [Pharmacological Action])) OR ((((((((((opioid[Title/Abstract]) OR buprenorphine[Title/Abstract]) OR tapentadol[Title/Abstract]) OR tramadol[Title/Abstract]) OR oxymorphone[Title/Abstract]) OR oxycodone[Title/Abstract]) OR morphine[Title/Abstract]) OR hydromorphone[Title/Abstract]) OR hydrocodone[Title/Abstract]) OR codeine[Title/Abstract])) OR ((((((((((opioid) OR buprenorphine) OR tapentadol) OR tramadol) OR oxymorphone) OR oxycodone) OR morphine) OR hydromorphone) OR hydrocodone) OR codeine)	161810
4	#1 AND #2 #3	1978
	1 AND #2 #3 FILTERS: humans AND clinical trilas	448

Supplemental Table 2. *Search strategy in EMBASE.*

No.	Query	Number of hits
#79	#40 AND #76 AND [humans]/lim AND [english]/lim AND [clinical study]/lim AND [<1966-2017]/py	1219
#78	#40 AND #76 AND [humans]/lim AND [english]/lim AND [clinical study]/lim	1250
#77	#40 AND #76	1705
#76	#30 AND #75	10726
#75	#73 OR #74	295437
#74	#49 OR #50 OR #51 OR #54 OR #55 OR #58 OR #59 OR #62 OR #63 OR #66 OR #67 OR #70 OR #71	295437
#73	#52 OR #53 OR #56 OR #57 OR #60 OR #61 OR #64 OR #65 OR #68 OR #69 OR #72	101310
#72	buprenorphine:ab,ti	7866
#71	Buprenorphine	16224
#70	Tapentadol	1255
#69	tapentadol:ab,ti	723
#68	tramadol:ab,ti	7179
#67	Tramadol	18880
#66	Oxymorphone	2213
#65	oxymorphone;ab,ti	765
#64	oxycodone:ab,ti	4939
#63	Oxycodone	16280
#62	Morphine	114205
#61	morphine:ab,ti	61517
#60	levorphanol:ab,ti	565

Supplemental Table 2. *Search strategy in EMBASE. (continued)*

No.	Query	Number of hits
#59	Levorphanol	2359
#58	Hydromorphone	8923
#57	hydromorphone:ab,ti	2325
#56	hydrocodone:ab,ti	1559
#55	Hydrocodone	6334
#54	fentanyl	61687
#53	fentanyl:ti,ab	24603
#52	'codeine':ti,ab	6423
#51	'codeine'	22354
#50	Opioid	86331
#49	Opiate	132714
#48	'opiate'/exp OR opiate	132714
#47	'narcotic analgesic agent'/exp	307206
#46	#40 OR #45	2288966
#45	#41 OR #42 OR #43 OR #44	1527553
#44	'evaluation study'/exp	216262
#43	evaluation AND studies:ti,ab	289108
#42	comparative AND study:ti,ab	547141
#41	comparative AND study	1092256
#40	#38 OR #39	870417
#39	#32 OR #34 OR #35	265157
#38	#31 OR #32 OR #34 OR #35 OR #36 OR #37	870417
#37	'randomization'/exp	78458
#36	'randomized controlled trial'/exp	504605
#35	'clinical trial (topic)'/exp	504605
#34	'controlled clinical trial (topic)'/exp	149762
#33	controlled AND clinical AND trials	260075
#32	'randomized controlled trial (topic)'/exp	143799
#31	randomized AND controlled AND trials	185294
#30	#27 OR #28 OR #29	181739
#29	#24 OR #25 OR #26	57734
#28	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	140714
#27	#1 OR #2 OR #3 OR #4 OR #5	106506
#26	'chronic low back pain'	7545
#25	chronic AND low AND back AND pain	17177
#24	'low back pain'	56504
#23	Clbp	1704
#22	Clbp	1704
#21	'clbp':ab,ti	7358
#20	'clbp':ab,ti	1694
#19	'chronic low back pain':ab,ti	7358
#18	'low back pain':ab,ti	31290
#17	'disc herniation':ab,ti	7271

Supplemental Table 2. *Search strategy in EMBASE. (continued)*

No.	Query	Number of hits
#16	'disc prolapse':ab,ti	900
#15	'disc degeneration':ab,ti	5016
#14	'spondylosis':ab,ti	3975
#13	vertebrogenic AND pain*:ab,ti	181
#12	sciatic*:ab,ti	32397
#11	coccydynia:ab,ti	165
#10	coccyx:ab,ti	985
#9	lumbar AND pain:ab,ti	36841
#8	back AND ache*:ab,ti	626
#7	backache*:ab,ti	3020
#6	back AND pain*:ab,ti	81813
#5	'dorsalgia'/exp	97072
#4	'spondylosis'/exp	7642
#3	'sciatic neuropathy'/exp	2655
#2	'back pain'/exp	97072
#1	'backache'/exp	97072

Supplemental Table 3. *Search strategy in the Cochrane database.*

ID	Search	Hits
#1	MeSH descriptor: [Back Pain] explode all trees	4740
#2	dorsalgia	59
#3	backache	3059
#4	MeSH descriptor: [Low Back Pain] explode all trees	3626
#5	lumbar next pain or coccyx or coccydynia or sciatica or spondylosis	1582
#6	MeSH descriptor: [Spine] explode all trees	4987
#7	MeSH descriptor: [Spinal Diseases] explode all trees	3950
#8	lumbargo or discitis or disc near degeneration or disc near prolapse or disc near herniation	1765
#9	spinal fusion	2253
#10	spinal neoplasms	688
#11	facet near joints	163
#12	MeSH descriptor: [Intervertebral Disc] explode all trees	310
#13	postlaminectomy	46
#14	arachnoiditis	67
#15	failed near back	280
#16	MeSH descriptor: [Cauda Equina] explode all trees	16
#17	lumbar near vertebra*	3345
#18	spinal near stenosis	942
#19	slipped near (disc* or disk*)	34
#20	degenerat* near (disc* or disk*)	1114
#21	stenosis near (spine or root or spinal)	976
#22	displace* near (disc* or disk*)	1171
#23	prolap* near (disc* or disk*)	265
#24	MeSH descriptor: [Sciatic Neuropathy] explode all trees	328

Supplemental Table 3. *Search strategy in the Cochrane database.*

ID	Search	Hits
#25	sciatic*	1645
#26	back disorder*	4141
#27	back near pain	11676
#28	{or #1-#27}	26008
#29	MeSH descriptor: [Analgesics, Opioid] explode all trees	6885
#30	opiate	5840
#31	opioid	15954
#32	codeine	1643
#33	fentanyl	11828
#34	hydrocodone	570
#35	hydromorphone	784
#36	levorphanol	43
#37	meperidine	1938
#38	morphine	11370
#39	oxycodone	1828
#40	oxymorphone	140
#41	pentazocine	679
#42	propoxyphene	189
#43	tramadol	3042
#44	tapentadol	252
#45	buprenorphine	2108
#46	{or #29-#45}	36912
#47	#28 and #46	2168

Supplemental Table 4. *Shows the study characteristics of the 2-arm randomized, controlled trials.*

Author	Year	Intervention	Control	SD	Location	Centres	PMS	REM	DB	RP	Age	Gender	Baseline pain score
											Inter-vention	Female	Inter-vention
Steiner	2011	Buprenorphine	PB	ES	USA	86	NRS-11	AMP IB	12	539	48.8 (12.55)	298	7.2 (1.26)
Gordan	2010	Buprenorphine	PB	CS	Canada	1	VAS	AMP	8	78	51.3 (11.4)	47	70.6
Rauck	2014	Hydrocodone	PB	ES	USA	59	NRS-11	HC, AMP	12	302	50.4 (10.94)	167	6.9 (1.5)
Wen	2015	Hydrocodone	PB	PS	USA	95	NC	OC	12	588	49.2 (13.51)	338	7.39 (1.12)
Hale	2010	Hydro morphine	PB	PS	USA	66	NRS-11	NA	12	268	47.8 (10.5)	134	6.3 (1.94)
Chu	2012	Morphine	PB	PS	USA	1	VAS	NR	4	139	44.1 (14.2)	61	49.5 (14.7)
Katz	2007	Oxymorphone ER	PB	PS	USA	29	VAS	OM	12	205	51.3 (13.9)	109	70.6 (12.2)
Hale	2007	Oxymorphone	PB	PS	USA	30	VAS	OM	12	143	48.2 (11.7)	64	67.6 (16.8)

Supplemental Table 4. *Shows the study characteristics of the 2-arm randomized, controlled trials. (continued)*

Author	Year	Intervention	Control	SD	Location	Centres	PMS	REM	DB	RP	Age	Gender	Baseline pain score
											Inter-vention	Female	Inter-vention
Baron	2014	Tapendatol	T+P	PS	Germany	48	NRS-11	AMP	8	313	58.5 (11.01)	181	8.0 (1.82)
Donnell1	2009	Tramadol	CC	PS	USA	56	NRS-11	NA	6	796	47.9 (14.5)	462	6.80 (0.08)
Donnell2	2009	Tramadol	CC	PS	USA	59	NRS-11	NA	6	802	47.1 (14.6)	450	6.83 (0.08)
Schnitzer	2000	Tramadol	PB	PS	USA	M	VAS	NC	4	254	-		
Ruoff	2003	Tramadol/ AMP	PB	PS	USA	29	VAS	AMP	81**	322	53.6 (11.9)	201	71.1 (14.5)
Peloso	2004	Tramadol/ AMP	PB	PS	USA	30	VAS	AMP	91**	338	57.5 (11.47)	126	67.9 (14.95)
HyupLee	2012	Tramadol/ AMP	PB	PS	Seoul	15	VAS	NR	23**	248	59.9 (10.7)	183	
Uberal	2012	Tramadol	PB	PS	Germany	31	NRS-11	DF	4	363	57.6 (12.4)	220	6 (1.2)
Vorsanger	2008	Tramadol	PB	ES	USA		VAS		12	386			
Kopecky	2017	Oxycodone	PB	ES	USA	1	NRS-11	AMP	12	52	68		7.2
Gimbel	2016	Buprenorphine	PB	ES	USA	66	NRS-11	HC/ AP	12	511	52.8 (11.13)	278	6.82 (1.27)
Bartoli	2015	Hydrocodone	PB	ES	USA	2	NRS-11	OC	12	129	53.6 (11.97)	83	7.2 (1.28)

Supplemental Table 5. *The study characteristics of the 3-arm randomized, controlled trials.*

Author	Year	IV	AC	CO	SD	Loca-tion	Centers	Instru-ment	RM	DB	RP	Age	Gender	Base-line Pain Score
Webster	2006	Oxyco-done	Oxytrex	PB	PS	USA	45	NRS-11	AMP	12	719	47.9	442	7.6 (1.36)
Buynak	2010	Oxyco-done	Tapentadol	PB	PS	USA	103	NRS-11	AMP	12	981	50 (14.2)	559	7.5 (1.21)
Khoromi	2007	Morphine	Morphine NT	PB	CS	USA	1	NRS-11	AMP	5	55	53	30	-

NC: not clear, AMP: acetaminophen, PB: placebo, NA: not allowed, NR: not reported, PS: parallel study design, CS: cross sectional study design, ES: Enriched study design, OC: oxycodone, IV: intervention, CO: comparator, HC: hydrocodone, IB: ibuprofen, REM: rescue medication, DB: double blind phase RP: randomization patients, T+ P; tapendatol + pregabalin, SD; study design, PMS: pain measure scale, NRS-11: numeric rating scale; VAS: visual analog scale, AC: active comparator;

Supplemental Table 6. *Risk of bias (PEDro) ratings for included studies.*

Study	Year	1	2	3	4	5	6	7	8	9	10	11	Total Score
Kopecky	2017	1	1	1	1	1	1	1	0	1	1	1	9
Gimbel	2016	1	1	0	1	1	1	1	1	1	1	1	9
Bartoli	2015	1	0	0	1	1	1	1	1	1	1	1	8
Wen	2015	1	1	1	1	1	1	1	1	1	1	1	10
Rauck	2014	0	1	1	0	1	1	1	0	0	1	1	7
Lee	2013	1	1	1	1	1	1	1	1	1	1	1	10
Chu	2012	1	1	1	1	1	1	1	0	0	1	1	8
Uberall	2012	1	1	1	1	1	1	1	1	1	1	1	10
Steiner	2011	1	1	1	1	1	1	1	1	1	1	1	10
Buynak	2010	0	1	1	1	1	1	1	0	0	1	1	8
Gordon	2010	0	1	1	0	1	1	1	0	0	1	1	7
Hale	2010	0	1	1	1	1	1	1	0	0	1	1	8
Donnel 1	2009	1	1	1	1	1	1	1	1	1	1	1	10
Donnel 2	2009	1	1	1	1	1	1	1	1	1	1	1	10
Vorsanger	2008	0	1	1	1	1	1	1	0	0	1	1	8
Hale	2007	0	1	1	1	1	1	1	0	0	1	1	8
Katz	2007	1	1	1	1	1	1	1	0	0	1	1	8
Khorimi	2007	1	1	1	1	1	1	1	0	1	1	1	9
Webster	2006	0	1	1	1	1	1	1	0	0	1	1	8
Gordon	2005	1	1	0	1	1	1	1	1	1	1	1	9
Peloso	2004	1	1	1	1	1	1	1	1	1	1	1	10
Ruoff	2003	0	1	1	1	1	1	1	0	0	1	1	8
Schnitzer	2000	0	1	0	0	1	1	1	0	0	1	1	6

PEDro items: 1. Eligibility criteria; 2. Randomisation; 3. Concealed allocation; 4. Baseline comparability; 5. Patient blinding; 6. Clinician blinding; 7. Assessor blinding; 8. Adequate follow-up > 85%, 9. Intention to treat analysis; 10. Between group statistical comparisons; 11. Point measures and measures of variability

Supplemental Table 7. *Model fit assessment and heterogeneity parameter in network meta-analyses.*

Outcome	Random Effects Model					Fixed Effect Model		
	SD	tau	PD	DIC	TRD	PD	DIC	TRD
30% pain reduction	0.62 (0.82-0.79)	2.54 (1.6-6.7)	29.37	217.7	27.64	26	302	98.66
50% pain reduction	0.39 (0.09-0.72)	6.45 (1.9-257.9)	20.4	152.6	20.72	20	198	48.2
Withdrawal	0.69 (0.53-0.75)	2.07 (1.74-3.54)	39.6	294.17	40.46	34	445	181

Supplemental Table 8. *Ranking probability and median ranking of opioids based on a 30% pain reduction.*

Intervention	Ranking Probability	Median Rank	95% CrI	
Oxymorphone	0.483	2	1	9
Morphine_nor	0.2721	2	1	10
Buprenorphine	0.02667	5	1	9
Hydromorphone	0.07995	5	1	11
Tramadol_AP	0.03014	5	1	9
Tapendatol	0.06138	5	1	11
Oxycodone	0.01925	6	2	11
Hydrocodone	0.009267	7	2	11
Morphine	0.01823	8	2	11
Placebo	0	9	7	11
Tramadol	3.33E-06	11	7	11

Supplemental Table 9. *Netleague tables showing the relative efficacy of opioids based on the number of patients who achieved 50% pain reduction from baseline to follow-up.*

	Placebo	Buprenorphine	Hydrocodone	Hydromorphone	Oxycodone	Oxymorphone	Tramadol_AP	Tramadol
Placebo								
Buprenorphine	**2.38 (1.09 - 5.24)**							
Hydrocodone	2.03 (0.92 - 4.58)	0.85 (0.27 - 2.64)						
Hydromorphone	2.62 (0.78 - 8.93)	1.09 (0.25 - 4.72)	1.28 (0.29 - 5.51)					
Oxycodone	1.73 (0.72 - 4.46)	0.72 (0.22 - 2.51)	0.84 (0.26 - 2.93)	0.65 (0.14 - 3.12)				
Oxymorphone	**5.10 (1.31 - 20.41)**	2.14 (0.44 - 10.46)	2.51 (0.51 - 12.24)	1.94 (0.31 - 12.24)	2.94 (0.55 - 14.97)			
Tramadol_AP	**2.11 (1.07 - 4.21)**	0.88 (0.31 - 2.51)	1.04 (0.35 - 2.95)	0.80 (0.19 - 3.25)	1.22 (0.37 - 3.67)	0.41 (0.08 - 1.9)		
Tramadol	1.08 (0.32 - 3.68)	0.45 (0.10 - 1.94)	0.53 (0.12 - 2.28)	0.41 (0.07 - 2.30)	0.62 (0.13 - 2.76)	0.21 (0.03 - 1.33)	0.51 (0.12 - 2.08)	
Tapendatol	1.82 (0.63 - 5.45)	0.76 (0.20 - 2.96)	0.89 (0.23 - 3.45)	0.69 (0.13 - 3.58)	1.05 (0.35 - 3.00)	0.35 (0.06 - 2.05)	0.86 (0.24 - 3.15)	1.68 (0.33 - 8.65)

Abbreviations: Tramadol_AP: Tramadol with acetaminoph

Supplemental Table 10. *Ranking probability and median ranking of opioids based on a 50% pain reduction.*

Intervention	Ranking Probability	Median Rank	95% CrI	
Oxymorphone	0.6442	1	1	7
Hydromorphone	0.158	3	1	9
Buprenorphine	0.06295	4	1	8
Tramadol_AP	0.02845	4	1	8
Hydrocodone	0.03348	5	1	8
Tapendatol	0.04108	5	1	9
Oxycodone	0.2087	6	2	9
Placebo	0	8	6	9
Tramadol	0.01097	8	2	9

Supplemental Table 11. *League tables showing the relative safety of opioids based on the total number of patients who withdrew from the clinical trial.*

	Placebo	Buprenorphine	Hydrocodone	Hydromorphone	Morhine_ nort	Morphine	Oxytrex	Oxycodone	Oxymorphone	Tapendatol_ Preg	Tapendatol	Tramadol_AP
Placebo												
Buprenorphine	0.73 (0.31 - 1.71)											
Hydrocodone	0.33 (0.14 - 0.77)	0.44 (0.13 - 1.47)										
Hydromorphone	0.5 (0.11 - 2.09)	0.67 (0.12 - 3.56)	1.50 (0.28 - 8.01)									
Morhine_nort	1.01 (0.20 - 4.89)	1.36 (0.22 - 8.15)	3.04 (0.50 - 18.27)	2.01 (0.23 - 17.07)								
Morphine	1.20 (0.38 - 3.80)	1.63 (0.39 - 6.79)	3.64 (0.88 - 15.07)	2.41 (0.38 - 15.18)	1.19 (0.24 - 5.83)							
Oxytrex	1.02 (0.27 - 3.78)	1.38 (0.29 - 6.53)	3.09 (0.65 - 14.61)	2.05 (0.29 - 14.32)	1.01 (0.13 - 7.84)	0.84 (0.15 - 4.78)						
Oxycodone	0.82 (0.34 - 1.95)	1.10 (0.33 - 3.71)	2.47 (0.73 - 8.30)	1.64 (0.30 - 8.77)	0.81 (0.13 - 4.90)	0.67 (0.16 - 2.84)	0.79 (0.21 - 2.89)					
Oxymorphone	1.82 (0.63 - 5.26)	2.46 (0.63 - 9.53)	5.48 (1.42 - 21.31)	3.64 (0.61 - 21.86)	1.80 (0.27 - 12.06)	1.51 (0.31 - 7.18)	1.77 (0.33 - 9.63)	2.21 (0.56 - 8.82)				
Tapendatol_Preg	0.76 (0.10 - 5.34)	1.02 (0.12 - 8.60)	2.29 (0.27 - 19.21)	1.52 (0.13 - 17.06)	0.75 (0.06 - 9.24)	0.63 (0.06 - 6.07)	0.74 (0.07 - 7.15)	0.92 (0.13 - 6.53)	0.41 (0.04 - 3.8)			
Tapendatol	0.67 (0.18 - 2.40)	0.90 (0.19 - 4.16)	2.02 (0.43 - 9.37)	1.34 (0.19 - 9.15)	0.66 (0.08 - 5.07)	0.55 (0.10 - 3.07)	0.65 (0.11 - 3.62)	0.81 (0.22 - 2.92)	0.36 (0.06 - 1.92)	0.88 (0.20 - 3.84)		
Tramadol_AP	0.90 (0.39 - 2.08)	1.21 (0.37 - 3.99)	2.71 (0.83 - 8.93)	1.80 (0.34 - 9.53)	0.89 (0.15 - 5.31)	0.74 (0.18 - 3.07)	0.87 (0.18 - 4.15)	1.09 (0.33 - 3.67)	0.49 (0.12 - 1.89)	1.18 (0.14 - 9.90)	1.34 (0.29 - 6.15)	
Tramadol	1.55 (0.75 - 3.18)	2.10 (0.69 - 6.32)	4.68 (1.54 - 14.23)	3.10 (0.62 - 15.57)	1.53 (0.27 - 8.72)	1.28 (0.33 - 4.96)	1.51 (0.34 - 6.72)	1.89 (0.61 - 5.88)	0.85 (0.23 - 3.05)	2.04 (0.25 - 16.33)	2.31 (0.53 - 9.98)	1.72 (0.57 - 5.18)

Abbreviations: Tramadol_AP: Tramadol with acetaminophen, Morphine_nort: Morphine with Nortriptyline

Supplemental Table 12. *Ranking probability and median rankings of opioids based on total withdrawal from the clinical trial.*

Intervention	Ranking Probability	Median Rank	95% CrI	
Hydrocodone	0.4385	2	1	6
Hydromorphone	0.2231	3	1	12
Buprenorphine	0.02587	5	1	12
Tapendatol	0.05907	5	1	12
Oxycodone	0.01146	6	2	12
Tapendatol_Preg	0.1396	6	1	13
Tramadol_AP	0.009693	7	2	12
Placebo	0	8	4	11
Morhine_nort	0.056	8	1	13
Oxytrex	0.02764	8	1	13
Morphine	0.00801	9	2	13
Tramadol	1.03E-04	11	5	13
Oxymorphone	9.47E-04	12	4	13