Methodologic Considerations in the Evaluation of Opioids and Medical Cannabis for Chronic Pain

Methodological consideration in the evaluation of effectiveness and harms of opioids and medical cannabis for chronic pain

By

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Abstract

Opioids are commonly prescribed for chronic pain, particularly in North America; however, growing awareness of their modest benefits and risk of serious harms has raised concerns whether their wide-spread use is evidence-based. Moreover, there are multiple opioids available for use, including both short-acting and sustained-release formulations, and their comparative effectiveness for chronic pain has not been established. It remains possible that some types of opioids may be associated with greater net benefits than others. The first chapter of my thesis presents the results of a network meta-analysis that explores the relative effectiveness of opioids available for the management of chronic non-cancer pain.

The strength of inferences from the results of network meta-analyses depends on the certainty of the evidence, and different approaches are available to make this appraisal. The second chapter of my thesis explores the concordance of two approaches for assessing the certainty of evidence from network meta-analyses, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) working group system, and the Confidence in Network Meta-Analysis (CINeMA) approach.

Concerns over increasing rates of opioid-related overdose and death have generated enthusiasm for reducing opioid dose among chronic pain patients managed with long-term opioid therapy. My third chapter presents a systematic review of the impact of medical cannabis on opioid use among people living with chronic pain.

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List of abbrevations

GRADE: Grading of Recommendations Assessment, Development and Evaluation

CINeMA: Confidence in Network Meta-Analysis

AE: Adverse event

GI: Gastrointestinal

MD: Mean difference

MID: Minimally important difference

NMA: Network meta-analysis

MPH: Morphine

FEN: Fentanyl

BUP: Buprenorphine

OXY: Oxycodone

TPN: Tapentadol

TRA: Tramadol

HMOR: Hydromorphone

OMOR: Oxymorphone

COD: Codein

HYD: Hydrocodone

ER: Extended-released

NR: Normal-released

Declaration of academic achievement

This thesis is a sandwich thesis, which combines four studies published, under review, or prepared for submission in peer-reviewed journals. This is an original thesis and I am the principal contributor and first author of all the manuscripts contained in this thesis. The details of my contributions are included in the following:

Chapter 1: This chapter is unpublished and A. Noori is the sole author.

Chapter 2: This chapter is published in the journal Medicine. Conceptualize and design of the study: A. Noori, J.W. Busse, G.H. Guyatt; Designed systematic search strategy: R. Couban; drafted the manuscript: A. Noori; Provided methodological advice: R. Siemieniuk, L. Wang; Revised the manuscript: J.W. Busse, B. Sadeghirad, R. Siemieniuk, L. Wang, D. N. Juurlink, L. Thabane, G.H. Guyatt. All authors reviewed, provided critical feedback, and approved

this protocol.

Chapter 3: This chapter has been prepared for submission. Conceptualize and design of the study: A. Noori, J.W. Busse, G.H. Guyatt; Designed systematic search strategy: R. Couban; Screened studies for eligibility: A. Noori, E. Kum, MJ, MS; Performed data abstraction: A. Noori, E. Kum, L. Wang, M. Jeddi, M. Shokoohi, L. Montoya, P. Jiho Hong, E Zhou; Assessed risk of bias: A. Noori, E. Kum, M. Shokoohi, L. Montoya; Performed data analysis: A. Noori; Interpreted the data analysis: A. Noori, J.W. Busse, B. Sadeghirad, D. N. Juurlink, M. Bhandari, G.H. Guyatt. Assessed the certainty of evidence: A. Noori, R. Siemieniuk, J.W. Busse, E. Kum. Provided methodological

advice: J.W. Busse, B. Sadeghirad, M. Shokoohi, R. Siemieniuk, L. Thabane, L. Wang. Wrote the first draft of manuscript: A. Noori. All authors reviewed, provided critical feedback, and approved this manuscript.

Chapter 4: This chapter has been prepared for submission. A. Noori, J.W. Busse, G.H. Guyatt conceived and designed the study. A. Noori drafted the manuscript. Interpretation of results: A. Noori, J.W. Busse, R. A. Siemieniuk, B. Sadegigirad, L. Thabane, M. Bhandari. All authors reviewed or critically revised the manuscript. Study supervison: J.W. Busse, G.H. Guyatt.

Chapter 5: this chapter has been accepted for publication in BMJ Open. A. Noori was the primary investigators. J.W. Busse, A. Noori, G.H. Guyatt conceived and designed the study. R. Couban performed the literature search. A. Noori, A. Miroshnychenko, Y. Shergill, V. Ashoorion and Y. Rehman selected the studies, extracted the relevant information, and assessed the risk of bias of selected studies. A. Noori synthesised the data. A. Noori wrote the first draft of the paper. A. Noori, J.W. Busse, G.H. Guyatt and T. Agoritsas critically revised the manuscript for important intellectual content. Noori, J.W. Busse, L. Thabane, G.H. Guyatt, M. Bhandari and N. Buckley interpreted the findings. J.W. Busse, L. Thabane and G.H. Guyatt provided methodological support. All authors reviewed the paper and approved the final version.

Chapter 6: This chapter is unpublished and A. Noori is the sole author.

Chapter 1: Introduction of the Thesis

Introduction

Chronic pain has been defined as pain that lasts for at least 3 months as a result of an underlying medical condition, injury, inflammation, medical intervention, or unknown cause.[1] The prevalence of chronic pain varies in different settings, but is common.[2, 3] The estimated prevalence rate of chronic pain among United States adults range between 11 to 40 percent.[4] A 2011 cross-sectional study in Canada found that among the 16,989 participants surveyed, 17% suffered from persistent pain and preliminary analysis by health Canada estimated that the total number of people living with chronic pain conditions will increase by 17.5% from 2019 to 2030 as population get older.[5, 6] A 2006 survey in Europe found that 21% of respondents had suffered from chronic pain for more than 20 years and among them, 40% were not satisfied with their pain relief.[7]

A study by the world health organization revealed that depression and anxiety are four times more prevalent among individuals who are suffering from chronic pain.[8] Persistent pain related to cancer negatively affects patients' sleep and overall quality of life.[9, 10] Chronic pain is also associated with substantial economic burden.[11] The direct and indirect economic costs of chronic pain in Canada have been estimated at approximately $7.2 billion per year.[12]

A 2018 systematic review assessed the effectiveness of opioids for chronic non-cancer pain and evidence from 42 randomized trials showed a small effect on pain reduction (weighted mean difference of −0.69 cm on a 10cm visual analogue scale, 95%CI −0.82 to −0.56 cm; the minimally important difference is 1cm); however, this pooled estimate was associated with substantial heterogeneity (I^2 = 64%).[13] This review,

and prior reviews, pooled across different types of opioids and this may introduce heterogeneity if the effects of some opioids are systematically different from others.[14].

Chapter two and three present a protocol and a network meta-analysis (NMA), respectively. The NMA explores whether there are differences in benefits and harms for individual opioids prescribed for chronic noncancer pain. A specific focus of this review is to explore the implications of evaluating comparative effectiveness with the surface under the cumulative ranking curve (SUCRA) approach, which focusses on point estimates, or a minimally contextualized approach that also considers the certainty of evidence.[15]

There are competing systems for appraising the certainty of evidence from a NMA. One approach is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[16] Salanti et al.[17] have proposed an alternate approach, facilitated though an online application, titled Confidence in Network Meta-Analysis (CINeMA). In chapter four I apply both systems to the NMA reported in chapter three to explore the concordance of results.

Opioids are commonly prescribed for chronic pain, particularly in North America; however, increasing recognition of their modest benefits and risks of rare but serious harms[18, 19] has generated enthusiasm for alternative approaches, including medical cannabis. Several cross-sectional surveys and observational data before and after a number of US states have legalized medical cannabis have suggested that providing access to cannabis may result in substitution for prescription opioids.[20-24] In the fifth

chapter of my thesis, I present a systematic review and meta-analysis of observational and randomized trials to explore the impact of providing medical cannabis to patients with chronic pain prescribed long-term opioid therapy.

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Chapter 2: Individual opioids, and long- versus short-acting opioids, for chronic noncancer pain: Protocol for a network meta-analysis of randomized controlled trials

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Author contribution

Conceptualize and design of the study: A. Noori, J.W. Busse, G.H. Guyatt; Designed systematic search strategy: R. Couban; drafted the manuscript: A. Noori; Provided methodological advice: R. Siemieniuk, L. Wang; Revised the manuscript: J.W. Busse, B. Sadeghirad, R. Siemieniuk, L. Wang, D. N. Juurlink, L. Thabane, G.H. Guyatt. All authors reviewed, provided critical feedback, and approved

Study Protocol Systematic Review

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Individual opioids, and long- versus short-acting opioids, for chronic noncancer pain

Protocol for a network meta-analysis of randomized controlled trials

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Abstract

Background: Opioids are frequently prescribed for the management of patients with chronic non-cancer pain (CNCP). Previous meta-analyses of efficacy and harms have combined treatment effects across all opioids; however, specific opioids, pharmacokinetic properties (ie, long acting vs short acting), or the type of formulation (ie, immediate vs extended release) may be a source of heterogeneity for pooled effects.

Methods: We will conduct a network meta-analysis (NMA) of randomized controlled trials evaluating opioids for CNCP. We will acquire eligible studies through systematic searches of EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, and the Cochrane Central Registry of Controlled Trials (CENTRAL). Eligible studies will have randomly allocated adult CNCP patients to an oral or transdermal opioid versus another type of opioid (or formulation) or placebo, and follow patients for ≥4 weeks. We will collect outcome data for pain intensity, physical function, nausea, vomiting, and constipation. Pairs of reviewers will, independently and in duplicate, abstract data from eligible trials and assess risk of bias using a modified Cochrane tool. We will assess coherence of our networks through both a global test, and by comparing direct and indirect evidence for each comparison with node-splitting.

Results: Using a frequentist approach, we will conduct random effects multiple treatment meta-analysis to establish treatment effects of individual opioids for each outcome. The certainty of evidence for pooled treatment effects will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. We will categorize interventions from most to least effective based on the effect estimates obtained from NMAs and their associated certainty of evidence, as follows: superior to both placebo and alternatives; superior to placebo, but inferior to alternatives; and no better than placebo.

Conclusion: This NMA will determine the relative effectiveness and adverse effects of individual opioids among patients with CNCP. Our results will help inform the appropriateness of assuming similar beneficial and adverse effects of varying opioid formulations.

Systematic review registration: This systematic review is registered with Prospective Register of Systematic Reviews, an international prospective register of systematic reviews (registration no.: CRD42018110331), available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=110331.

Ethics approval and consent for publication: Since our study is an analysis of published evidence and no individual-level data is captured, ethical approval and consent for publication is not required.

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Dr David Juurlink reports being a volunteer member of Physicians for Responsible Opioid Prescribing and has received payment for expert testimony and lectures related to opioids.

The rest authors have no conflicts of interest to disclose.

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Abbreviations: CNCP = chronic noncancer pain, GRADE = Grading of Recommendations, Assessment, Development, and Evaluation, LA = long acting, NMA = network meta-analysis, SA = short acting.

Keywords: adverse-events, chronic noncancer pain, extended-release, immediate-release, long acting, network meta-analysis, opioids, short acting, systematic review

1. Introduction

Chronic noncancer pain (CNCP) is defined as pain, not due to malignancy, that has persisted for at least 3 months.[1] Estimates of the prevalence of chronic pain vary between 15% and 19% among Canadian adults,[2] and opioids are widely prescribed for the treatment of chronic pain, particularly in North America.[3] Despite widespread use, a 2018 systematic review that explored 96 randomized controlled trials of opioids for CNCP found only modest effects for pain and physical function versus placebo; however, heterogeneity of pooled effect estimates was high (I^2 70% and 64%, respectively) and not explained by subgroup analyses based on: risk of bias, enriched enrollment versus nonenrichment trials, parallel versus cross-over trial design, reported versus converted change scores for treatment effects, and length of follow-up.

Moreover, opioid formulations have been classified based on the onset and duration of action as long acting (LA) or short acting (SA). The pharmacokinetic properties of LA opioids allow for less frequent administration of drug relative to SA opioids, as they provide analgesic effect for 8 to 72 hours (depending on the formulation).[4] There is recommendation regarding the prescription of SA instead of LA opioids for opioid naïve patients with chronic pain.[5]

It is possible that some of the heterogeneity in pooled effects of opioids for CNCP may be explained by systematic differences in treatment effect across individual opioids, or by LA and SA profiles. We therefore propose a network meta-analysis (NMA) to explore for differences in treatment effects and harms between individual opioids, and LA versus SA opioids, in patients with CNCP.

2. Methods

We registered our protocol on Prospective Register of Systematic Reviews (CRD42018110331) and will adhere to the Preferred Reporting Items for Systematic Review and Meta-analysis for NMA (PRISMA NMA) guidelines (see PRISMA checklist).[6]

2.1. Search strategy

An academic librarian will develop database-specific search strategies with no language restriction (see supplemental content 1-search result for our proposed search strategy for MEDLINE, http://links.lww.com/MD/D307), and we will systematically search EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, and the Cochrane Central Registry of Controlled Trials (CENTRAL). Reference lists from eligible trials and relevant literature reviews will be scanned for additional trials that may meet our inclusion criteria. No publication status or date limit will be used.

2.2. Eligibility criteria

We will include trials that will have randomized patients with CNCP to any currently available oral or transdermal opioid compared to an alternative opioid treatment or placebo, and will have followed participants for at least 4 weeks. We will exclude abstracts, and trial/trial arms with combination products, interventions rarely prescribed in North America or have been taken off the market such as cebranopadol, asimadoline, propoxyphene, or fedotozine.

2.3. Study selection

Pairs of reviewers, working independently and in duplicate, will screen titles and abstracts of identified articles and assess the full-text publication for eligibility when one or both reviewers consider a study as potentially eligible. Reviewers will resolve disagreements by consensus and, if disagreements are unresolved, discuss discrepancies with a more experienced team member with relevant expertise. We will pilot this step on 10 randomly selected articles. All screening will be assessed using Rayyan, online systematic review software (https://rayyan.qcri.org/welcome). All eligible articles will be saved in the Endnote X7 library.

2.4. Data extraction

Reviewers will extract data independently and in duplicate from eligible studies using standardized forms and a detailed instruction manual. All reviewers will test the data extraction form prior to beginning data abstraction. Our outcomes of interest will be pain intensity, physical function, and adverse events including nausea, vomiting, and constipation. The following information will be abstracted from each study: author, year of publication, baseline characteristics of participants, trial duration, type of intervention and comparison(s), and above-listed outcomes. We will contact study authors if limitations in reporting lead to uncertainties in eligibility, risk of bias, or outcome. If patients provided multiple reports of pain or physical function during follow-up, we will record the last measurement. If pain outcome is available in different measures such as "pain on movement" or "pain at rest" or different time points such as "pain during morning," "pain midday," or "pain in the evening" we will use "pain at rest" and "pain in the evening."

2.5. Classification of intervention nodes

Regarding pharmacokinetics' properties, LA opioids are distinguished from SA ones by producing less frequent serum-level fluctuations and releasing the drug more gradually into the bloodstream, thus having a longer half-life (Table 1).[4,7] Different opioid formulations, such as extended release (eg, prolonged release, sustained release, control release, and transdermal forms), prolong the duration that the drug is released into bloodstream, as opposed to immediate release formulations (eg, normal release, or buccal form). We will distinguish between pharmacokinetic properties of opioids (LA or SA opioids) and release formulation (extended release or immediate release) for defining the nodes.

Table 1

Pharmacokinetics of opioids available for chronic noncancer pain conditions[1–4].

Opioid	Bioavailability	Plasma half-life, h*	Onset of action, h
Buprenorphine	Sublingual tablet: 29% Patch: ~15%	Sublingual tablet: ~37 Patch: ~26	Patch: achieve steady by day 3 Duration of effect: up to 24
Codeine	53%	~ 3	0.5–1 Peak effect: 1–1.5 Duration of effect: 4–6
Fentanyl	Buccal: 71% Sublingual tablet: 54%	Patch: 20-27 Trans-mucosal products: 3-14	Patch: 6 Trans-mucosal: 5–15 minutes Duration of effect: Patch may last ~72-96
Hydromorphone	62%	IR tablet: 2–3 ER tablet: ~11	IR tablet: 15–30 minutes, ER tablet: 4–5; peak effect: 0.5–1 Duration of effect: IR tablet: 3–4 ER tablet: ~13
Hydrocodone	~20%	2–4	10–20 minutes Duration of effect: 4–8
Levorphanol	~70%	11–16	10–60 minutes Duration of effect: 4–8
Methadone	~80%	12–24	0.5–1 Duration of effect: 6–8; this duration extends to 8–12 with repeated dosing.
Morphine	17% to 33%	IR tablet: 2–4 Avinza: ~24	IR tablet: ~30 minutes Duration of effect: IR tablet: 3–6 ER tablet: 8–24
Oxycodone	60% to 87%	2.5–3	IR tablet: 10–15 minutes ER tablet: 1 Duration of effect: IR tablet: 3–4 ER tablet: 8-12
Oxymorphone	Tablet: ~10%	IR tablet: 7–9 ER tablet: 9–11	IR tablet: 0.5 ER tablet: 2–3 Duration of effect: IR tablet: 4–6 ER tablet: ~12
Tramadol	IR tablet: 75% ER tablet: 85% to 90%	~6–8	IR tablet: ~1 Duration of effect: IR tablet: 6–9 ER tablet: 12-24
Tapentadol	~32%	IR tablet: ~4 ER tablet: ~5–6	20–40 minutes Duration of effect: IR tablet: 4–6 ER tablet: 12

ER = extended release, IR = immediate release.

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* Plasma half-life: it is defined as the duration of time required for the concentration of drug in the plasma or amount of the drug in the body to be reduced by 50%.

2.6. Geometry of the network

The network geometry will be presented to graphically depict the available evidence (each line connecting 2 nodes will indicate a direct comparison between 2 opioids) and may guide readers for the initial interpretation of results.

2.7. Risk of bias assessment of individual studies

We will assess the following risk of bias issues in eligible trials: random sequence generation; allocation concealment, blinding of study participants, personnel, and outcome assessors and incomplete outcome data (≥20% missing data will be considered to be at high risk of bias). For this purpose, 2 independent reviewers in duplicate will use a modified Cochrane risk of bias tool for RCTs with the following responses: "definitely or probably yes" (considered as low risk of bias), or "definitely or probably no" (considered as high risk of bias).[8] We will consider allocation concealment adequate if the following methods will have been used: central allocation approaches ("definitely yes"), sequentially numbered drugs with similar appearance, sealed

envelopes, opaque, and when patients and investigators will have been blinded ("probably yes").[8] Discrepancies in assessment of risk of bias will be resolved by discussion, or third party adjudication if needed.

2.8. Data synthesis and statistical methods

For each direct comparison, we will calculate the weighted mean difference and the associated 95% confidence intervals (CIs) for continuous outcomes. For dichotomous outcomes, we will calculate odds ratio with corresponding 95% CIs. We will use the methods described in the Cochrane Handbook[9] to impute the mean and standard deviation (SD) when median, range, and sample size are reported, and to impute the SD if the standard error or SD for the differences are not reported. If pain or physical functioning was measured by different instruments, we will abstract the most commonly reported scale, for example, 0 to 10 numerical rating scale or visual analogue scale for pain; and SF-36 physical component summary score, physical functioning subdomain, or WOMAC function subscale for physical functioning. We will use change scores from baseline to end of follow-up rather than end-of-study scores, in order to account for inter-patient variability. We will calculate change score for studies that do not report them using the baseline and end-of-study score and a correlation coefficient derived from the largest trial at lowest risk of bias. We will perform pairwise meta-analysis of the available direct comparisons using the DerSimonian–Laird random-effects model for all outcomes.

We will use the network estimate of treatment effects for continuous outcomes to calculate the risk difference for achieving the minimally important difference; the smallest change in a patient-reported outcome that patients perceive as important is one minimally important difference. We will perform NMA to synthesize the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will use a frequentist random-effects model using the methodology of multivariate meta-analysis to assess the comparative effectiveness of eligible interventions.

2.9. Assessment of inconsistency

We will identify issues of incoherence (direct and indirect effect estimates are not similar) by comparing direct evidence (ie, estimates from pairwise comparisons) with indirect evidence (ie, estimates from NMA) using the node splitting method.[10] In this approach, incoherence is assessed locally by statistical evaluation of the difference between direct and indirect estimates for a specific comparison in the loop. We will assume a common heterogeneity estimate across the network. In case of incoherence in a closed loop of evidence, the certainty of evidence of each estimate can lead us to decide which estimate to believe.[11] We will also address the coherence assumption in the entire network using "design-by-treatment" model as described by Higgins et al.[12] In case we find significant incoherence in the network (highly significant P value from design-by-treatment model), we will perform NMA using inconsistency model. If we have at least 10 studies, we will construct a contour enhanced funnel plot for each treatment comparison to assess for small-study effects. To assess the funnel plot asymmetry we will use Harbord et al[13] rank correlation and Egger et al test[14] as well as visual inspection. We will use Stata (StataCorp, Release 15.1, College Station, TX) for all analysis. All comparisons will be 2 tailed using a threshold $P \leq 0.05$.

2.10. Ranking of competing opioids

We will estimate ranking probabilities using the surface under the cumulative ranking curve (SUCRA: values range from 0 "the worst possible SUCRA" to 100 "the best possible"). We will also use a novel approach in which we will classify opioids first based on their effectiveness versus placebo and then versus other competing interventions and finally according to Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) certainty of evidence ratings. Opioids will be sorted into 3 groups: among the most effective (superior to both placebo and to at least 1 intervention superior to placebo or no treatment); superior to placebo, but not superior to any other intervention; or no more effective than placebo. The standard for superiority will be excluding a relative effect of 1.0. For harms, the categorization will be least harmful (no different from placebo); more harmful than placebo but no more harmful than any other intervention; and more harmful than at least 1 other intervention. Within each group of 3 categories we will separate those interventions with moderate or high certainty evidence from those with only low or very low certainty evidence relative to placebo.

2.11. Additional analysis

We will use the Q statistic and I^2 to determine statistical heterogeneity for direct meta-analysis. We will assess the impact of studies with shorter duration of follow-up, higher risk of bias, and enriched study design by removing them from the pairwise meta-analysis. If the produced results will not be robust with the results obtained from primary model, we will remove them from further analysis. We will also, conduct network meta-regression assuming a common fixed coefficient across comparisons to explore the effect of opioids formulation (extended vs immediate release) on all outcomes, if we will have enough studies.

2.12. Certainty of the evidence

We will use the GRADE approach[15] to evaluate the certainty of evidence on an outcome-by-outcome basis and classify evidence as high, moderate, low, or very low certainty based on the limitations in risk of bias, imprecision, inconsistency, indirectness, and publication bias. The GRADE approach also will be used to assess the certainty of evidence from indirect and network (mixed) effect estimates in duplicate and independently. We will visually examine the network map to find the dominant lowest-order loop[16] available for indirect comparisons; the certainty of evidence will be the lower of the ratings for the informing direct estimates contributing to the loop of evidence.[17] In the GRADE approach for NMA, indirect effect estimates may be further rated down for intransitivity (the transitivity assumption implies to the similarity of trials in population, intervention, comparison, and trial methodology informing the indirect comparison in a closed-loop of evidence). When the certainty of the direct evidence is judged to be high and the contribution of it to the network estimate is at least as great as that of the indirect evidence, the certainty rating of network estimate will be only based on the direct evidence.[11] When there is no indirect evidence, the certainty of network estimate will be graded according to the direct evidence.

3. Discussion

The results of our proposed study will provide the comparative effectiveness of individual opioids for the treatment of CNCP population. This is common that in systematic review individual opioids or different formulations of opioids (extended or immediate release) have pooled, assuming similar effect size; this NMA will inform whether this historical practice of pooling across individual opioids is a source of heterogeneity or not.

Our planned review has several strengths including a comprehensive search of published and unpublished results; comparing all individual opioids in terms of the benefits and harms; and our study will use an innovative approach for sorting opioids to provide a clear guide for action for health care providers. However, there might be some challenges for the current review as well. For instance, if the number of included studies will be inadequate, the ability to explore the source of anticipated inconsistencies would be restricted.

For knowledge translation purpose, we will publish our results in an accessible peer-reviewed journal and present our findings at international and national scientific conferences.

Author contributions

Conceptualize and design of the study: Atefeh Noori, Jason W. Busse, Gordon H. Guyatt.
Designed systematic search strategy: Rachel Couban.
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All authors reviewed, provided critical feedback, and approved this protocol.

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Chapter 3: Comparative effectiveness of individual opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized trials

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Author contribution

Conceptualize and design of the study: AN, JWB, GHG. Designed systematic search strategy**:** RC. Screened studies for eligibility: AN, EK, MJ, MS. Performed data abstraction: AN, EK, MJ, MS, LM, PJH, EZh. Assessed risk of bias: AN, EK, MS, LM. Performed data analysis: AN. Interpreted the data analysis: AN, JWB, BS, DJ, MB, GHG. Assessed the certainty of evidence: AN, RS, JWB, EK. Provided methodological advice: JWB, MS, RS, BS, LT, LW. Wrote the first draft of manuscript: AN. All authors reviewed, provided critical feedback, and approved this manuscript.

Comparative effectiveness of individual opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized trials

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Abstract

Systematic reviews of opioids for chronic pain have pooled across different opioid analgesics with the expectation they have similar benefits and harms; however, this assumption has not been empirically tested. This systematic review examined the comparative effectiveness of individual opioids for chronic noncancer pain by performing a network meta-analysis of randomized controlled trials. We searched MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of controlled trials to March 2021, for studies that enrolled patients with chronic noncancer pain, randomized them to receive different opioids, or opioids vs placebo, and followed them for ≥4 weeks. Certainty of evidence was evaluated using the GRADE approach. We identified 82 eligible studies (22,619 participants) that evaluated 14 opioids.

Compared with placebo, several opioids showed superiority to other opioids for pain relief and physical functioning; however, when restricted to moderate certainty evidence, all opioids showed significant benefit over placebo and no opioid was superior. Similarly, opioids showed modest improvement in physical function versus placebo, but no opioid was superior to others. Among opioids with moderate-certainty evidence, all increased the risk of gastrointestinal adverse events compared to placebo while no opioids were more harmful than others. Our findings support the pooling of effect estimates across different types of opioids to inform effectiveness for chronic noncancer pain.

Systematic review registration PROSPERO CRD42018110331

INTRODUCTION

Opioids are commonly prescribed for the treatment of chronic noncancer pain.[1] Despite extensive use, a 2018 systematic review and meta-analysis of 96 randomized controlled trials of opioids for chronic noncancer pain (CNCP) found only modest benefits for pain and physical function versus placebo and pooled effect estimates were associated with substantial heterogeneity (I^2 of 70% and 66%, respectively).[2] Variability between studies was not explained by subgroup analyses based on, for example, risk of bias or use of an enrichment design. One possibility that was not explored was whether individual opioids may have systematically different treatment effects.[3]

Moreover, opioid formulations have been classified based on their duration of effect as long-acting (LA) or short-acting (SA). The pharmacokinetic properties of LA opioids allow for less frequent administration of drugs relative to SA opioids, as they provide analgesic effects for 8 to 72 hours (depending on the formulation).[4] Some guidelines recommend prescribing SA opioids instead of extended-release/LA opioids for initiating opioid therapy among patients with chronic pain,[5] whereas other guidelines recommend LA opioids over SA for chronic pain.[6, 7] We explored the relative effectiveness of both individual opioids, and LA versus SA opioids, for CNCP.

METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analyses,[8] registered our review with PROSPERO (CRD42018110331), and published our protocol.[9]

Information sources

An academic librarian (RJC) developed database-specific search strategies, without language restrictions, for MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials (Appendix 3.1). We searched all databases from inception to 20 March 2021. In addition, we reviewed the reference lists of eligible reports and relevant systematic reviews to identify additional studies.

Study selection

We included randomized controlled trials (RCTs) that enrolled patients with chronic non-cancer pain (i.e., pain lasting ≥3 months), followed them for at least 4 weeks, and compared oral or transdermal opioids vs. another opioid or placebo. We excluded conference abstracts, combination products (e.g., oxycodone + paracetamol, morphine + acetaminophen), and opioids not currently prescribed in North America. Two teams of paired reviewers completed calibration exercises to improve reliability and independently

screened titles, abstracts and full-text studies for eligibility using online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net/). Reviewers resolved conflicts through discussion or consulted with an adjudicator when necessary.

Data abstraction

Using standardized, pilot-tested forms, each eligible trial underwent duplicate data abstraction by the same pair of reviewers working independently. We collected information regarding study characteristics, duration of treatment, patient features, details of interventions, and five outcomes: (1) pain, (2) physical function, (3) vomiting, (4) constipation, and (5) nausea. All opioids administered in eligible randomized trials were reviewed and classified by a clinical pharmacologist (DJ), blinded to study results. Our selection of adverse events was guided by a systematic review of patients' values and preferences that identified GI events as the most important harms for people living with chronic pain prescribed long-term opioid therapy.[10] If a study reported outcomes at several time points, we used the longest follow-up.

Risk of bias assessment

Using a modified Cochrane risk of bias tool, [11] a pair of reviewers independently assessed the risk of bias of each eligible study according to the following domains: allocation

concealment, blinding of participants, study personnel, outcome assessors and data analyst, and loss to follow-up (≥20% missing data was assigned high risk of bias).

Data Synthesis

We converted all measures of pain intensity to a 10cm visual analog scale (VAS) and all outcomes assessing physical function to the 100-point 36-item Short Form Survey (SF-36) physical component summary (PCS) score, using linear transformation and assuming instruments reporting on shared domains have similar measurement properties.[12] For each direct comparison of pain reduction and physical functioning reported by at least 2 studies, we pooled effects as the weighted mean difference (WMD) and associated 95% confidence interval (CI) using change scores from baseline to the end of the follow-up to address interpatient variability. When trials did not report a change score, we estimated them using the baseline and end-of-study score and the median correlation coefficient derived from trials at low risk of bias that contributed to the pooled estimate.[13] For adverse events, which were reported as dichotomous outcomes, we calculated the pooled odds ratios (ORs) and corresponding 95% CIs.

For all conventional pairwise meta-analyses, we used DerSimonian–Laird random-effects models. Subsequently, we performed a frequentist NMA using the methodology of multivariate meta-analysis assuming a common heterogeneity parameter, using the *mvmeta* command in Stata.[14] For comparisons informed by at least 3 studies, we

performed sensitivity analyses using Knapp and Hartung random-effects models for conventional pairwise meta-analysis.

We used the side-splitting method to assess local incoherence (incoherence was assessed using the difference in point estimates and overlap of the confidence intervals). We assessed the incoherence of the entire network using a global I^2 statistic.[15, 16] In the presence of incoherence between direct and indirect estimates for a particular comparison, we rated down for incoherence, or we relied on the direct or indirect estimate of effect rather than the network estimate if one was supported by higher certainty of evidence. For all direct comparisons, we performed Egger's and Harbord's tests[17] to assess for small-study effects when 10 or more studies were available for continuous and binary outcomes, respectively. We estimated the ranking probabilities by using the surface under the cumulative ranking curves (SUCRA), mean ranks, and rankograms. We used STATA (StataCorp., Release 15.1. College Station, TX) for all analyses.

Subgroup analysis, meta-regression and sensitivity analyses

We evaluated heterogeneity of all pooled estimates from direct comparisons using the I^2 statistic. Guided by the Cochrane Collaboration, we considered heterogeneity of 0% to 40% as 'might not be important, 30% to 60% as 'moderate heterogeneity', 50% to 90% as 'substantial heterogeneity', and 75% to 100% as 'considerable heterogeneity'.[13] We planned to perform subgroup analysis assuming greater benefits with: (1) shorter vs. longer duration of follow-up; (2) higher vs. lower risk of bias on a criterion-by-criterion

basis; and (2) enriched enrolment vs. not. We assumed similar directions of subgroup effects for harms, except for enriched study design. Enrichment trials precede randomization with an open-label treatment phase and exclude participants who report problematic adverse events or no improvement during the run-in period.

Optimizing interpretation of results

To optimize the interpretation of results of statistically significant continuous outcomes (i.e., pain, physical functioning),[18] we used the network estimate to model the risk difference (RD) for achieving the minimally important difference (MID).[12] We used a MID of 1 cm for the 10cm VAS for pain and 5-points for the 100-point 36-item SF-36 PCS score.[19, 20] For adverse events, we applied the baseline risk to the ORs and 95% CIs to calculate absolute effects. We used the median risk for each adverse event from the placebo control arms among eligible trials as the baseline risk. We used MAGICapp (www.magicapp.org) to calculate absolute effects.

Assessment of certainty of the evidence

Two reviewers independently used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[21] to assess the certainty of evidence on an outcome-by-outcome basis and resolved discrepancies by discussion. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on

considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.

We began with the certainty of evidence associated with the source of evidence, direct or indirect, that contributed ≥60% of the weight to the network estimate. If neither contributed 60% or more, then we used the highest certainty of the direct and indirect estimates.[22] Certainty could then be further rated down for incoherence or imprecision. For the judgment of the imprecision, we rated down for this domain if the 95% CI of the network estimate for continuous outcomes included half the MID (i.e., 0.5cm for pain; 2.5 points for physical function). For dichotomous outcomes (i.e., adverse events), we rated down for imprecision if the associated measure of precision for the RD included 5%. In cases where the network estimate was both statistically significant and precise, we rated down for imprecision if the comparison was informed by less than 300 observations for continuous outcomes or 300 events for binary outcomes.[23]

Categorization of interventions

We used a minimally contextualized approach[24] with a null effect as the threshold of importance. For pain and physical function, we created groups of interventions as follows: 1) opioids that showed an effect no different from placebo, which we refer to as "among the least effective"; 2) opioids superior to placebo but not superior to other opioids, which we describe as "inferior to the most effective, but superior to the least effective" (category 2 interventions); and 3) opioids that proved superior to at least one

category 2 opioid, which we defined as "among the most effective". We used the same approach for adverse events, but designated opioids as 1) no more harmful than placebo; 2) less harmful than some opioids, but more harmful than placebo, and 3) among the most harmful. We then categorized opioids as those with moderate or high certainty evidence, and those with low or very low certainty evidence relative to placebo.

RESULTS

Of 45,367 records, 80 articles met eligibility criteria and were included in our review (Figure 3.1). Two articles [25, 26] reported 2 RCTs each, resulting in 82 eligible trials that enrolled 22,619 participants. Four studies that assessed pain[27-30] and seven that measured physical function[27, 29, 31-34,35] were included in our review but excluded from meta-analysis of effect estimates because they only reported end-of-study data without baseline scores, precluding conversion to change scores.

The median of mean age among included studies was 57 years (interquartile range [IQR] 50 to 62). Among the 75 trials reporting sex distribution, the median of the proportion of female participants was 56% (IQR 47% to 62%), and the median of mean duration of chronic pain was 97 months (IQR 41 to 125). Nine studies included patients with different types of chronic pain[26, 27, 36-42], 34 included patients with nociceptive pain (e.g. osteoarthritis)[1, 29, 32, 34, 35, 43-72], 20 with neuropathic pain (e.g. sciatica)[25, 26, 30, 33, 48, 73-82], and 20 with nociplastic pain (e.g. fibromyalgia) (Appendix 3.2). Twenty-one trials (26%) used an enriched enrollment design.[25, 31, 50, 55, 60, 61, 69, 70, 78, 85-88, 94-96, 98, 100-102]

Among included trials, 70 (85%) reported receiving industry funding, 7 (9%) reported receiving no industry funding, and 5 (6%) did not report funding details (Appendix 3.3).

Risk of bias among included studies

Nine studies (11%) were judged at low risk of bias in all domains. All other studies (88% [72 of 82]) had frequent missing (≥15-20%) outcome data (87% [71 of 82]) or unblinding of patients (13% [11 of 82]). (Appendix 3.3)

Outcomes

Pain relief

Seventy-eight RCTs involving 21,906 participants reported the effect of opioids on pain relief. In 15 of the 22 direct comparisons there were at least two studies for conventional pairwise meta-analysis, and among them four comparisons showed high heterogeneity (I^2 ≥65%; Appendix 3.9). We did not find evidence of global or loop-specific incoherence (Appendix 3.19, 3.20). The network map presented in Appendix 3.4.

Moderate certainty evidence showed that, compared with placebo, normal release tramadol (-1.09 cm [95%CI -1.55 to -0.64] on a 10-cm VAS for pain; RD for achieving the MID 17%), extended release (ER) morphine (WMD -0.87 cm [95%CI -1.18 to -0.55]; RD 15%), buprenorphine-buccal (-0.87 cm [95%CI -1.11 to -0.63]; RD 6%), tapentadol-ER (-0.81 cm [95%CI -1.09 to -0.52]; RD 9%), and tramadol-ER (-0.80 cm [95%CI -1.06

to -0.55]; RD 10%) reduced pain intensity. No opioid demonstrated superiority to another opioid (Figure 3.2).

Low to very-low certainty evidence suggested that codeine-ER (-2.03 cm [95%CI -3.31 to -0.75] on a 10-cm VAS for pain; RD for achieving the MID 33%), oxymorphone-ER (-1.47 cm [95%CI -2.03 to -0.91]; RD 6%), and normal release oxycodone (-0.99 cm [95%CI -1.85 to -0.14]) were superior to both placebo and at least one other category 2 opioid. Fentanyl patches (-0.78 cm [95%CI -1.19 to -0.37]; RD 10%), buprenorphine patches (-0.71 cm [95%CI -1.02 to -0.40]; RD 10%), oxycodone-ER (-0.67 cm [95%CI -0.91 to -0.44]; RD 7%), hydrocodone-ER (-0.53 cm [95%CI -0.99 to -0.07]; RD 6%), and hydromorphone-ER (-0.51 cm [95%CI -0.89 to -0.14]; RD 4%) were more effective than placebo but inferior to the most effective opioids for reducing pain. Very low certainty evidence suggested that normal release tapentadol may not be more effective than placebo for relieving pain (-1.09 cm, 95% CI -2.27 to 0.09) (Figures 3.2, 3.3).

The SUCRA ranking suggested codeine -ER (94.2%), oxymorphone-ER (89%), tramadol-NR (73%), and oxycodone-NR (60%) as the best opioids for pain relief (Appendix 3.25); however, their effect estimates were supported by only low certainty evidence (Figure 3.3). All comparisons supported by moderate–to-high certainty evidence demonstrated that opioids were more effective than placebo for pain relief, but that none were superior to others (Figure 3.3).

Physical function

Thirty-nine studies involving 13,134 patients reported the effect of opioids on physical functioning. This evidence included 17 direct comparisons, among which 6 had only one study that precluded conventional pairwise meta-analysis; heterogeneity was substantial in four of them (I^2 ≥65%; Appendix 3.10). We found no evidence of global or loop-specific incoherence (Appendix 3.21).

No comparison was supported by moderate or high-certainty evidence. Low to very low certainty evidence suggested that codeine-ER (17.76 points [95%CI 7.35 to 28.17 points] on the 100-point SF-36 physical component score; MID of 5 points; RD for achieving the MID 11%) and hydromorphone-ER (3.45 points [95%CI 1.28 to 5.61] points; RD 7%) may improve physical functioning more than placebo and at least one other category 2 opioid. Low to very low certainty evidence suggested that tapentadol-ER (2.13 points [95%CI 0.67 to 3.59 points]; RD 5%) and oxycodone-ER (1.21 points [95%CI 0.01 to 2.40 points]; RD 2%) were inferior to codeine-ER and hydromorphone-ER, but superior to placebo. Low or very low certainty evidence suggested that morphine-ER (1.98 points, 95%CI -0.3 to 4.26 points), tramadol-ER (1.81 points, 95%CI -0.32 to 3.95 points), oxymorphone-ER (1.67 points, 95%CI -1.4 to 4.75 points), fentanyl patches (1.53 points, 95%CI -0.6 to 3.65 points), buprenorphine patches (2.16 points, 95%CI -0.6 to 4.92 points), and hydrocodone-ER (-1.13 points, 95%CI -6.23 to 3.97 points) provided no difference in physical functioning versus placebo (Figure 3.2, 3.3). As with pain relief, SUCRA ratings concluded that some opioids were superior to others. (Appendix 3.26)

Vomiting

Fifty-three studies involving 20,283 patients reported vomiting, and reported 21 direct comparisons. In 13 comparisons there were two or more studies available for conventional pairwise meta-analysis, and heterogeneity was substantial in two of them (I^2 ≥65%; Appendix 3.11). We found no evidence of global incoherence, but we observed incoherence in one loop of evidence (Appendix 3.22), in which the difference between direct and indirect comparisons was statistically significant for hydromorphone-ER vs placebo, oxycodone-ER vs hydromorphone-ER, and tapentadol-ER vs oxycodone-ER. As such, for tapentadol-ER vs oxycodone-ER, we used the higher certainty evidence from the direct comparison (moderate certainty) rather than network estimate.

Compared with placebo, moderate certainty evidence showed that oxycodone-ER (OR 7.12 [95%CI 5.42 to 9.35]; RD 111 more per 1000 [95%CI 83 to 146 more]) increased the risk of vomiting (Figure 3.2, 3.4). Low to very low certainty evidence suggested that, compared with placebo, oxymorphone-ER, fentanyl patches, morphine-ER, buprenorphine-buccal, hydromorphone-ER, tramadol-NR, oxycodone-NR, tramadol-ER, buprenorphine patches, tapentadol-ER, and hydrocodone-ER may increase the risk of vomiting. Very low certainty evidence suggested that tapentadol-NR did not increase the risk of vomiting versus placebo (Figures 3.2, 3.4).

Constipation

Sixty-four studies reported constipation, involving 22,531 patients, addressed 22 direct comparisons. In 16 comparisons there were two or more studies available for conventional pairwise meta-analysis and four of them showed substantial heterogeneity. (Appendix 3.12) We detected a global test of inconsistency and incoherence for two loops. (Appendix 3.23) In each case we used the higher certainty evidence from the direct or indirect estimates, instead of the network estimate.

Compared with placebo, moderate certainty evidence suggested that oxycodone-ER (OR 6.34 [95%CI 5.21 to 7.71]; RD 169 more per 1000 [95%CI 138 to 203 more]), hydromorphone-ER (OR 5.71 [95%CI 4.15 to 7.85]; RD 152 more per 1000 [95%CI 107 to 206 more]), and tramadol-ER (OR 4.5 [95%CI 3.37 to 6]; RD 118 more per 1000 [95%CI 83 to 160 more]) increased the risk of constipation (Figures 3.2, 3.4).

Low to very low certainty evidence existed that codeine-ER, oxymorphone-ER, morphine-ER, oxycodone-NR, fentanyl patches, tramadol-NR, buprenorphine patches, tapentadol-ER, hydrocodone-ER, and buprenorphine-buccal may increase the risk of constipation compared to placebo. Very low certainty evidence suggested that tapentadol-NR may be no more harmful than placebo. (Figures 3.2, 3.4).

Nausea

Sixty-seven studies, involving 22,681 patients, reported nausea. There were 21 comparisons, among which 16 were reported by sufficient studies for conventional pairwise meta-analysis; three of these comparisons showed substantial heterogeneity

(Appendix 3.13). The global test of inconsistency was significant and we found evidence of incoherence in two loops; (Appendix 3.24) we therefore used the direct effect estimates from conventional meta-analysis rather network estimations for tapentadol-ER vs placebo and morphine-ER vs fentanyl patches (both moderate certainty evidence).

Compared with placebo, moderate certainty evidence showed that oxycodone-ER (4.43 [3.25 to 6.04]; RD 186 more per 1000 [131 to 249 more]), tramadol-ER (3.34 [2.41 to 4.61]; RD 135 more per 1000 [87 to 193 more]), and tapentadol-ER (3.04 [2.39 to 3.87]; RD 120 more per 1000 [85 to 161 more]) increased the risk of nausea (Figures 3.2, 3.4).

Relative to placebo, low to very low certainty evidence suggested that oxymorphone-ER, morphine-ER, hydromorphone-ER, tramadol-NR, fentanyl patches, buprenorphine-patch, and buprenorphine-buccal may increase the risk of nausea. Low to very low certainty evidence also suggested that hydrocodone-ER, tapentadol-NR, and oxycodone-NR did not significantly increase nausea compared with placebo (Figures 3.2, 3.4).

Long-acting vs. short-acting opioids

Low to very-low certainty evidence suggested no significant differences between LA and SA opioids for pain relief, physical functioning, vomiting, constipation or nausea (Appendix 3.30-34).

DISCUSSION

In this network meta-analysis of randomized trials enrolling patients with chronic noncancer pain, the SUCRA approach found important difference in benefits and harms between individual opioids. However, effect estimates supported by moderate certainty evidence showed that individual opioids were similarly effective vs. placebo for pain relief, with no opioid showing superiority to another. Similarly, when restricted to moderate certainty evidence, no opioid showed superiority for improvement of physical functioning. Similarly, among opioids supported by moderate certainty evidence, all increased the risk of the GI adverse events, while none were more harmful than others. Low to very-low certainty evidence suggests that LA vs SA opioids may provide similar benefits for pain relief and physical functioning, and similar GI harms.

Our NMA, which is the first to compare the relative effectiveness of both individual and LA vs SA opioids for chronic noncancer pain, has several strengths. Importantly, while SUCRA rankings concluded there were important differences between opioids, we have shown that a minimally contextualized approach that considers the certainty of evidence supports individual opioids as similarly effective. We also improved the interpretation of results by presenting effect estimates in both relative and absolute effects. Our review also has limitations. There was limited direct evidence comparing individual opioids, and although we found that short and long-acting opioids were similarly effective the evidence to support this finding was only low to very-low in certainty.

Our findings are consistent with a 2014 qualitative systematic review of 6 trials that found short and long-acting opioid formulations were similarly effective for short-term pain relief.[103] We have complemented these findings with 80 new trials and by quantifying the effects of short and long-acting formulations on pain, physical function, and GI adverse events. Another 2014 narrative review assessed 17 opioids for acute and chronic pain and concluded there was insufficient evidence to determine whether individual opioids were more or less effective.[104] Our review has extended these findings, and found moderate certainty evidence to support that individual opioids are similarly effective. Some clinical practice guidelines have recommended avoiding extended release opioids when starting opioid therapy for chronic pain to reduce the risk of overdose; [5,6] However, our review was not designed to address this issue.

Conclusion

Our review found that, when restricted to pooled effect estimates supported by moderate certainty evidence, individual opioids were similarly effective for pain relief and physical function. Among opioids with moderate-certainty evidence, all increased the risk of gastrointestinal adverse events compared to placebo while no opioids were more harmful than others. Several effect estimates failed to achieve statistical significance due to wide estimates of precision. Our findings support the pooling of effect estimates across different types of opioids to inform the effect on chronic noncancer pain, and highlights the potential for the SUCRA approach to mislead readers vs. a minimally contextualized approach when ranking competing interventions.

Conflict of interest: Dr. David Juurlink reports being a volunteer member of Physicians for Responsible Opioid Prescribing and has received payment for expert testimony and lectures related to opioids. The remaining authors have no conflicts of interest to disclose.

Funding Source: This was an unfunded study.

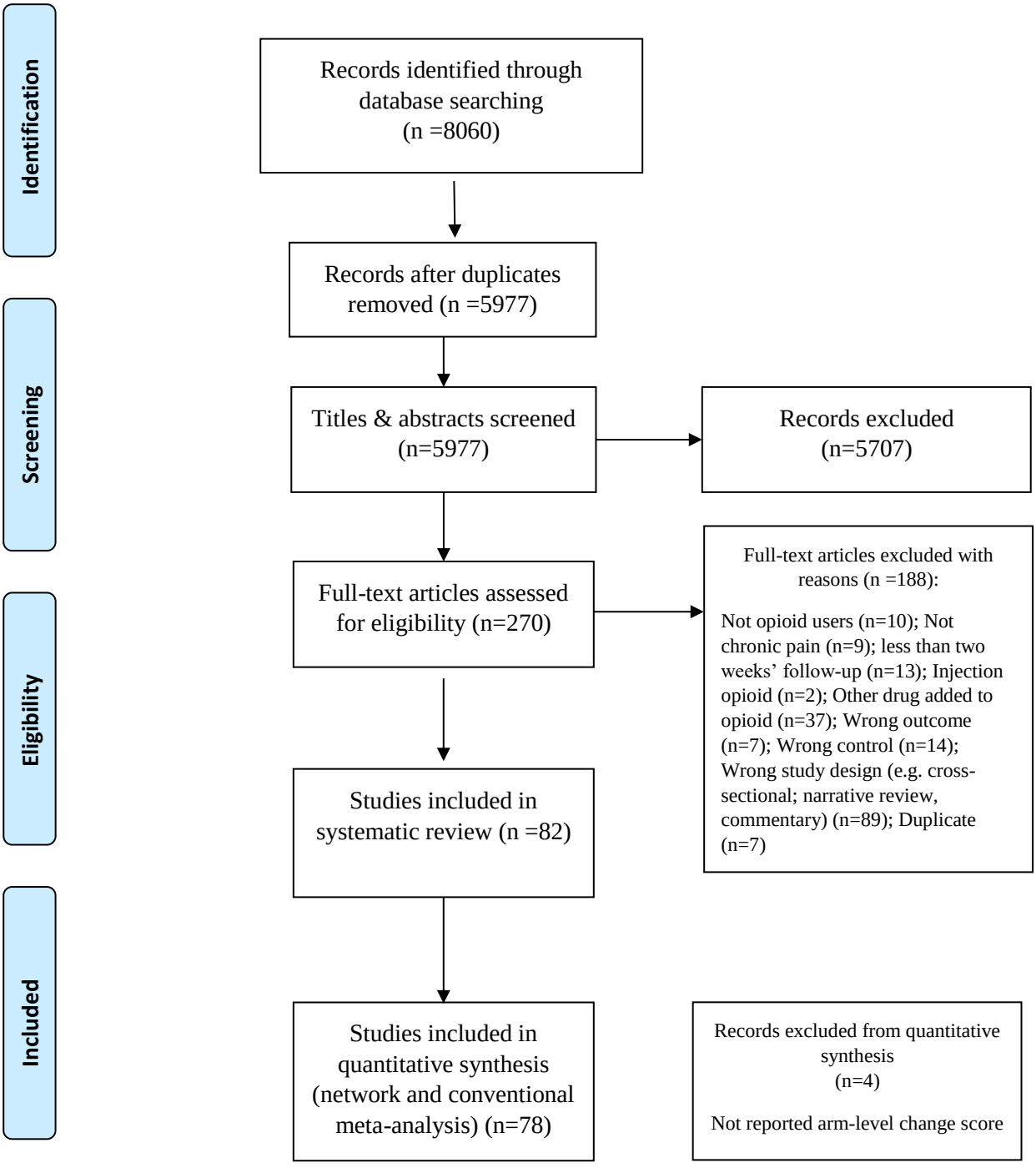

Figure 3. 1: Flow diagram for study selection

Figure 3. 2: NMA results, sorted based on GRADE certainty of evidence and effect estimate for the comparisons of opioids versus placebo for effectiveness and harm outcomes.

Opioid	**Effectiveness outcomes**		**Harms outcomes**		
	Pain relief MD (95% CI)	Physical function MD (95% CI)	Constipation RD (95% CI)	Nausea RD (95% CI)	Vomiting RD (95% CI)
			Placebo: 40 per 1000	Placebo: 73 per 1000	Placebo: 21 per 1000
TRA-NR	-1.09 (-1.55 to -0.64)	-	99 (47 to 177)	128 (48 to 243)	63 (18 to 152)
MPH-ER	-0.87 (-1.18 to -0.55)	1.98 (-0.3 to 4.26)	149 (102 to 207)[£]	143 (68 to 242)	137 (83 to 213)
BUP-Buccal	-0.87 (-1.11 to -0.63)	3.67 (-0.02 to 7.37)	57 (16 to 123)	65 (7 to 155)	81 (38 to 147)
TPN-ER	-0.81 (-1.09 to -0.52)	2.13 (0.67 to 3.59)	66 (46 to 89)	120[¥] (85 to 161)	37 (22 to 55)
TRA-ER	-0.80 (-1.06 to -0.55)	1.81 (-0.32 to 3.95)	118 (83 to 160)	135 (87 to 193)	59 (31 to 99)
COD-ER	-2.03 (-3.31 to -0.75)	17.76 (7.35 to 28.17)	195 (60 to 418)	-	-
OMOR-ER	-1.47 (-2.03 to -0.91)	1.67 (-1.4 to 4.75)	153 (97 to 225)	214 (95 to 370)	275 (165 to 414)
OXY-NR	-0.99 (-1.85 to -0.14)	-	127 (43 to 267)	78 (-17 to 272)	59 (12 to 161)
FEN-PTCH	-0.78 (-1.19 to -0.37)	1.53 (-0.6 to 3.65)	102 (64 to 151)	120 (49 to 216)	153 (91 to 239)
BUP-PTCH	-0.71 (-1.01 to -0.40)	2.16 (-0.6 to 4.92)	89 (52 to 138)	112 (60 to 180)	51 (27 to 85)
OXY-ER	-0.67 (-0.90 to -0.44)	1.21 (0.01 to 2.4)	169 (138 to 203)	186 (131 to 249)	111 (83 to 146)

HYD-ER	-0.53 (-0.99 to -0.07)	-1.13 (-6.23 to 3.97)	62 (18 to 133)	40 (-12 to 126)	19 (1 to 51)
HMOR-ER	-0.51 (-0.89 to -0.14)	3.45 (1.28 to 5.61)	152 (107 to 206)	133 (49 to 253)	71 (35 to 128)
TPN-NR	-1.09 (-2.27 to 0.09)	-	34 (-9 to 122)	15 (-50 to 212)	19 (-6 to 82)

Figure key:

Certainty of evidence	**Effectiveness outcomes**	**Harmful outcomes**
High to Moderate	Superior to placebo	More harmful than placebo
Low to very-low	May be among the most effective	May be more harmful than a placebo
	May be inferior to the most effective, but superior to placebo	May be no more harmful than placebo
	May be no more effective than placebo	

Results are the MD on a scale of 0 to 10cm or 0 to 100 point or absolute risk difference (associated 95% Confidence interval) between the opioids and placebo from the NMA. For pain relief, scores range from 0 to 10 cm; lower is better (MID is 1 cm). For physical function, scores range from 0 to 100 points; higher is better (MID is 5 point).
AE = adverse event; GI = gastrointestinal; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; MID = minimally important difference; NMA = network meta-analysis; OR = odds ratio. MPH=morphine; FEN=fentanyl; BUP=buprenorphine; OXY=oxycodone; TPN=tapentadol; TRA=tramadol; HMOR= hydromorphone; OMOR= oxymorphone; COD= codein; HYD= hydrocodone. ER= Extended-released; NR=Normal-released; PTCH=patch.
[¥]Because of incoherence, this effect estimate is from the direct comparison instead of the network estimate.
[£]Because of incoherence, this effect estimate is from the indirect comparison instead of the network estimate.

Figure 3. 3: NMA results and SUCRA values sorted on the basis of GRADE certainty of evidence for the comparisons of opioids versus placebo for pain relief and physical function.

Effectiveness outcomes	Certainty of evidence	Classification	Opioid	MD (95% CI)	SUCRA %	RD for achieving MID %
Pain relief	High (high-to-moderate)	Superior to placebo	TRA-NR	-1.09 (-1.55 to -0.64)	73	17
			MPH-ER	-0.87 (-1.18 to -0.55)	55	15
			BUP-Buccal	-0.87 (-1.11 to -0.63)	53	6
			TPN-ER	-0.81 (-1.09 to -0.52)	50	9
			TRA-ER	-0.80 (-1.06 to -0.55)	49	10
	Low (low-to-very-low)	May be among the most effective	COD-ER	-2.03 (-3.31 to -0.75)	94	33
			OMOR-ER	-1.47 (-2.03 to -0.91)	89	6
			OXY-NR*	-0.99 (-1.85 to -0.14)	60	-
		May be inferior to the most effective, but superior to placebo	FEN-PTCH	-0.78 (-1.19 to -0.37)	46	10
			BUP-PTCH	-0.71 (-1.01 to -0.40)	37	10
			OXY-ER	-0.67 (-0.90 to -0.44)	31	7
			HYD-ER	-0.53 (-0.99 to -0.07)	23	6
			HMOR-ER	-0.51 (-0.89 to -0.14)	20	4

		May be no more effective than placebo	TPN-NR	-1.09 (-2.27 to 0.09)	64	-
Physical function	Low (low to very low)	May be among the most effective	COD-ER	17.76 (7.35 to 28.17)	99.7	11
			HMOR-ER	3.45 (1.28 to 5.61)	76.1	7
		May be inferior to the most effective, but superior to placebo	TPN-ER	2.13 (0.67 to 3.59)	55.3	5
			OXY-ER	1.21 (0.01 to 2.4)	33.2	2
		May be no more effective than placebo	BUP-Buccal	3.67 (-0.02 to 7.37)	73.6	-
			BUP-PTCH	2.16 (-0.6 to 4.92)	53.9	-
			MPH-ER	1.98 (-0.3 to 4.26)	50.8	-
			TRA-ER	1.81 (-0.32 to 3.95)	47.3	-
			OMOR-ER	1.67 (-1.4 to 4.75)	45.2	-
			FEN-PTCH	1.53 (-0.6 to 3.65)	40.9	-
			HYD-ER	-1.13 (-6.23 to 3.97)	13.9	-

GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; MID = minimally important difference; NMA = network meta-analysis; RD=Risk difference. MPH=morphine; FEN=fentanyl; BUP=buprenorphine; OXY=oxycodone; TPN=tapentadol; TRA=tramadol; HMOR= hydromorphone; OMOR= oxymorphone; COD= codein; HYD= hydrocodone. ER= Extended-released; NR=Normal-released; PTCH=patch.
*not compared vs placebo directly and not able to calculate RD for achieving MID.

Figure 3. 4: NMA results and SUCRA values sorted on the basis of GRADE certainty of evidence for the comparisons of opioids versus placebo for GI adverse events.

Harm outcomes	Certainty of evidence	Classification	Opioid	OR (95% CI)	SUCRA %	RD (95% CI)
Vomiting	High (high to moderate)	More harmful than placebo	OXY-ER	7.12 (5.42 to 9.35)	26.5	111 (83 to 146)
	Low (low to very low)	May be more harmful than placebo	OMOR-ER	19.57 (10.68 to 35.86)	0.3	275 (165 to 414)
			FEN-PTCH	9.83 (5.90 to 16.38)	11.9	153 (91 to 239)
			MPH-ER	8.77 (5.40 to 14.25)	17.6	137 (83 to 213)
			BUP-Buccal	5.28 (2.95 to 9.45)	37.9	81 (38 to 147)
			HMOR-ER	4.75 (2.77 to 8.14)	44.9	71 (35 to 128)
			TRA-NR	4.28 (1.87 to 9.78)	53.6	63 (18 to 152)
			OXY-NR	4.06 (1.59 to 10.39)	50.9	59 (12 to 161)
			TRA-ER	4.04 (2.57 to 6.34)	55.7	59 (31 to 99)
			BUP-PTCH	3.59 (2.33 to 5.54)	59.6	51 (27 to 85)
			TPN-ER	2.85 (2.11 to 3.84)	74.3	37 (22 to 55)
			HYD-ER	1.94 (1.04 to 3.61)	84.2	19 (1 to 51)
		May be no more harmful than placebo	TPN-NR	1.93 (0.7 to 5.33)	83.6	19 (-6 to 82)
Constipation	High	More harmful than placebo	OXY-ER	6.34 (5.21 to 7.71)	15.9	169 (138 to 203)

	(high to moderate)		HMOR-ER	5.71 (4.15 to 7.85)	24.5	152 (107 to 206)
			TRA-ER	4.5 (3.37 to 6)	42.2	118 (83 to 160)
	Low (low to very low)	May be more harmful than placebo	COD-ER	7.37 (2.68 to 20.29)	17.8	195 (60 to 418)
			OMOR-ER	5.74 (3.81 to 8.65)	24.7	153 (97 to 225)
			MPH-ER[£]	5.58 (3.97 to 7.89)	11.1	149 (102 to 207)
			FEN-PTCH	3.96 (2.78 to 5.65)	52.1	102 (64 to 151)
			OXY-NR	4.82 (2.18 to 10.64)	37.1	127 (43 to 267)
			BUP-PTCH	3.55 (2.43 to 5.19)	59.6	89 (52 to 138)
			TRA-NR	3.89 (2.28 to 6.66)	52.9	99 (47 to 177)
			TPN-ER	2.85 (2.27 to 3.57)	75.1	66 (46 to 89)
			HYD-ER	2.72 (1.47 to 5.01)	74.1	62 (18 to 133)
			BUP-Buccal	2.58 (1.42 to 4.69)	77.3	57 (16 to 123)
		May be no more harmful than placebo	TPN-NR	1.91 (0.78 to 4.65)	86.1	34 (-9 to 122)
Nausea	High (high to moderate)	More harmful than placebo	OXY-ER	4.43 (3.25 to 6.04)	12.6	186 (131 to 249)
			TRA-ER	3.34 (2.41 to 4.61)	34.4	135 (87 to 193)
			TPN-ER[¥]	3.04 (2.39 to 3.87)	57.8	120 (85 to 161)
	Low (low to very low)	May be more harmful than placebo	OMOR-ER	5.1 (2.57 to 10.12)	10.9	214 (95 to 370)
			MPH-ER	3.49 (2.09 to 5.84)	31.6	143 (68 to 242)

			HMOR-ER	3.29 (1.77 to 6.14)	36.8	133 (49 to 253)
			TRA-NR	3.2 (1.75 to 5.86)	38.8	128 (48 to 243)
			FEN-PTCH	3.03 (1.77 to 5.17)	44	120 (49 to 216)
			BUP-Patch	2.89 (1.94 to 4.3)	46.5	112 (60 to 180)
			BUP-Buccal	2.03 (1.1 to 3.75)	70.1	65 (7 to 155)
		May be no more harmful than placebo	OXY-NR	2.26 (0.76 to 6.68)	57.8	78 (-17 to 272)
			HYD-ER	1.62 (0.83 to 3.15)	79.8	40 (-12 to 126)
			TPN-NR	1.22 (0.3 to 5.05)	83	15 (-50 to 212)

An OR greater than 1 indicates that the opioid is associated with a higher likelihood of harms compared with placebo.
AE = adverse event; GI = gastrointestinal; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NMA = network meta-analysis; OR = odds ratio; RD=Risk difference. MPH=morphine; FEN=fentanyl; BUP=buprenorphine; OXY=oxycodone; TPN=tapentadol; TRA=tramadol; HMOR= hydromorphone; OMOR= oxymorphone; COD= codein; HYD= hydrocodone. ER= Extended-released; NR=Normal-released; PTCH=patch.
[£]the best estimates are from indirect rather than network because of the incoherence.
[¥]the best estimates are from the direct rather than network because of the incoherence.

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Appendix 3. 1: Literature Search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid

MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word,

keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique

identifier, synonyms] (58120)

2 Chronic Pain/ (9487)

3 exp Osteoarthritis/ (54546)

4 osteoarthrit*.mp. (75997)

5 osteo-arthritis.mp. (367)

6 degenerative arthrit*.mp. (1219)

7 exp Arthritis, Rheumatoid/ (104666)

8 exp Neuralgia/ (17706)

9 Diabetic Neuropathies/ (13601)

10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)

11 neuralg*.mp. (23772)

12 zoster.mp. (19225)

13 Irritable Bowel Syndrome/ (6066)

14 (IBS or irritable colon or irritable bowel).mp. (14347)

15 Migraine Disorders/ (23014)

16 migraine.mp. (34507)

17 Fibromyalgia/ (7573)

18 fibromyalg*.mp. (10324)

19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)

20 (complex regional pain syndromes or causalgia).mp. (2139)

21 Pain, Intractable/ (6021)

22 Phantom Limb/ (1737)

23 Hyperalgesia/ (10026)

24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16519)

25 or/1-24 (374187)

26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)

27 Radiculopathy/ or radiculopathy.mp. (8057)

28 musculoskeletal pain/ or headache/ (27891)

29 exp Arthralgia/ (10991)

30 exp Headache Disorders/ (31166)

31 headache*.mp. (83353)

32 Temporomandibular Joint Dysfunction Syndrome/ (4838)

33 ((TMJ or TMJD) and pain*).mp. (2434)

34 whiplash.mp. or exp whiplash injury/ (3756)

35 exp Cumulative Trauma Disorders/ (12612)

36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)

37 Pain Measurement/de [Drug Effects] (6352)

38 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*

or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)

39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*

or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or

cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)

40 or/26-39 (299548)

41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)

42 40 not 41 (252546)

43 25 or 42 (532409)

44 exp Analgesics, Opioid/ (103616)

45 (opioid* or opiate*).mp. (114059)

46 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or

dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or

ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or

levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine

or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or

promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)

47 or/44-46 (199233)

48 exp Narcotics/ (111500)

49 narcotic*.mp. (57165)

50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo

or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or

dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or

duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or

Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or

isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or

lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms

contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or

oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or

skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or

tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin

or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin

or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, original title, name of

substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9563)

51 or/44-50 (227775)

52 43 and 51 (22678)

53 epidemiologic studies/ (7641)

54 exp Case-Control Studies/ (904344)

55 exp Cohort Studies/ (1723417)

56 Case control.tw. (106622)

57 (cohort adj (study or studies)).tw. (151570)

58 Cohort analy$.tw. (6083)

59 (Follow up adj (study or studies)).tw. (44718)

60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)

61 Longitudinal.tw. (201362)

62 Retrospective.mp. or prospective.tw. (1247587)

63 Cross sectional.tw. (272577)

64 Cross-sectional studies/ (260504)

65 or/53-64 (2717825)

66 exp animals/ not humans.sh. (4438182)

67 65 not 66 (2649950)

68 52 and 67 (3763)

69 randomized controlled trial.pt. (456617)

70 controlled clinical trial.pt. (92277)

71 randomized.ab. (406479)

72 placebo.ab. (187496)

73 drug therapy.fs. (2003496)

74 randomly.ab. (287373)

75 trial.ab. (422125)

76 groups.ab. (1777409)

77 or/69-76 (4167722)

78 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5199787)

79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)

80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)

81 or/78-80 (5214838)

82 77 or 81 (6680171)

83 exp animals/ not humans.sh. (4438182)

84 82 not 83 (5604099)

85 43 and 51 and 84 (14496)

86 limit 85 to yr="2010 -Current" (6438)

87 68 or 86 (8377)

88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (256038)

89 43 and 51 and 88 (881)

90 87 or 89 (8697)

91 exp Sleep Apnea Syndromes/ (30607)

92 sleep apn?ea.mp. (38637)

93 sleep-disordered breathing.mp. (5685)

94 hypogonadism.mp. or Hypogonadism/ (13040)

95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)

96 OPIAD.mp. (10)

97 or/91-96 (64161)

98 52 and 97 (144)

99 90 or 98 (8736)

PsycInfo

Database: PsycINFO via OVID

Search Strategy:

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1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests &

measures] (19944)

2 chronic pain/ (12078)

3 exp arthritis/ (3853)

4 osteoarthrit*.mp. (1758)

5 osteo-arthritis.mp. (8)

6 degenerative arthrit*.mp. (15)

7 exp neuralgia/ (892)

8 exp neuropathy/ (5931)

9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)

10 neuralg*.mp. (1530)

11 zoster.mp. (550)

12 irritable bowel syndrome/ (1055)

13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key

concepts, original title, tests & measures] (1832)

14 migraine headache/ (8772)

15 migraine.mp. (11715)

16 fibromyalgia/ (1768)

17 fibromyalg*.mp. (3042)

18 complex regional pain syndromes.mp. (55)

19 "complex regional pain syndrome (type i)"/ (137)

20 (complex regional pain syndromes or causalgia).mp. (109)

21 somatosensory disorders/ (1266)

22 hyperalgesi*.mp. (3914)

23 somatoform pain disorder/ (801)

24 somatoform disorders/ (7528)

25 conversion disorder/ (998)

26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)

27 or/1-26 (58879)

28 back pain.mp. or exp Back Pain/ (5353)

29 radiculopathy.mp. (202)

30 musculoskeletal pain.mp. (1410)

31 Arthralgia.mp. (105)

32 headache.mp. or exp HEADACHE/ (19164)

33 ((TMJ or TMJD) and pain*).mp. (142)

34 WHIPLASH/ or whiplash.mp. (571)

35 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*

or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5452)

36 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*

or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or

cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)

37 or/28-36 (39808)

38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)

39 37 not 38 (35095)

40 27 or 39 (71492)

41 exp opiates/ (22978)

42 (opioid* or opiate*).mp. (27750)

43 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or

dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or

ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or

levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine

or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or

promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)

44 exp narcotic drugs/ (27031)

45 narcotic*.mp. (5729)

46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo

or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or

dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or

duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or

Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or

isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or

lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms

contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or

oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or

skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or

tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin

or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin

or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (928)

47 or/41-46 (47945)

48 37 and 47 (2028)

49 animals/ not humans/ (7067)

50 animal models/ (29760)

51 animal research/ (368)

52 exp rodents/ (201732)

53 (rat or rats or mouse or mice).ti. (110418)

54 or/49-53 (226624)

55 48 not 54 (1547)

Database: AMED (Allied and Complementary Medicine) via OVID

Search Strategy:

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1 analgesics opioid/ (335)

2 (opioid* or opiate*).mp. (1449)

3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or

dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or

ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or

levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine

or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or

promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words,

title] (1097)

4 narcotics/ (177)

5 narcotic*.mp. (345)

6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo

or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or

dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or

duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or

Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or

isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or

lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms

contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or

oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or

skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or

tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin

or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin

or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=abstract, heading words, title] (109)

7 or/1-6 (2268)

8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)

9 exp arthritis/ (5636)

10 arthralgia/ (189)

11 fibromyalgia/ (1656)

12 neuralgia/ (157)

13 diabetic neuropathies/ (264)

14 (neuropath* adj5 (pain* or diabet*)).mp. (981)

15 neuralg*.mp. [mp=abstract, heading words, title] (335)

16 osteoarthrit*.mp. [mp=abstract, heading words, title] (3321)

17 irritable bowel syndrome/ (133)

18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)

19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)

20 Migraine/ or migraine.mp. (651)

21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)

22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)

23 pain intractable/ (431)

24 hyperalgesia/ or phantom limb/ (181)

25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract,

heading words, title] (675)

26 or/8-25 (15230)

27 exp backache/ (6186)

28 radiculopathy.mp. (290)

29 exp Headache/ or headache.mp. (1709)

30 Temporomandibular joint syndrome/ (67)

31 ((TMJ or TMJD) and pain*).mp. (28)

32 Whiplash injuries/ or whiplash.mp. (594)

33 repetition strain injury/ (312)

34 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi*

or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (2429)

35 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint*

or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or

cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)

36 or/27-35 (17684)

37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)

38 36 not 37 (16319)

39 26 or 38 (25280)

40 7 and 39 (532)

41 (rat or rats or mouse or mice).ti. (5925)

42 animals/ not humans/ (7083)

43 exp Rodents/ (8142)

44 41 or 42 or 43 (10161)

45 40 not 44 (512)

Central (Cochrane Library via Wiley)

Description:

ID Search Hits

#1 chronic near/3 pain 9973

#2 MeSH descriptor: [Chronic Pain] explode all trees 1178

#3 MeSH descriptor: [Osteoarthritis] explode all trees 4754

#4 osteoarthrit* 10561

#5 osteo-arthritis 69

#6 degenerative arthrit* 359

#7 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 4858

#8 MeSH descriptor: [Neuralgia] explode all trees 1049

#9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1397

#10 neuropath* near/5 (pain* or diabet*) 4465

#11 neuralg* 1913

#12 zoster 1641

#13 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees 674

#14 irritable (colon or bowel) 2448

#15 IBS 1629

#16 MeSH descriptor: [Migraine Disorders] explode all trees 1959

#17 migraine 4659

#18 MeSH descriptor: [Fibromyalgia] explode all trees 851

#19 fibromyalg* 1987

#20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238

#21 complex regional pain syndromes or causalgia 203

#22 MeSH descriptor: [Pain, Intractable] explode all trees 273

#23 MeSH descriptor: [Phantom Limb] explode all trees 75

#24 MeSH descriptor: [Hyperalgesia] explode all trees 454

#25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107

#26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797

#27 MeSH descriptor: [Back Pain] explode all trees 3879

#28 MeSH descriptor: [Radiculopathy] explode all trees 303

#29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478

#30 MeSH descriptor: [Arthralgia] explode all trees 1313

#31 MeSH descriptor: [Headache Disorders] explode all trees 2415

#32 MeSH descriptor: [Headache] explode all trees 1798

#33 headache* 26942

#34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179

#35 ((TMJ or TMJD) and pain*) 266

#36 MeSH descriptor: [Whiplash Injuries] explode all trees 208

#37 whiplash 460

#38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668

#39 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or

fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* 13481

#40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or

joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or

cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955

#41 radiculopathy 893

#42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41

60275

#43 acute or emergency or preoperative or postoperative 200646

#44 42 not 43 59058

#45 #26 or #44 97623

#46 opioid* or opiate* 17932

#47 narcotic* 6752

#48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462

#49 MeSH descriptor: [Narcotics] explode all trees 7246

#50 alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or

dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or

ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or

levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine

or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or

promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420

#51 adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or

Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or

dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan

or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora

or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon

or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or

levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or

morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or

oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or

prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or

theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal

or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or

tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram 5622

#52 #46 or #47 or #48 or #49 or #50 or #51 42294

#53 #45 and #52 26

Appendix 3. 2: Characteristics of included studies (N=82)

Author[1-80]	Total # randomized	Pain condition	Age (year)	Sex (female%)	Duration of chronic pain(month)	# of arms	Intervention 1	Intervention 2	Intervention 3
Adler 2002[1]	146	Osteoarthritis	62.55	58.5	NR	2	Tramadol-ER	Tramadol-NR	-
Afilalo(2010)[2]	1030	Osteoarthritis	58.3	60.95	NR	3	Tapentadol-ER	Oxycodone-ER	Placebo
Allan 2001[3]	488	Mixed neuropathic and nociceptive	54.05	61.5	124.75	2	Fentanyl-PATCH	Morphine-ER	-
Allan(2005)	680	Mixed neuropathic and nociceptive	50.5	46.85	9.3	2	Fentanyl-PATCH	Morphine-ER	-
Arai(2015) [£]	150	Mixed neuropathic & non-neuropathic conditions	66	67	NR	2	Fentanyl-PATCH	-	Placebo
Arai(2015)	163	Mixed neuropathic	66	49	NR	2	Fentanyl-PATCH	-	Placebo
Babul(2004)	246	Osteoarthritis	61	61	154	2	Tramadol-ER	-	Placebo
Beaulieu 2007	154	Osteoarthritis	57.5	57	NR	2	Tramadol-ER	Tramadol-NR	-
Binsfeld(2010)	504	Mixed neuropathic & non-neuropathic conditions	57.5	58.3	NR	2	Hydromorphone-ER	Oxycodone-ER	-
Boureau(2003)	127	Postherpetic neuralgia	65.7	62.3	6.7	2	Tramadol-ER	-	Placebo
Breivik(2010)	199	Osteoarthritis	50	58	NR	2	Buprenorphine-PATCH	-	Placebo
Burch(2007)	646	Osteoarthritis	62	63	NR	2	Tramadol-ER	-	Placebo
Buynak(2010)	981	Low back pain	49.7	58	NR	3	Tapentadol-ER;	Oxycodone-ER	Placebo

Caldwell(2002)	295	Osteoarthritis	61	62.3	NR	4	Morphine-ER	-	Placebo
Caldwell(1999)	70	Osteoarthritis	57	53	NR	3	Oxycodone-ER	-	Placebo
Christoph(2017)	252	neuropathic & non-neuropathic conditions		62	NR	5	Tapentadol-ER	-	Placebo
Chu(2012)	139	Low back pain	45	44	NR	2	Morphine-ER	-	Placebo
DeLemos(2011)	808	Osteoarthritis	60	100	96.7	2	Tramadol-ER	-	Placebo
Fishman(2007)	552	Osteoarthritis	61	62	NR	4	Tramadol-ER	-	Placebo
Fleischmann(2001)	129	Osteoarthritis	62	62	364	2	Tramadol-NR	-	Placebo
Friedmann(2011)	412	Osteoarthritis	58	70	NR	2	Oxycodone-ER	-	Placebo
Gana(2006)	1020	Osteoarthritis	58	62	NR	5	Tramadol-ER	-	Placebo
Gimbel(2003)	159	Painful diabetic neuropathy			54.5	2	Oxycodone-ER	-	Placebo
Gilron(2005)	57	Postherpetic neuralgia & painful diabetic neuropathy	50	56	NR	2	Morphine-ER	-	Placebo
Gimbel(2016)	511	Low back pain	59	48	NR	2	Buprenorphine-Buccal	-	Placebo
Gordon(2010)	78	Low back pain	54	47	NR	2	Buprenorphine-PATCH	-	Placebo
Gordon(2010)	79	Mixed neuropathic & non-neuropathic conditions	50	60	170	2	Buprenorphine-PATCH	-	Placebo

Hale(2007-a)[30]	143	Low back pain	56.2	55.3	NR	2	Oxymorphone-ER	-	Placebo
Hale(2007-b)[28]	140	Moderate or severe osteoarthritis	47	45	NR	2	Hydromorph-ER	Oxycodone-ER	-
Hale(2010)	268	Low back pain	48	50	NR	2	Hydromorphone-ER	-	Placebo
Hale(2015)	370	Low back pain	51	51	NR	2	Hydrocodone-ER	-	Placebo
Hale(2009)	878	Low back pain or osteoarthritis	63.5	68.5	NR	2	Tapentadol-NR	Oxycodone-NR	-
Harati(1998)	131	Painful diabetic neuropathy	59	40	NR	2	Tramadol-NR	-	Placebo
Huse(2001)	12	Phantom limb pain	50.6	17	NR	2	Morphine-ER	-	Placebo
James(2010)	238	Osteoarthritis	64.35	63.5	NR	2	Buprenorphine-PATCH	Buprenorphine-Buccal	-
Karlsson(2009)	135	moderate to severe osteoarthritis	64.3	59.2	NR	2	Buprenorphine-PATCH	Tramadol-ER	-
Katz(2007)	205	Low back pain	49	53	NR	2	Oxymorphone-ER	-	Placebo
Katz(2015)	389	Low back pain	49	53	NR	2	Oxycodone-ER	-	Placebo
Khoromi(2007)	55	Lumbar radiculopathy			NR	2	Morphine-ER	-	Placebo
Kawamata 2019	130	Low back pain	53	45	NR	2	Oxycodone-ER	-	Placebo
Langford(2006)	399	Osteoarthritis	63	67	NR	2	Fentanyl-PATCH	-	Placebo
Leng(2015)	280	Mixed neuropathic & non-neuropathic conditions	56.95	67.65	207.5	2	Buprenorphine-PATCH	Tramadol-ER	-

Lin(2016)	21	Low back pain	41.9	33	97.2	2	Morphine-ER	-	Placebo
Ma(2008)	116	Chronic neck pain	55.7	38	NR	2	Oxycodone-ER	-	Placebo
Markenson (2005)	107	Osteoarthritis	63	38.4	NR	2	Oxycodone-ER	-	Placebo
Matsumoto(2005)	491	Osteoarthritis	62.55	61.95	NR	4	Oxymorphone-ER	Oxycodone-ER	Placebo
Mayorga(2016)	98	Osteoarthritis	59	56	NR	4	Oxycodone-ER	-	Placebo
Mitra(2013)	46	Chronic non-cancer pain	49	52	120	2	Fentanyl-PATCH	Buprenorphine-PATCH	-
Moran (1991)	15	Osteoarthritis		5	NR	2	Morphine-ER	-	Placebo
Moulin(1996)	61	Chronic post- traumatic pain	40	59	40.8	2	Morphine-ER	-	Placebo
Munera(2010)	315	Osteoarthritis	61	67	NR	2	Buprenorphine-PATCH	-	Placebo
Nicholson(2006)	112	Osteoarthritis	51.15	51.75	NR	2	Morphine-ER	Oxycodone-ER	-
Niesters(2014)	25	Painful diabetic neuropathy	63	41.6	NR	2	Tapentadol-ER	-	Placebo
Norrbrink(2009)	36	Post-traumatic neuralgia	51	78	NR	2	Tramadol-NR	-	Placebo
Peloso(2000)	103	Osteoarthritis	61.6	40	NR	2	Codeine-ER	-	Placebo
Raja(2002)	76	Postherpetic neuralgia			NR	2	Morphine-ER	-	Placebo

Rauck(2006)	392	Low back pain	50	49	NR	2	Morphine-ER	Oxycodone-ER	-
Rauck(2013)	990	Osteoarthritis	50	56	NR	3	Hydromorphone-ER	-	Placebo
Rauck(2014)	302	Low back pain	50	63	NR	2	Hydrocodone-ER	-	Placebo
Rauck(2016)	420	Low back pain	59	64	NR	2	Buprenorphine-Buccal	-	Placebo
Russell(2000)	69	Fibromyalgia	48.8	94	NR	2	Tramadol-ER	-	Placebo
Schnitzer(2000)	254	Low back pain	47.1	50	NR	2	Tramadol-NR	-	Placebo
Schwartz(2011)	395	Painful diabetic neuropathy	62	43	76	2	Tapentadol-ER	-	Placebo
Serrie(2017)	990	Osteoarthritis	62.1	69.3	NR	3	Tapentadol-ER	Oxycodone-ER	Placebo
Simpson(2016)	186	Diabetic neuropathy	62.9	33	NR	2	Buprenorphine-PATCH	-	Placebo
Sindrup 1999		Painful diabetic neuropathy	57	24	36		Tramadol-ER	-	Placebo
Sindrup(2012)	64	Painful polyneuropathy			NR	3	Tramadol-ER	-	Placebo
Steiner(2011a)[68]	541	Low back pain	49	55	108.6	2	Buprenorphine- PATCH	-	Placebo
Steiner(2011b)[67]	662	Low back pain	49.85	46.8	108	2	Buprenorphine-PATCH	Oxycodone-NR	-

Thorne(2008)	100	Osteoarthritis	61	55	NR	2	Tramadol-ER	-	Placebo
Tominaga(2016)[£]	91	neuropathic & non-neuropathic conditions			NR	2	Tapentadol-ER	-	Placebo
Tominaga(2016)	91	Postherpetic neuralgia & painful diabetic neuropathy			NR	2	Tapentadol-ER	-	Placebo
Uberall (2012)	240	Low back pain			NR	2	Tramadol-ER	-	Placebo
Ueberall (2015)	309	Low back pain	46.35	88.5	NR	2	Morphine-ER	Oxycodone-ER	-
Vinik (2014)	320	Painful diabetic neuropathy	58	41	NR	2	Tapentadol-ER	-	Placebo
Vojtassak (2011)	288	Osteoarthritis	65.5	72	NR	2	Hydromorphone-ER	-	Placebo
Vorsanger(2008)	386	Low back pain	47	50	NR	3	Tramadol-ER	-	Placebo
Watson(1998)	50	Postherpetic neuralgia	70	44	31	2	Oxycodone-ER	-	placebo
Webster(2006)	307	Low back pain	47.9	61.2	NR	4	Oxycodone-ER	-	Placebo
Wen(2015)	588	Low back pain	48	57	NR	2	Hydrocodone	-	Placebo
Wild(2010)	1117	Low back pain or osteoarthritis	57.45	56.85	NR	2	Tapentadol-ER	Oxycodone-ER	-
Wu(2008)	60	postamputation pain of 6 months or longer	63	21	51.3	2	Morphine-ER	-	Placebo

Appendix 3. 3: Risk of Bias of Included Studies (N=82)

Study	Sequence generation	Allocation concealment	Blinding of patients to the intervention	Blinding of healthcare providers to the intervention	Blinding of data collectors	Blinding of outcome assessors/ adjudicators	Missing outcome data	Missing %	Funding
Adler 2002	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	D highrisk	48	Industry
Afilalo 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	51	Industry
Allan 2001	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	23	Industry
Allan 2005	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	50	Industry
Arai 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	54	Industry
Arai-a 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	49	Industry
Babul 2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	49	Industry
Beaulieu 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	29	Industry
Binsfeld 2010	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	55	Industry
Boureau 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P lowrisk	15	Not-reported
Breivik 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	44.2	Industry
Burch 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	24	Not-reported
Buynak 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	53.4	Industry

Caldwell 1999	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	33.6	Industry
Caldwell 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	37.6	Not-reported
Christoph 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	29.8	Industry
Chu 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	26	No-industry
DeLemos 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	48	Industry
Fishman 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	43.7	Industry
Fleischmann 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	71.3	Industry
Friedmann 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	36.2	Industry
Gana 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	45.3	Industry
Gilron 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P lowrisk	10	Industry
Gimbel 2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	27.7	Industry
Gimbel 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	30.9	Industry
Gordon-a 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	35.4	Industry
Gordon-b 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	37.2	Industry
Hale-a 2007	Low risk	High risk	High risk	High risk	High risk	High risk	D highrisk	39	Industry
Hale 2009	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	D highrisk	45	Industry

Hale-b 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	53	Industry
Hale 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P highrisk	19	Industry
Hale 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	59	Industry
Harati 1998	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	37	Industry
Huse 2001	Low risk	High risk	High risk	High risk	High risk	High risk	P highrisk	16	Industry
James 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	57	Industry
Karlsson 2009	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	26	Industry
Katz 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	42	Industry
Katz 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	42	Industry
Kawamata 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	36	Industry
Khoromi 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P highrisk	16	No-industry
Langford 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	52	Industry
Leng 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	26	Industry
Lin 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	0	No-industry
Ma 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	89	No-industry
Markenson 2005	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	D highrisk	66	Industry

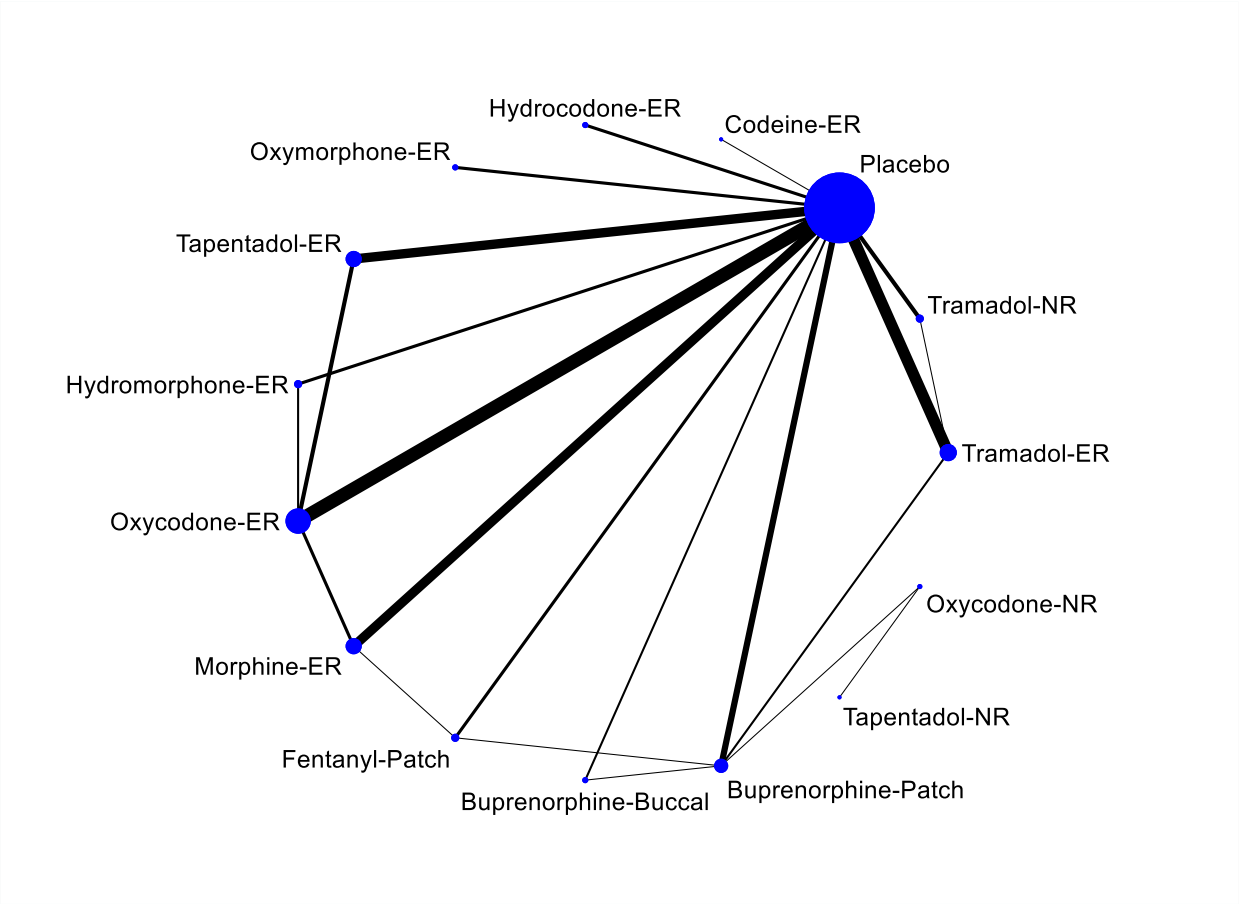
Matsumoto 2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	45	Industry
Mayorga 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	61	Industry
Mitra 2013	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	35	Industry
Moran 1991	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	80	Industry
Moulin 1996	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	24	Industry
Munera 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	50	Industry
Nicholson 2006	Low risk	High risk	High risk	High risk	High risk	High risk	D highrisk	63	Industry
Niesters 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	0	Industry
Norrbrink 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	36	No-industry
Peloso 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	35	Not-reported
Raja 2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	42	No-industry
Rauck 2006	Low risk	High risk	High risk	High risk	High risk	High risk	D highrisk	44	Industry
Rauck 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	9	Industry
Rauck 2013	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	D highrisk	51	Industry
Rauck 2014	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	D highrisk	39	Industry
Russell 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	1.4	Industry

Schnitzer 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	42	Industry
Schwartz 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	33	Industry
Serrie 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	46	Industry
Simpson 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	32	Industry
Sindrup 1999	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P highrisk	20	Industry
Sindrup 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	8.3	Industry
Steiner-a 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	34	Industry
Steiner-b 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	31	Industry
Thorne 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	25	Industry
Tominaga -a 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	P lowrisk	13	Industry
Tominaga -b 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D lowrisk	8	Industry
Uberall 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	24	Industry
Ueberall 2015	Low risk	High risk	High risk	High risk	High risk	High risk	D highrisk	37	No-industry
Vinik 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	29	Industry
Vojtassak 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	30	Industry
Vorsanger 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	37	Industry

Watson 1998	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	22	Industry
Webster 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	54	Not-reported
Wen 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	25	Industry
Wild 2010	Low risk	Low risk	High risk	High risk	High risk	High risk	D highrisk	56	Industry
Wu 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	D highrisk	41	Industry

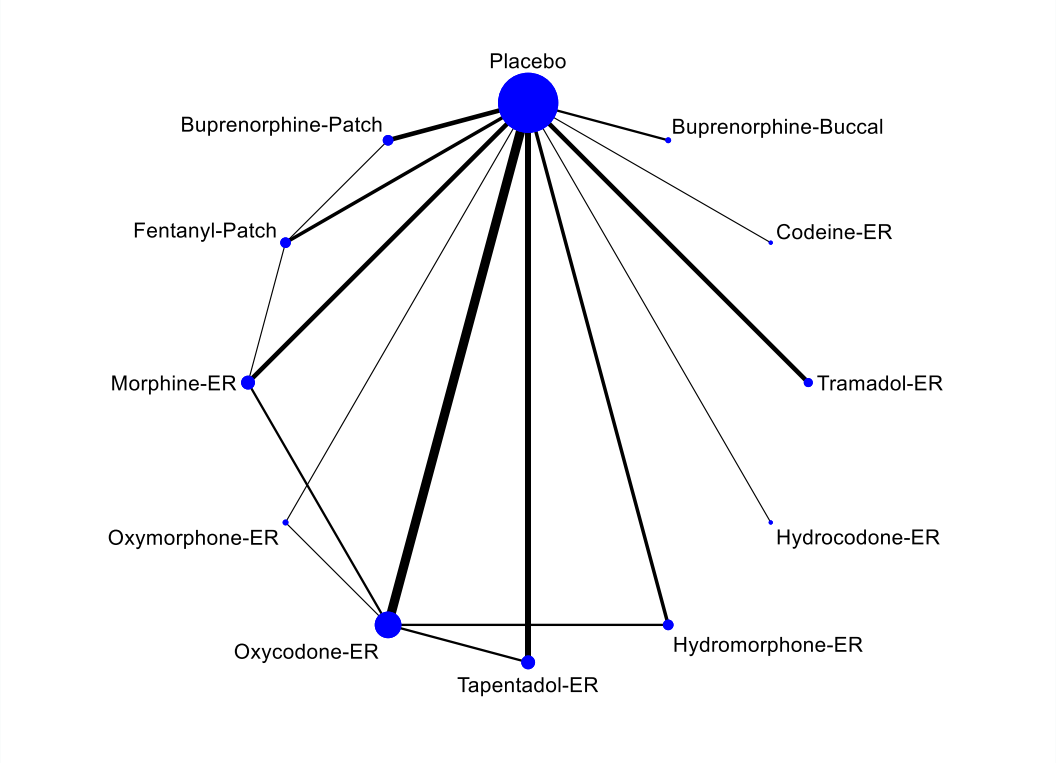
D=definitely, P=probably

Appendix 3. 4: Network map for pain relief



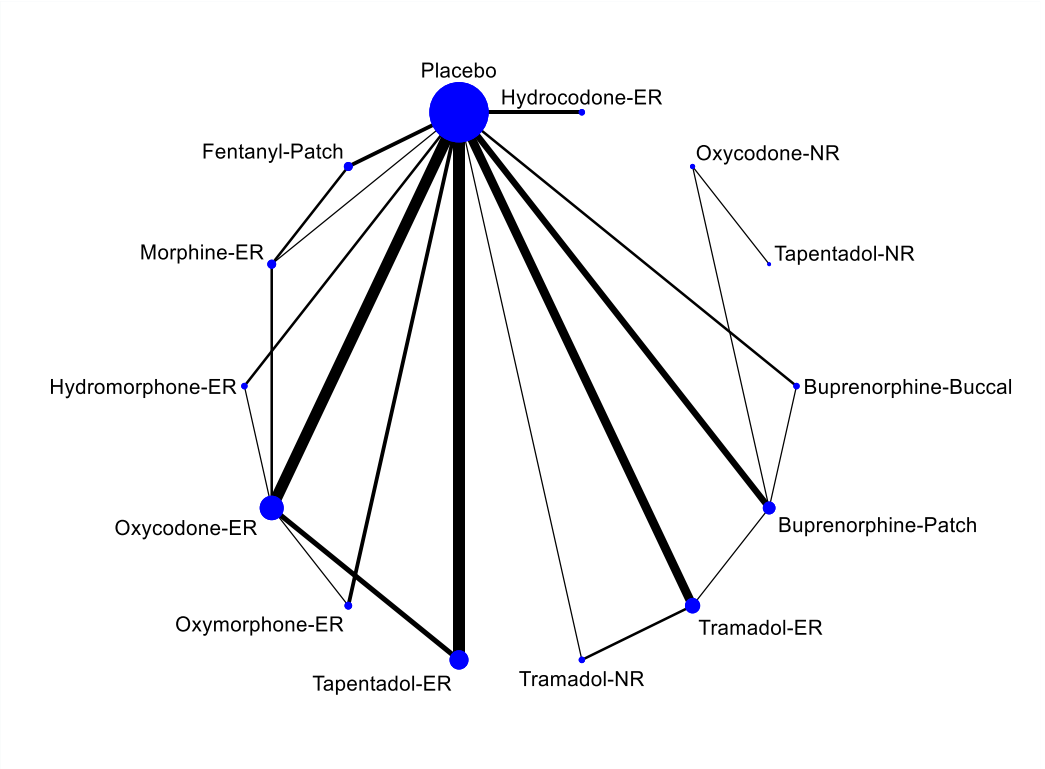
The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Appendix 3. 5: Network map for physical function



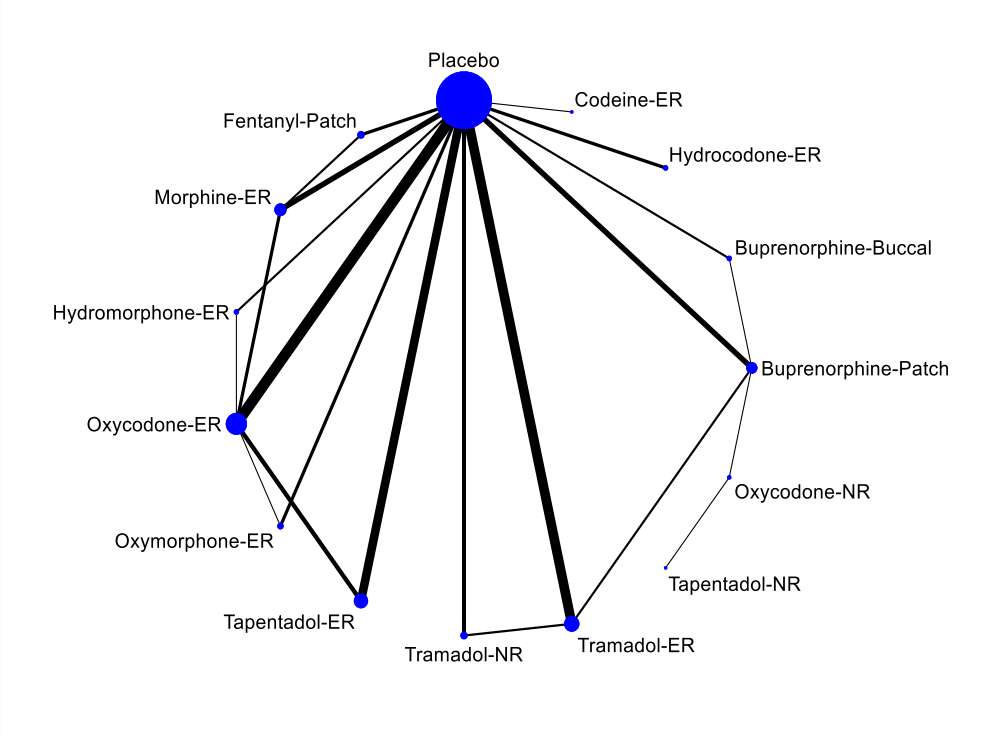
39 studies totally included with 12 nodes and 17 direct comparisons. The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Appendix 3. 6: Network map for vomiting



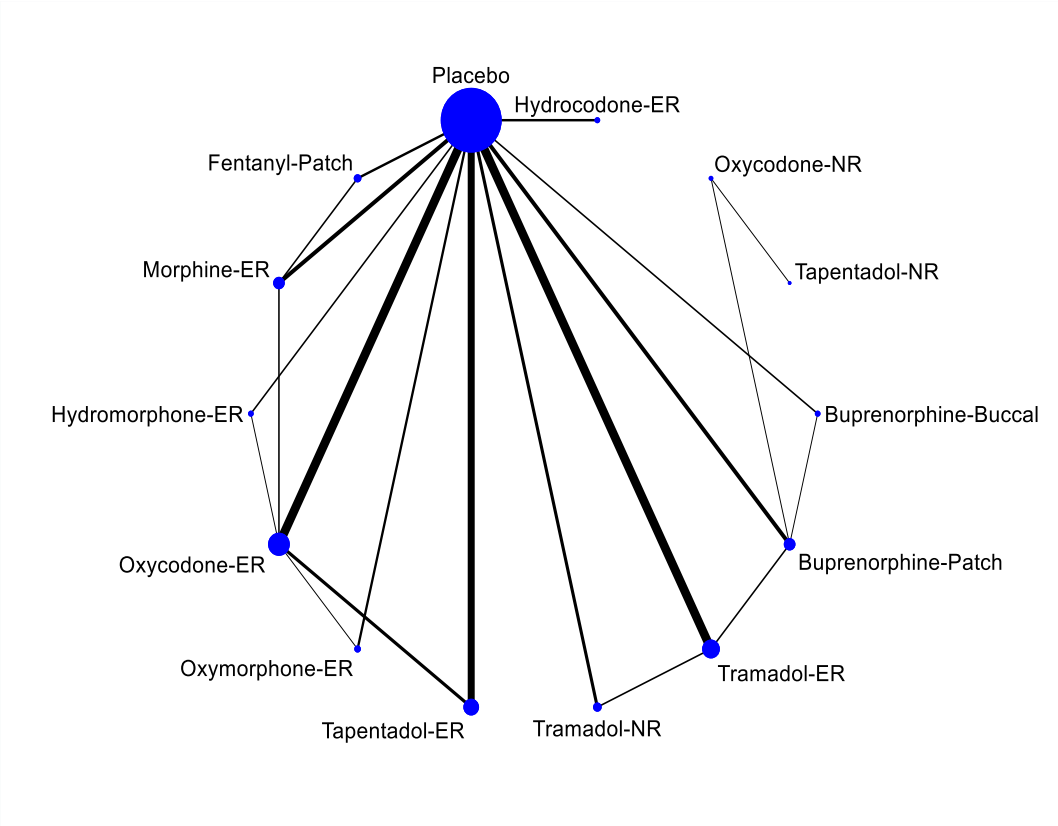
53 studies totally included with 13 opioids and 21 direct comparisons. The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Appendix 3. 7: Network map for constipation



The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Appendix 3. 8: Network map for nausea



The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Appendix 3. 9: Direct, indirect, and NMA estimates for pain relief (on a 0-10 cm VAS) with the GRADE certainty of evidence

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
BUP-Buccal vs	Placebo	-0.87 (-1.11 to -0.63)	2	59	930	M	-0.92 (-2.09 to 0.24)	L	-0.86 (-1.35 to -0.38)	M*	ROB, intransitivity, imprecision
BUP-PATCH vs	Placebo	-0.61 (-0.78 to -0.45)	6	0	1471	L	-0.8 (-1.35 to -0.25)	M	-0.71 (-1 to -0.41)	L*	ROB, imprecision
COD-ER vs	Placebo	-2.03 (-3.09 to -0.97)	1	NA	66	M	NA	NA	-2.03 (-3.28 to -0.78)	L	ROB, imprecision[1]
FEN-PATCH vs	Placebo	-0.73 (-1.06 to -0.39)	3	0	712	M	-0.83 (-1.47 to -0.19)	L	-0.78 (-1.18 to -0.39)	L	ROB, intransitivity, imprecision
HMOR-ER vs	Placebo	-0.41 (-1.1 to 0.27)	3	90	1521	L	-0.64 (-1.29 to 0)	L	-0.52 (-0.88 to -0.16)	VL	ROB, heterogeneit, imprecision
HYD-ER vs	Placebo	-0.53 (-0.74 to -0.32)	3	0	1260	M	NA	NA	-0.53 (-0.97 to -0.09)	L	ROB, imprecision
MPH-ER vs	Placebo	-0.93 (-1.23 to -0.62)	9	0	880	M	-0.75 (-1.25 to -0.25)	M	-0.86 (-1.17 to -0.56)	M	ROB
OMOR-ER vs	Placebo	-1.51 (-2.3 to -0.72)	3	73	619	L	NA	NA	-1.47 (-2.03 to -0.91)	L	ROB, heterogeneity
OXY-ER vs	Placebo	-0.76 (-1.18 to -0.35)	13	85	3579	L	-0.6 (-1.03 to -0.16)	M	-0.66 (-0.89 to -0.44)	L	ROB, heterogeneity, imprecision[2]
TPN-ER vs	Placebo	-0.73 (-1.02 to -0.43)	9	62	3085	M	-1.2 (-1.9 to -0.49)	L	-0.81 (-1.08 to -0.53)	M	ROB
TPN-NR vs	Placebo	NA	NA	NA	NA	NA	-1.09 (-2.22 to 0.04)	M	-1.09 (-2.22 to 0.04)	L	ROB, imprecision

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
TRA-ER vs	Placebo	-0.74 (-0.94 to -0.54)	11	37	4202	M	-0.93 (-1.56 to -0.3)	L	-0.80 (-1.05 to -0.55)	M	ROB
TRA-NR vs	Placebo	-1.13 (-1.76 to -0.5)	4	66	545	M	-0.97 (-2.03 to 0.1)	L	-1.09 (-1.54 to -0.65)	M	ROB, heterogeneit, intransitivity
OXY-NR vs	Placebo	NA	NA	NA	NA	NA	-0.99 (-1.81 to -0.17)	M	-0.99 (-1.81 to -0.17)	L	ROB, imprecision
BUP-PATCH vs	BUP-Buccal	0.21 (-0.65 to 1.07)	1	NA	102	M	0.13 (-0.51 to 0.78)	L	0.16 (-0.38 to 0.69)	L	ROB, imprecision
COD-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	-1.17 (-2.51 to 0.18)	L	-1.17 (-2.51 to 0.18)	VL	ROB, intransitivity, imprecision
FEN-PATCH vs	BUP-Buccal	NA	NA	NA	NA	NA	0.08 (-0.54 to 0.7)	M	0.08 (-0.54 to 0.7)	L	ROB, imprecision
HMOR-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0.35 (-0.25 to 0.95)	L	0.35 (-0.25 to 0.95)	VL	ROB, imprecision
HYD-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0.33 (-0.32 to 0.98)	M	0.33 (-0.32 to 0.98)	L	ROB, imprecision
MPH-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0 (-0.57 to 0.57)	L	0 (-0.57 to 0.57)	VL	ROB, intransitivity, imprecision
OMOR-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	-0.6 (-1.34 to 0.13)	L	-0.6 (-1.34 to 0.13)	VL	ROB, imprecision
OXY-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0.2 (-0.33 to 0.73)	L	0.2 (-0.33 to 0.73)	VL	ROB, imprecision
TPN-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0.06 (-0.5 to 0.61)	M	0.06 (-0.5 to 0.61)	L	ROB, imprecision

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
TPN-NR vs	BUP-Buccal	NA	NA	NA	NA	NA	-0.22 (-1.44 to 0.99)	L	-0.22 (-1.44 to 0.99)	VL	ROB, intransitivity, imprecision
TRA-ER vs	BUP-Buccal	NA	NA	NA	NA	NA	0.06 (-0.47 to 0.6)	M	0.06 (-0.47 to 0.6)	L	ROB, imprecision
TRA-NR vs	BUP-Buccal	NA	NA	NA	NA	NA	-0.23 (-0.88 to 0.43)	VL	-0.23 (-0.88 to 0.43)	VL	ROB, intransitivity, imprecision
OXY-NR vs	BUP-Buccal	NA	NA	NA	NA	NA	-0.12 (-1.05 to 0.81)	L	-0.12 (-1.05 to 0.81)	VL	ROB, intransitivity, imprecision
COD-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	-1.32 (-2.61 to -0.03)	L	-1.32 (-2.61 to -0.03)	VL	ROB, intransitivity, imprecision
FEN-PATCH vs	BUP-PATCH	0.53 (-0.22 to 1.28)	1	NA	46	M	-0.24 (-0.78 to 0.3)	L	-0.08 (-0.54 to 0.39)	L	ROB, imprecision[1]
HMOR-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	0.19 (-0.27 to 0.66)	L	0.19 (-0.27 to 0.66)	VL	ROB, imprecision
HYD-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	0.18 (-0.35 to 0.71)	L	0.18 (-0.35 to 0.71)	VL	ROB, imprecision
MPH-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	-0.15 (-0.57 to 0.27)	L	-0.15 (-0.57 to 0.27)	L	ROB, intransitivity
OMOR-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	-0.76 (-1.39 to -0.13)	L	-0.76 (-1.39 to -0.13)	VL	ROB, imprecision
OXY-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	0.05 (-0.32 to 0.41)	L	0.05 (-0.32 to 0.41)	VL	ROB, imprecision
TPN-ER vs	BUP-PATCH	NA	NA	NA	NA	NA	-0.1 (-0.5 to 0.31)	L	-0.1 (-0.5 to 0.31)	VL	ROB, imprecision

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
TPN-NR vs	BUP-PATCH	NA	NA	NA	NA	NA	-0.38 (-1.47 to 0.71)	L	-0.38 (-1.47 to 0.71)	VL	ROB, imprecision
TRA-ER vs	BUP-PATCH	-0.23 (-0.65 to 0.19)	2	46	400	L	-0.06 (-0.49 to 0.38)	L	-0.09 (-0.44 to 0.26)	L	ROB¥
TRA-NR vs	BUP-PATCH	NA	NA	NA	NA	NA	-0.38 (-0.91 to 0.15)	L	-0.38 (-0.91 to 0.15)	VL	ROB, imprecision
OXY-NR vs	BUP-PATCH	-0.28 (-0.64 to 0.08)	1	NA	423	M	NA	NA	-0.28 (-1.04 to 0.48)	L	ROB, imprecision
FEN-PATCH vs	COD-ER	NA	NA	NA	NA	NA	1.25 (-0.07 to 2.56)	M	1.25 (-0.07 to 2.56)	L	ROB, imprecision
HMOR-ER vs	COD-ER	NA	NA	NA	NA	NA	1.51 (0.21 to 2.82)	VL	1.51 (0.21 to 2.82)	VL	ROB, intransitivity, imprecision
HYD-ER vs	COD-ER	NA	NA	NA	NA	NA	1.5 (0.17 to 2.83)	L	1.5 (0.17 to 2.83)	VL	ROB, intransitivity, imprecision
MPH-ER vs	COD-ER	NA	NA	NA	NA	NA	1.17 (-0.12 to 2.46)	M	1.17 (-0.12 to 2.46)	L	ROB, imprecision
OMOR-ER vs	COD-ER	NA	NA	NA	NA	NA	0.56 (-0.81 to 1.93)	VL	0.56 (-0.81 to 1.93)	VL	ROB, intransitivity, imprecision
OXY-ER vs	COD-ER	NA	NA	NA	NA	NA	1.37 (0.09 to 2.64)	VL	1.37 (0.09 to 2.64)	VL	ROB, intransitivity, imprecision
TPN-ER vs	COD-ER	NA	NA	NA	NA	NA	1.22 (-0.06 to 2.51)	L	1.22 (-0.06 to 2.51)	VL	ROB, intransitivity, imprecision
TPN-NR vs	COD-ER	NA	NA	NA	NA	NA	0.94 (-0.75 to 2.63)	L	0.94 (-0.75 to 2.63)	VL	ROB, intransitivity, imprecision

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
TRA-ER vs	COD-ER	NA	NA	NA	NA	NA	1.23 (-0.05 to 2.51)	L	1.23 (-0.05 to 2.51)	VL	ROB, intransitivity, imprecision
TRA-NR vs	COD-ER	NA	NA	NA	NA	NA	0.94 (-0.39 to 2.27)	L	0.94 (-0.39 to 2.27)	VL	ROB, imprecision
OXY-NR vs	COD-ER	NA	NA	NA	NA	NA	1.04 (-0.46 to 2.54)	L	1.04 (-0.46 to 2.54)	VL	ROB, intransitivity, imprecision
HMOR-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	0.27 (-0.26 to 0.8)	L	0.27 (-0.26 to 0.8)	VL	ROB, imprecision
HYD-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	0.25 (-0.34 to 0.84)	M	0.25 (-0.34 to 0.84)	L	ROB, imprecision
MPH-ER vs	FEN-PATCH	0.26 (0.24 to 0.28)	1	NA	553	M	-0.32 (-0.9 to 0.26)	M	-0.08 (-0.51 to 0.36)	L	ROB, imprecision
OMOR-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	-0.68 (-1.37 to 0)	L	-0.68 (-1.37 to 0)	VL	ROB, imprecision
OXY-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	0.12 (-0.32 to 0.56)	L	0.12 (-0.32 to 0.56)	VL	ROB, imprecision
TPN-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	-0.02 (-0.5 to 0.46)	M	-0.02 (-0.5 to 0.46)	L	ROB, imprecision
TPN-NR vs	FEN-PATCH	NA	NA	NA	NA	NA	-0.3 (-1.49 to 0.88)	M	-0.3 (-1.49 to 0.88)	L	ROB, imprecision
TRA-ER vs	FEN-PATCH	NA	NA	NA	NA	NA	-0.02 (-0.50 to 0.45)	M	-0.02 (-0.50 to 0.45)	L	ROB, imprecision
TRA-NR vs	FEN-PATCH	NA	NA	NA	NA	NA	-0.31 (-0.9 to 0.29)	L	-0.31 (-0.9 to 0.29)	VL	ROB, imprecision

Comparison	Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
OXY-NR vs FEN-PATCH	NA	NA	NA	NA	NA	-0.2 (-1.1 to 0.69)	M	-0.2 (-1.1 to 0.69)	L	ROB, imprecision
HYD-ER vs HMOR-ER	NA	NA	NA	NA	NA	-0.02 (-0.59 to 0.55)	L	-0.02 (-0.59 to 0.55)	VL	ROB, imprecision
MPH-ER vs HMOR-ER	NA	NA	NA	NA	NA	-0.34 (-0.8 to 0.12)	VL	-0.34 (-0.8 to 0.12)	VL	ROB, intransitivity, imprecision
OMOR-ER vs HMOR-ER	NA	NA	NA	NA	NA	-0.95 (-1.62 to -0.29)	L	-0.95 (-1.62 to -0.29)	VL	ROB
OXY-ER vs HMOR-ER	-0.01 (-0.31 to 0.28)	2	0	341	M	-0.24 (-0.78 to 0.29)	L	-0.15 (-0.52 to 0.23)	L	ROB, imprecision
TPN-ER vs HMOR-ER	NA	NA	NA	NA	NA	-0.29 (-0.73 to 0.15)	L	-0.29 (-0.73 to 0.15)	VL	ROB, imprecision
TPN-NR vs HMOR-ER	NA	NA	NA	NA	NA	-0.57 (-1.76 to 0.61)	L	-0.57 (-1.76 to 0.61)	VL	ROB, imprecision
TRA-ER vs HMOR-ER	NA	NA	NA	NA	NA	-0.28 (-0.72 to 0.15)	L	-0.28 (-0.72 to 0.15)	VL	ROB, imprecision
TRA-NR vs HMOR-ER	NA	NA	NA	NA	NA	-0.57 (-1.15 to 0)	VL	-0.57 (-1.15 to 0)	VL	ROB, intransitivity, imprecision
OXY-NR vs HMOR-ER	NA	NA	NA	NA	NA	-0.47 (-1.36 to 0.42)	L	-0.47 (-1.36 to 0.42)	VL	ROB, imprecision
MPH-ER vs HYD-ER	NA	NA	NA	NA	NA	-0.33 (-0.86 to 0.21)	L	-0.33 (-0.86 to 0.21)	VL	ROB, intransitivity, imprecision
OMOR-ER vs HYD-ER	NA	NA	NA	NA	NA	-0.94 (-1.65 to -0.22)	L	-0.94 (-1.65 to -0.22)	VL	ROB, imprecision

Comparison	Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
OXY-ER vs HYD-ER	NA	NA	NA	NA	NA	-0.13 (-0.62 to 0.36)	L	-0.13 (-0.62 to 0.36)	VL	ROB, imprecision
TPN-ER vs HYD-ER	NA	NA	NA	NA	NA	-0.27 (-0.79 to 0.25)	M	-0.27 (-0.79 to 0.25)	L	ROB, imprecision
TPN-NR vs HYD-ER	NA	NA	NA	NA	NA	-0.56 (-1.77 to 0.65)	M	-0.56 (-1.77 to 0.65)	L	ROB, imprecision
TRA-ER vs HYD-ER	NA	NA	NA	NA	NA	-0.27 (-0.77 to 0.24)	M	-0.27 (-0.77 to 0.24)	L	ROB, imprecision
TRA-NR vs HYD-ER	NA	NA	NA	NA	NA	-0.56 (-1.18 to 0.07)	VL	-0.56 (-1.18 to 0.07)	VL	ROB, intransitivity, imprecision
OXY-NR vs HYD-ER	NA	NA	NA	NA	NA	-0.46 (-1.38 to 0.47)	M	-0.46 (-1.38 to 0.47)	L	ROB, imprecision
OMOR-ER vs MPH-ER	NA	NA	NA	NA	NA	-0.61 (-1.25 to 0.03)	VL	-0.61 (-1.25 to 0.03)	VL	ROB, intransitivity, imprecision
OXY-ER vs MPH-ER	0.23 (-0.12 to 0.58)	3	0	672	M	0.15 (-0.29 to 0.59)	VL	0.2 (-0.14 to 0.53)	L	ROB, intransitivity
TPN-ER vs MPH-ER	NA	NA	NA	NA	NA	0.05 (-0.34 to 0.45)	L	0.05 (-0.34 to 0.45)	L	ROB, intransitivity
TPN-NR vs MPH-ER	NA	NA	NA	NA	NA	-0.23 (-1.39 to 0.94)	L	-0.23 (-1.39 to 0.94)	VL	ROB, intransitivity, imprecision
TRA-ER vs MPH-ER	NA	NA	NA	NA	NA	0.06 (-0.33 to 0.45)	L	0.06 (-0.33 to 0.45)	L	ROB, intransitivity
TRA-NR vs MPH-ER	NA	NA	NA	NA	NA	-0.23 (-0.77 to 0.31)	L	-0.23 (-0.77 to 0.31)	VL	ROB, imprecision

Comparison	Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
OXY-NR vs MPH-ER	NA	NA	NA	NA	NA	-0.13 (-1 to 0.74)	L	-0.13 (-1 to 0.74)	VL	ROB, intransitivity, imprecision
OXY-ER vs OMOR-ER	NA	NA	NA	NA	NA	0.81 (0.2 to 1.41)	L	0.81 (0.2 to 1.41)	VL	ROB, imprecision
TPN-ER vs OMOR-ER	NA	NA	NA	NA	NA	0.66 (0.04 to 1.29)	L	0.66 (0.04 to 1.29)	VL	ROB, imprecision
TPN-NR vs OMOR-ER	NA	NA	NA	NA	NA	0.38 (-0.88 to 1.64)	L	0.38 (-0.88 to 1.64)	VL	ROB, imprecision
TRA-ER vs OMOR-ER	NA	NA	NA	NA	NA	0.67 (0.06 to 1.28)	L	0.67 (0.06 to 1.28)	VL	ROB, imprecision
TRA-NR vs OMOR-ER	NA	NA	NA	NA	NA	0.38 (-0.34 to 1.09)	L	0.38 (-0.34 to 1.09)	VL	ROB, imprecision
OXY-NR vs OMOR-ER	NA	NA	NA	NA	NA	0.48 (-0.51 to 1.47)	L	0.48 (-0.51 to 1.47)	VL	ROB, imprecision
TPN-ER vs OXY-ER	-0.27 (-0.5 to -0.05)	4	40	2462	L	0.04 (-0.47 to 0.54)	L	-0.14 (-0.44 to 0.16)	L	ROB, heterogeneity
TPN-NR vs OXY-ER	NA	NA	NA	NA	NA	-0.43 (-1.57 to 0.72)	L	-0.43 (-1.57 to 0.72)	VL	ROB, imprecision
TRA-ER vs OXY-ER	NA	NA	NA	NA	NA	-0.14 (-0.47 to 0.19)	L	-0.14 (-0.47 to 0.19)	L	ROB
TRA-NR vs OXY-ER	NA	NA	NA	NA	NA	-0.43 (-0.92 to 0.07)	L	-0.43 (-0.92 to 0.07)	VL	ROB, imprecision
OXY-NR vs OXY-ER	NA	NA	NA	NA	NA	-0.33 (-1.17 to 0.52)	L	-0.33 (-1.17 to 0.52)	VL	ROB, imprecision

Comparison	Direct Estimates MD (95%CI)	# of Studies	I^2 %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
TPN-NR vs TPN-ER	NA	NA	NA	NA	NA	-0.28 (-1.44 to 0.88)	M	-0.28 (-1.44 to 0.88)	L	ROB, imprecision
TRA-ER vs TPN-ER	NA	NA	NA	NA	NA	0.01 (-0.36 to 0.38)	L	0.01 (-0.36 to 0.38)	L	ROB
TRA-NR vs TPN-ER	NA	NA	NA	NA	NA	-0.28 (-0.81 to 0.24)	VL	-0.28 (-0.81 to 0.24)	VL	ROB, intransitivity, imprecision
OXY-NR vs TPN-ER	NA	NA	NA	NA	NA	-0.18 (-1.04 to 0.68)	M	-0.18 (-1.04 to 0.68)	L	ROB, imprecision
TRA-ER vs TPN-NR	NA	NA	NA	NA	NA	0.29 (-0.85 to 1.43)	L	0.29 (-0.85 to 1.43)	VL	ROB, intransitivity, imprecision
TRA-NR vs TPN-NR	NA	NA	NA	NA	NA	0 (-1.21 to 1.21)	L	0 (-1.21 to 1.21)	VL	ROB, intransitivity, imprecision
OXY-NR vs TPN-NR	0.1 (-0.29 to 0.49)	1	0	849	M	NA	NA	0.1 (-0.68 to 0.88)	L	ROB, imprecision
TRA-NR vs TRA-ER	-0.17 (-0.91 to 0.57)	1	0	146	M	-0.32 (-0.9 to 0.25)	L	-0.29 (-0.78 to 0.19)	L	ROB, imprecision
OXY-NR vs TRA-ER	NA	NA	NA	NA	NA	-0.19 (-1.03 to 0.65)	L	-0.19 (-1.03 to 0.65)	VL	ROB, intransitivity, imprecision
OXY-NR vs TRA-NR	NA	NA	NA	NA	NA	0.1 (-0.82 to 1.03)	L	0.1 (-0.82 to 1.03)	VL	ROB, intransitivity, imprecision

Footnote: Results are mean difference (95% CIs). Direct estimations are from DerSimonian and Laird random-effects meta-analysis.
Direct estimations rated down if there were risk of bias (ROB), indirectness, publication bias, or heterogeneity.
Indirect estimations rated down if there was intransitivity.
Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the half MID in either side of 95%CI, or because the evidence is provided by a small number of participants- a total number of obseravation less than the optimal information size [≤400]).
Small-study effects were assessed when there were at least 10 studies using Egger test.
H: high certainty of evidence; M: moderate; L: low; VL: very low. MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released.
[1]Rated down on the basis of imprecision since did not meet OIS.
[2]Not rated down twice for heterogenety and imprecision.
[¥]Rated down twice for ROB
*The best estimate is from the direct rather than network because of the inflated 95%CI.

Appendix 3. 10: Direct, indirect, and NMA estimates for physical function (on a 0-100 point Sf-36 physical component score) with the GRADE certainty of evidence.

Comparison		Direct Estimates MD (95%CI)	# of Studies	I^{2} %	# of Patients	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons
BUP-Buccal	Placebo	3.73 (0.7 to 6.76)	2	0	857	M	NA	NA	3.67 (-0.02 to 7.37)	L	ROB, imprecision
BUP-PTCH	Placebo	2.03 (-0.27 to 4.34)	4	0	581	M	2.33 (-7.56 to 12.23)	M	2.16 (-0.6 to 4.92)	L	ROB, imprecision
COD-ER	Placebo	17.76 (7.78 to 27.74)	1	0	66	M	NA	NA	17.76 (7.35 to 28.17)	L	ROB, imprecision[£]
FEN-PTCH	Placebo	1 (-0.27 to 2.29)	3	0	712	M	2.56 (-1.25 to 6.37)	M	1.53 (-0.6 to 3.65)	L	ROB, imprecision
HMOR-ER	Placebo	2.95 (0.53 to 5.36)	3	37	1522	M	4.77 (0.76 to 8.78)	L	3.45 (1.28 to 5.61)	L	ROB, imprecision
HYD-ER	Placebo	-1.13 (-5.28 to 3.02)	1	0	370	M	NA	NA	-1.13 (-6.23 to 3.97)	L	ROB, imprecision
MPH-ER	Placebo	5.37 (1.76 to 8.98)	4	0	568	M	0.45 (-2.19 to 3.08)	M	1.98 (-0.3 to 4.26)	L	ROB, imprecision, incoherence[1]
OMOR-ER	Placebo	2.15 (0.3 to 4)	1	0	447	M	-0.06 (-6.92 to 6.81)	L	1.67 (-1.4 to 4.75)	L	ROB, imprecision
OXY-ER	Placebo	1.03 (-0.2 to 2.28)	8	82	2659	L	1.93 (-0.94 to 4.8)	L	1.21 (0.01 to 2.4)	L	ROB, heterogeneity
TPN-ER	Placebo	1.93 (0.36 to 3.5)	5	88.5	2177	L	4.18 (-0.69 to 9.05)	L	2.13 (0.67 to 3.59)	L	ROB, heterogeneity, imprecision[2]
TRA-ER	Placebo	2.09 (-0.3 to 4.49)	4	74.5	2438	L	NA	NA	1.81 (-0.32 to 3.95)	L	ROB, heterogeneity, imprecision[2]
BUP-PTCH	BUP-Buccal	NA	NA	NA	NA	NA	-1.51 (-6.12 to 3.09)	L	-1.51 (-6.12 to 3.09)	VL	ROB, intransitivity imprecision
COD-ER	BUP-Buccal	NA	NA	NA	NA	NA	14.09 (3.04 to 25.13)	L	14.09 (3.04 to 25.13)	L	ROB, intransitivity

FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	NA	-2.15 (-6.41 to 2.11)	L	-2.15 (-6.41 to 2.11)	VL	ROB, intransitivity imprecision
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	-0.23 (-4.51 to 4.05)	L	-0.23 (-4.51 to 4.05)	VL	ROB, intransitivity imprecision
HYD-ER	BUP-Buccal	NA	NA	NA	NA	NA	-4.8 (-11.1 to 1.49)	L	-4.8 (-11.1 to 1.49)	VL	ROB, intransitivity imprecision
MPH-ER	BUP-Buccal	NA	NA	NA	NA	NA	-1.7 (-6.04 to 2.65)	L	-1.7 (-6.04 to 2.65)	VL	ROB, intransitivity imprecision
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	-2 (-6.81 to 2.81)	L	-2 (-6.81 to 2.81)	VL	ROB, intransitivity imprecision
OXY-ER	BUP-Buccal	NA	NA	NA	NA	NA	-2.47 (-6.35 to 1.42)	VL	-2.47 (-6.35 to 1.42)	VL	ROB, intransitivity imprecision
TPN-ER	BUP-Buccal	NA	NA	NA	NA	NA	-1.54 (-5.51 to 2.43)	VL	-1.54 (-5.51 to 2.43)	VL	ROB, intransitivity imprecision
TRA-ER	BUP-Buccal	NA	NA	NA	NA	NA	-1.86 (-6.13 to 2.41)	VL	-1.86 (-6.13 to 2.41)	VL	ROB, intransitivity imprecision
COD-ER	BUP-PTCH	NA	NA	NA	NA	NA	15.6 (4.83 to 26.37)	VL	15.6 (4.83 to 26.37)	L	ROB, intransitivity
FEN-PTCH	BUP-PTCH	-0.8 (-9.69 to 8.09)	1	0	30	M	-0.61 (-4.23 to 3.01)	M	-0.63 (-4.01 to 2.74)	L	ROB, imprecision
HMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.29 (-2.22 to 4.79)	M	1.29 (-2.22 to 4.79)	L	ROB, imprecision
HYD-ER	BUP-PTCH	NA	NA	NA	NA	NA	-3.29 (-9.09 to 2.51)	L	-3.29 (-9.09 to 2.51)	VL	ROB, intransitivity imprecision
MPH-ER	BUP-PTCH	NA	NA	NA	NA	NA	-0.18 (-3.71 to 3.34)	M	-0.18 (-3.71 to 3.34)	L	ROB, imprecision
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	-0.48 (-4.61 to 3.65)	M	-0.48 (-4.61 to 3.65)	L	ROB, imprecision

OXY-ER	BUP-PTCH	NA	NA	NA	NA	NA	-0.95 (-3.95 to 2.05)	L	-0.95 (-3.95 to 2.05)	VL	ROB, imprecision
TPN-ER	BUP-PTCH	NA	NA	NA	NA	NA	-0.03 (-3.14 to 3.09)	L	-0.03 (-3.14 to 3.09)	VL	ROB, imprecision
TRA-ER	BUP-PTCH	NA	NA	NA	NA	NA	-0.35 (-3.83 to 3.14)	VL	-0.35 (-3.83 to 3.14)	VL	ROB, imprecision
FEN-PTCH	COD-ER	NA	NA	NA	NA	NA	-16.23 (-26.86 to -5.61)	L	-16.23 (-26.86 to -5.61)	L	ROB, intransitivity
HMOR-ER	COD-ER	NA	NA	NA	NA	NA	-14.31 (-24.94 to -3.68)	L	-14.31 (-24.94 to -3.68)	L	ROB, intransitivity
HYD-ER	COD-ER	NA	NA	NA	NA	NA	-18.89 (-30.48 to -7.3)	L	-18.89 (-30.48 to -7.3)	L	ROB, intransitivity
MPH-ER	COD-ER	NA	NA	NA	NA	NA	-15.78 (-26.44 to -5.13)	L	-15.78 (-26.44 to -5.13)	L	ROB, intransitivity
OMOR-ER	COD-ER	NA	NA	NA	NA	NA	-16.09 (-26.94 to -5.23)	L	-16.09 (-26.94 to -5.23)	L	ROB, intransitivity
OXY-ER	COD-ER	NA	NA	NA	NA	NA	-16.55 (-27.03 to -6.08)	VL	-16.55 (-27.03 to -6.08)	VL	ROB, intransitivity
TPN-ER	COD-ER	NA	NA	NA	NA	NA	-15.63 (-26.14 to -5.12)	VL	-15.63 (-26.14 to -5.12)	VL	ROB, intransitivity
TRA-ER	COD-ER	NA	NA	NA	NA	NA	-15.95 (-26.57 to -5.33)	VL	-15.95 (-26.57 to -5.33)	VL	ROB, intransitivity
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.92 (-1.09 to 4.93)	M	1.92 (-1.09 to 4.93)	L	ROB, imprecision
HYD-ER	FEN-PTCH	NA	NA	NA	NA	NA	-2.66 (-8.18 to 2.87)	M	-2.66 (-8.18 to 2.87)	L	ROB, intransitivity imprecision
MPH-ER	FEN-PTCH	-0.2 (-0.28 to -0.11)	1	0	553	M	1.5 (-2.28 to 5.28)	M	0.45 (-1.88 to 2.79)	L	ROB, imprecision
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.15 (-3.56 to 3.86)	M	0.15 (-3.56 to 3.86)	L	ROB, imprecision
OXY-ER	FEN-PTCH	NA	NA	NA	NA	NA	-0.32 (-2.67 to 2.03)	L	-0.32 (-2.67 to 2.03)	VL	ROB, imprecision
TPN-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.61 (-1.95 to 3.16)	L	0.61 (-1.95 to 3.16)	VL	ROB, imprecision

TRA-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.29 (-2.72 to 3.29)	VL	0.29 (-2.72 to 3.29)	VL	ROB, intransitivity imprecision
HYD-ER	HMOR-ER	NA	NA	NA	NA	NA	-4.58 (-10.11 to 0.96)	L	-4.58 (-10.11 to 0.96)	VL	ROB, intransitivity, imprecision
MPH-ER	HMOR-ER	NA	NA	NA	NA	NA	-1.47 (-4.57 to 1.63)	M	-1.47 (-4.57 to 1.63)	L	ROB, imprecision
OMOR-ER	HMOR-ER	NA	NA	NA	NA	NA	-1.77 (-5.48 to 1.94)	M	-1.77 (-5.48 to 1.94)	L	ROB, imprecision
OXY-ER	HMOR-ER	-3.66 (-6.51 to -0.81)	1	0	546	M	-1.54 (-4.46 to 1.39)	L	-2.24 (-4.54 to 0.06)	L	ROB, imprecision
TPN-ER	HMOR-ER	NA	NA	NA	NA	NA	-1.31 (-3.88 to 1.26)	L	-1.31 (-3.88 to 1.26)	VL	ROB, imprecision
TRA-ER	HMOR-ER	NA	NA	NA	NA	NA	-1.64 (-4.7 to 1.42)	VL	-1.64 (-4.7 to 1.42)	VL	ROB, intransitivity imprecision
MPH-ER	HYD-ER	NA	NA	NA	NA	NA	3.11 (-2.48 to 8.69)	L	3.11 (-2.48 to 8.69)	VL	ROB, intransitivity imprecision
OMOR-ER	HYD-ER	NA	NA	NA	NA	NA	2.8 (-3.15 to 8.76)	L	2.8 (-3.15 to 8.76)	VL	ROB, intransitivity imprecision
OXY-ER	HYD-ER	NA	NA	NA	NA	NA	2.34 (-2.9 to 7.57)	VL	2.34 (-2.9 to 7.57)	VL	ROB, intransitivity imprecision
TPN-ER	HYD-ER	NA	NA	NA	NA	NA	3.26 (-2.04 to 8.57)	VL	3.26 (-2.04 to 8.57)	VL	ROB, intransitivity imprecision
TRA-ER	HYD-ER	NA	NA	NA	NA	NA	2.94 (-2.59 to 8.47)	VL	2.94 (-2.59 to 8.47)	VL	ROB, intransitivity imprecision
OMOR-ER	MPH-ER	NA	NA	NA	NA	NA	-0.3 (-4.06 to 3.46)	M	-0.3 (-4.06 to 3.46)	L	ROB, imprecision
OXY-ER	MPH-ER	0.8 (-2.12 to 3.72)	2	21.5	382	M	-2.03 (-5.18 to 1.11)	VL	-0.77 (-3.11 to 1.56)	L	ROB, imprecision

TPN-ER	MPH-ER	NA	NA	NA	NA	NA	0.16 (-2.47 to 2.79)	L	0.16 (-2.47 to 2.79)	VL	ROB, imprecision
TRA-ER	MPH-ER	NA	NA	NA	NA	NA	-0.17 (-3.22 to 2.89)	VL	-0.17 (-3.22 to 2.89)	VL	ROB, intransitivity imprecision
OXY-ER	OMOR-ER	0.05 (-1.95 to 2.05)	1	0	348	M	-2.16 (-8.9 to 4.58)	L	-0.47 (-3.56 to 2.62)	L	ROB, imprecision
TPN-ER	OMOR-ER	NA	NA	NA	NA	NA	0.46 (-2.89 to 3.81)	L	0.46 (-2.89 to 3.81)	VL	ROB, imprecision
TRA-ER	OMOR-ER	NA	NA	NA	NA	NA	0.14 (-3.6 to 3.87)	L	0.14 (-3.6 to 3.87)	VL	ROB, intransitivity imprecision
TPN-ER	OXY-ER	1.18 (-1.26 to 3.62)	2	93.8	984	L	0.6 (-2.03 to 3.22)	L	0.93 (-0.72 to 2.57)	L	ROB, heterogeneity[2]
TRA-ER	OXY-ER	NA	NA	NA	NA	NA	0.61 (-1.79 to 3)	VL	0.61 (-1.79 to 3)	VL	ROB, intransitivity imprecision
TRA-ER	TPN-ER	NA	NA	NA	NA	NA	-0.32 (-2.87 to 2.23)	VL	-0.32 (-2.87 to 2.23)	VL	ROB, intransitivity imprecision

Footnote: Results are mean difference (95% CIs) from DerSimonian and Laird random-effects meta-analysis.
Direct estimations rated down if there were risk of bias (ROB), indirectness, publication bias, or heterogeneity.
Indirect estimations rated down if there was intransitivity.
Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the half MID in either side of 95%CI, or because the evidence is provided by a small number of participants- a total number of obseravation less than the optimal information size [≤400]).
H: high certainty of evidence; M: moderate; L: low; VL: very low. MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch.
[1]Not rated down twice because of the imprecision and incoherence.
[2] Not rated down twice because of the imprecision and heterogeneity
[£] Rated down on the basis of imprecision since did not meet OIS.

Appendix 3. 11: Direct, indirect, and NMA estimates for vomiting with the GRADE certainty of evidence

Comparison		Direct Estimates OR (95%CI)	# of Studies	I^{2} %	# of Patients	Direct GRADE	Indirect Estimates OR (95%CI)	Indirect GRADE	NMA estimate OR (95%CI)	NMA GRADE	Reasons
BUP-Buccal	Placebo	3.44 (1.46 to 8.12)	2	28.7	971	M	7.97 (3.67 to 17.31)	M	5.28 (2.95 to 9.45)	L	ROB, imprecision*
BUP-PTCH	Placebo	4.37 (2.51 to 7.58)	5	0	1332	M	2.61 (1.3 to 5.28)	M	3.59 (2.33 to 5.54)	L	ROB, imprecision*
FEN-PTCH	Placebo	11.1 (4.97 to 24.79)	3	0	729	M	9.05 (4.67 to 17.54)	M	9.83 (5.9 to 16.38)	L	ROB, imprecision*
HMOR-ER	Placebo	3.73 (2.01 to 6.89)	2	75.8	1249	L	11.43 (4.19 to 31.22)	M	4.75 (2.77 to 8.14)	L	ROB, heterogeneity, imprecision, *incoherence[1]
HYD-ER	Placebo	1.95 (1 to 3.8)	3	8.3	1260	M	NA	NA	1.94 (1.04 to 3.61)	L	ROB, imprecision*
MPH-ER	Placebo	7.92 (1.04 to 59.82)	1	NA	295	M	8.82 (5.35 to 14.55)	M	8.77 (5.4 to 14.25)	L	ROB, imprecision*
OMOR-ER	Placebo	6.07 (0.73 to 50.24)	3	65	712	L	55.48 (9.88 to 311.58)	M	19.57 (10.68 to 35.86)	L	ROB, heterogeneity, imprecision*
OXY-ER	Placebo	7.54 (5.41 to 10.5)	9	0	3091	M	5.6 (3.37 to 9.33)	L	7.12 (5.42 to 9.35)	M	ROB
TPN-ER	Placebo	3.21 (2.27 to 4.55)	9	0	3139	M	2.16 (0.99 to 4.74)	M	2.85 (2.11 to 3.84)	L	ROB, imprecision*
TPN-NR	Placebo	NA	NA	NA	NA	NA	1.93 (0.7 to 5.33)	L	1.93 (0.7 to 5.33)	VL	ROB, imprecision, intransitivity
TRA-ER	Placebo	4.51 (2.38 to 8.56)	7	19	3137	M	4.11 (1.71 to 9.85)	M	4.04 (2.57 to 6.34)	L	ROB, imprecision*
TRA-NR	Placebo	7.46 (0.37 to 147.49)	1	NA	127	M	4.08 (1.73 to 9.66)	M	4.28 (1.87 to 9.78)	L	ROB, imprecision*
OXY-NR	Placebo	NA	NA	NA	NA	NA	4.06 (1.59 to 10.39)	L	4.06 (1.59 to 10.39)	L	ROB, intransitivity

BUP-PTCH	BUP-Buccal	0.52 (0.28 to 0.97)	1	NA	238	M	1.35 (0.5 to 3.67)	L	0.68 (0.4 to 1.15)	L	ROB, imprecision
FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	NA	1.86 (0.86 to 4.04)	L	1.86 (0.86 to 4.04)	VL	ROB, imprecision, intransitivity
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	0.9 (0.41 to 1.99)	L	0.9 (0.41 to 1.99)	VL	ROB, imprecision, intransitivity
HYD-ER	BUP-Buccal	NA	NA	NA	NA	NA	0.37 (0.16 to 0.86)	M	0.37 (0.16 to 0.86)	L	ROB, intransitivity
MPH-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.66 (0.78 to 3.54)	L	1.66 (0.78 to 3.54)	VL	ROB, imprecision, intransitivity
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	3.71 (1.6 to 8.59)	L	3.71 (1.6 to 8.59)	L	ROB
OXY-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.35 (0.71 to 2.56)	L	1.35 (0.71 to 2.56)	VL	ROB, imprecision, intransitivity
TPN-ER	BUP-Buccal	NA	NA	NA	NA	NA	0.54 (0.28 to 1.04)	L	0.54 (0.28 to 1.04)	VL	ROB, imprecision, intransitivity
TPN-NR	BUP-Buccal	NA	NA	NA	NA	NA	0.37 (0.13 to 1.05)	L	0.37 (0.13 to 1.05)	VL	ROB, imprecision, intransitivity
TRA-ER	BUP-Buccal	NA	NA	NA	NA	NA	0.76 (0.39 to 1.51)	L	0.76 (0.39 to 1.51)	VL	ROB, imprecision, intransitivity
TRA-NR	BUP-Buccal	NA	NA	NA	NA	NA	0.81 (0.31 to 2.15)	L	0.81 (0.31 to 2.15)	VL	ROB, imprecision, intransitivity
OXY-NR	BUP-Buccal	NA	NA	NA	NA	NA	0.77 (0.29 to 2.06)	L	0.77 (0.29 to 2.06)	VL	ROB, imprecision, intransitivity
FEN-PTCH	BUP-PTCH	NA	NA	NA	NA	NA	2.74 (1.4 to 5.35)	M	2.74 (1.4 to 5.35)	M	ROB

HMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.32 (0.66 to 2.64)	L	1.32 (0.66 to 2.64)	VL	ROB, imprecision, intransitivity
HYD-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.54 (0.25 to 1.15)	M	0.54 (0.25 to 1.15)	L	ROB, imprecision
MPH-ER	BUP-PTCH	NA	NA	NA	NA	NA	2.44 (1.27 to 4.68)	M	2.44 (1.27 to 4.68)	M	ROB
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	5.45 (2.59 to 11.47)	M	5.45 (2.59 to 11.47)	M	ROB
OXY-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.98 (1.19 to 3.31)	L	1.98 (1.19 to 3.31)	L	ROB
TPN-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.79 (0.47 to 1.34)	M	0.79 (0.47 to 1.34)	L	ROB, imprecision
TPN-NR	BUP-PTCH	NA	NA	NA	NA	NA	0.54 (0.21 to 1.35)	L	0.54 (0.21 to 1.35)	VL	ROB, imprecision, intransitivity
TRA-ER	BUP-PTCH	1.09 (0.5 to 2.36)	1	NA	280	M	1.15 (0.56 to 2.34)	M	1.12 (0.67 to 1.9)	L	ROB, imprecision
TRA-NR	BUP-PTCH	NA	NA	NA	NA	NA	1.19 (0.5 to 2.85)	M	1.19 (0.5 to 2.85)	L	ROB, imprecision
OXY-NR	BUP-PTCH	1.12 (0.49 to 2.6)	1	NA	660	M	NA		1.13 (0.49 to 2.6)	L	ROB, imprecision
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.48 (0.23 to 1)	L	0.48 (0.23 to 1)	VL	ROB, imprecision, intransitivity
HYD-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.2 (0.09 to 0.44)	M	0.2 (0.09 to 0.44)	M	ROB
MPH-ER	FEN-PTCH	0.9 (0.67 to 1.22)	2	0	1041	M	0.74 (0.27 to 2)	M	0.89 (0.67 to 1.19)	L	ROB, imprecision
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.99 (0.94 to 4.21)	L	1.99 (0.94 to 4.21)	VL	ROB, imprecision, intransitivity
OXY-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.72 (0.44 to 1.19)	M	0.72 (0.44 to 1.19)	L	ROB, imprecision
TPN-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.29 (0.17 to 0.49)	M	0.29 (0.17 to 0.49)	M	ROB

TPN-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.2 (0.06 to 0.61)	L	0.2 (0.06 to 0.61)	L	ROB, intransitivity
TRA-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.41 (0.21 to 0.81)	M	0.41 (0.21 to 0.81)	M	ROB
TRA-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.44 (0.16 to 1.15)	M	0.44 (0.16 to 1.15)	L	ROB, imprecision
OXY-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.41 (0.14 to 1.2)	L	0.41 (0.14 to 1.2)	VL	ROB, imprecision, intransitivity
HYD-ER	HMOR-ER	NA	NA	NA	NA	NA	0.41 (0.18 to 0.93)	L	0.41 (0.18 to 0.93)	L	ROB, intransitivity
MPH-ER	HMOR-ER	NA	NA	NA	NA	NA	1.85 (0.91 to 3.74)	L	1.85 (0.91 to 3.74)	VL	ROB, imprecision, intransitivity
OMOR-ER	HMOR-ER	NA	NA	NA	NA	NA	4.12 (1.87 to 9.08)	L	4.12 (1.87 to 9.08)	L	ROB
OXY-ER	HMOR-ER	1.5 (0.57 to 3.93)	1	NA	138	M	2.29 (1.14 to 4.61)	L	1.5 (0.85 to 2.64)	L	ROB, imprecision, incoherence[1,¥]
TPN-ER	HMOR-ER	NA	NA	NA	NA	NA	0.6 (0.33 to 1.08)	L	0.6 (0.33 to 1.08)	VL	ROB, imprecision, intransitivity
TPN-NR	HMOR-ER	NA	NA	NA	NA	NA	0.41 (0.13 to 1.28)	VL	0.41 (0.13 to 1.28)	VL	ROB, imprecision, intransitivity
TRA-ER	HMOR-ER	NA	NA	NA	NA	NA	0.85 (0.42 to 1.72)	L	0.85 (0.42 to 1.72)	VL	ROB, imprecision, intransitivity
TRA-NR	HMOR-ER	NA	NA	NA	NA	NA	0.9 (0.34 to 2.42)	L	0.9 (0.34 to 2.42)	VL	ROB, imprecision, intransitivity
OXY-NR	HMOR-ER	NA	NA	NA	NA	NA	0.86 (0.29 to 2.53)	VL	0.86 (0.29 to 2.53)	VL	ROB, imprecision, intransitivity
MPH-ER	HYD-ER	NA	NA	NA	NA	NA	4.52 (2.05 to 9.95)	M	4.52 (2.05 to 9.95)	M	ROB

OMOR-ER	HYD-ER	NA	NA	NA	NA	NA	10.09 (4.23 to 24.04)	L	10.09 (4.23 to 24.04)	L	ROB, intransitivity
OXY-ER	HYD-ER	NA	NA	NA	NA	NA	3.67 (1.86 to 7.24)	M	3.67 (1.86 to 7.24)	M	ROB
TPN-ER	HYD-ER	NA	NA	NA	NA	NA	1.47 (0.74 to 2.93)	M	1.47 (0.74 to 2.93)	L	ROB, imprecision
TPN-NR	HYD-ER	NA	NA	NA	NA	NA	1 (0.3 to 3.28)	L	1 (0.3 to 3.28)	VL	ROB, imprecision, intransitivity
TRA-ER	HYD-ER	NA	NA	NA	NA	NA	2.08 (0.96 to 4.49)	M	2.08 (0.96 to 4.49)	L	ROB, imprecision
TRA-NR	HYD-ER	NA	NA	NA	NA	NA	2.21 (0.78 to 6.21)	M	2.21 (0.78 to 6.21)	L	ROB, imprecision
OXY-NR	HYD-ER	NA	NA	NA	NA	NA	2.09 (0.68 to 6.46)	L	2.09 (0.68 to 6.46)	VL	ROB, imprecision, intransitivity
OMOR-ER	MPH-ER	NA	NA	NA	NA	NA	2.23 (1.08 to 4.61)	VL	2.23 (1.08 to 4.61)	VL	ROB, intransitivity
OXY-ER	MPH-ER	0.85 (0.49 to 1.47)	2	0	648	M	0.72 (0.31 to 1.67)	M	0.81 (0.51 to 1.28)	L	ROB, imprecision
TPN-ER	MPH-ER	NA	NA	NA	NA	NA	0.32 (0.2 to 0.54)	M	0.32 (0.2 to 0.54)	M	ROB
TPN-NR	MPH-ER	NA	NA	NA	NA	NA	0.22 (0.07 to 0.68)	L	0.22 (0.07 to 0.68)	L	ROB, intransitivity
TRA-ER	MPH-ER	NA	NA	NA	NA	NA	0.46 (0.24 to 0.89)	M	0.46 (0.24 to 0.89)	M	ROB
TRA-NR	MPH-ER	NA	NA	NA	NA	NA	0.49 (0.19 to 1.27)	M	0.49 (0.19 to 1.27)	L	ROB, imprecision
OXY-NR	MPH-ER	NA	NA	NA	NA	NA	0.46 (0.16 to 1.33)	L	0.46 (0.16 to 1.33)	VL	ROB, imprecision, intransitivity
OXY-ER	OMOR-ER	0.29 (0.15 to 0.55)	1	NA	365	M	1.39 (0.3 to 6.46)	L	0.36 (0.21 to 0.64)	L	ROB, imprecision*
TPN-ER	OMOR-ER	NA	NA	NA	NA	NA	0.15 (0.08 to 0.27)	L	0.15 (0.08 to 0.27)	L	ROB

TPN-NR	OMOR-ER	NA	NA	NA	NA	NA	0.1 (0.03 to 0.32)	VL	0.1 (0.03 to 0.32)	VL	ROB, intransitivity
TRA-ER	OMOR-ER	NA	NA	NA	NA	NA	0.21 (0.1 to 0.44)	VL	0.21 (0.1 to 0.44)	VL	ROB, intransitivity
TRA-NR	OMOR-ER	NA	NA	NA	NA	NA	0.22 (0.08 to 0.61)	VL	0.22 (0.08 to 0.61)	VL	ROB, intransitivity
OXY-NR	OMOR-ER	NA	NA	NA	NA	NA	0.21 (0.07 to 0.63)	VL	0.21 (0.07 to 0.63)	VL	ROB, intransitivity
TPN-ER	OXY-ER	0.36 (0.28 to 0.48)	4	20	3099	M	0.84 (0.41 to 1.7)	M	0.4 (0.32 to 0.5)	L	ROB, incoherence¥
TPN-NR	OXY-ER	NA	NA	NA	NA	NA	0.27 (0.09 to 0.78)	L	0.27 (0.09 to 0.78)	L	ROB, intransitivity
TRA-ER	OXY-ER	NA	NA	NA	NA	NA	0.57 (0.33 to 0.96)	M	0.57 (0.33 to 0.96)	M	ROB
TRA-NR	OXY-ER	NA	NA	NA	NA	NA	0.6 (0.25 to 1.44)	M	0.6 (0.25 to 1.44)	L	ROB, imprecision
OXY-NR	OXY-ER	NA	NA	NA	NA	NA	0.57 (0.21 to 1.52)	L	0.57 (0.21 to 1.52)	VL	ROB, imprecision, intransitivity
TPN-NR	TPN-ER	NA	NA	NA	NA	NA	0.68 (0.24 to 1.95)	L	0.68 (0.24 to 1.95)	VL	ROB, imprecision, intransitivity
TRA-ER	TPN-ER	NA	NA	NA	NA	NA	1.42 (0.82 to 2.43)	M	1.42 (0.82 to 2.43)	L	ROB, imprecision
TRA-NR	TPN-ER	NA	NA	NA	NA	NA	1.5 (0.62 to 3.62)	M	1.5 (0.62 to 3.62)	L	ROB, imprecision
OXY-NR	TPN-ER	NA	NA	NA	NA	NA	1.43 (0.53 to 3.82)	L	1.43 (0.53 to 3.82)	VL	ROB, imprecision, intransitivity
TRA-ER	TPN-NR	NA	NA	NA	NA	NA	2.09 (0.73 to 6.01)	L	2.09 (0.73 to 6.01)	VL	ROB, imprecision, intransitivity
TRA-NR	TPN-NR	NA	NA	NA	NA	NA	2.21 (0.62 to 7.85)	L	2.21 (0.62 to 7.85)	VL	ROB, imprecision, intransitivity

OXY-NR	TPN-NR	2.1 (1.43 to 3.08)	1	NA	849	M	NA		2.1 (1.43 to 3.09)	L	ROB, imprecision*
TRA-NR	TRA-ER	1.02 (0.49 to 2.11)	2	0	390	M	1.87 (0.09 to 38.3)	M	1.06 (0.52 to 2.15)	L	ROB, imprecision
OXY-NR	TRA-ER	NA	NA	NA	NA	NA	1.01 (0.38 to 2.69)	L	1.01 (0.38 to 2.69)	VL	ROB, imprecision, intransitivity
OXY-NR	TRA-NR	NA	NA	NA	NA	NA	0.95 (0.28 to 3.17)	L	0.95 (0.28 to 3.17)	VL	ROB, imprecision, intransitivity

Footnote: Results are Odds Ratio (95% CIs). Direct estimates are from DerSimonian and Laird random-effects meta-analysis.
Risk of bias (ROB), indirectness, publication bias, and heterogeneity were assessed for direct comparisons.
Transitivity was checked for indirect estimates.
Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of events- a total number of events less than the optimal information size [<300]).
Small-study effects were assessed when there were at least 10 studies using Harbord test.
[¥] The best estimate of effect was obtained from direct evidence because there was incoherence.
* Rated down on the basis of imprecision since did not meet OIS.
[1] not rated down twice for imprecision and incoherence.
H: high certainty of evidence; M: moderate; L: low; VL: very low.

Appendix 3. 12: Direct, indirect, and NMA estimates for constipation with the GRADE certainty of evidence

Comparison		Direct Estimates OR (95%CI)	# of participants	I^{2} %	# of studies	Direct GRADE	Indirect Estimates OR (95%CI)	Indirect GRADE	NMA estimate OR (95%CI)	NMA GRADE	Reasons
BUP-Buccal	Placebo	2.06 (0.87 to 4.86)	971	0	2	M	3.29 (1.36 to 7.94)	M	2.58 (1.42 to 4.69)	L	ROB, imprecision[1]
BUP-PTCH	Placebo	3.21 (1.71 to 6.01)	1332	40	5	M	5 (2.64 to 9.47)	L	3.55 (2.43 to 5.19)	L	ROB, intransitivity, imprecision[1]
COD-ER	Placebo	7.37 (2.67 to 20.29)	103	0	1	M	NA	NA	7.37 (2.68 to 20.29)	L	ROB, imprecision[1]
FEN-PTCH	Placebo	2.54 (0.78 to 8.21)	729	66	3	L	5.31 (2.8 to 10.04)	M	3.96 (2.78 to 5.65)	L	ROB, heterogeneity, imprecision, incoherence[¥1,2]
HMOR-ER	Placebo	4.01 (1.48 to 10.8)	1249	68	2	L	8.08 (3.35 to 19.68)	M	5.71 (4.15 to 7.85)	M	ROB, heterogeneity
HYD-ER	Placebo	3.12 (1.01 to 9.62)	1262	48	2	L	NA	NA	2.72 (1.47 to 5.01)	L	ROB, heterogeneity, imprecision
MPH-ER	Placebo	14.79 (7.57 to 28.9)	565	0	5	M	5.58 (3.97 to 7.89)	M	6.86 (5.05 to 9.31)	L	ROB, imprecision, incoherence[¥,2]
OMOR-ER	Placebo	4.6 (2.6 to 8.15)	711	0	3	M	9.68 (3.45 to 27.05)	M	5.74 (3.81 to 8.65)	L	ROB, imprecision
OXY-ER	Placebo	6.07 (4.85 to 7.61)	3424	0	10	M	7.1 (4.37 to 11.43)	M	6.34 (5.21 to 7.71)	M	ROB
TPN-ER	Placebo	3.19 (2.33 to 4.38)	3119	0	8	M	2.41 (1.32 to 4.41)	M	2.85 (2.27 to 3.57)	M	ROB
TPN-NR	Placebo	NA	NA	NA	NA	NA	1.91 (0.78 to 4.65)	L	1.91 (0.78 to 4.65)	VL	ROB, intransitivity, imprecision

TRA-ER	Placebo	5.01 (3.63 to 6.92)	4168	0	9	M	2.59 (1.32 to 5.07)	L	4.5 (3.37 to 6)	M	ROB
TRA-NR	Placebo	4.64 (0.78 to 27.51)	166	74	3	L	3.97 (2.02 to 7.88)	L	3.89 (2.28 to 6.66)	L	ROB, heterogeneity, imprecision[1]
OXY-NR	Placebo	NA	NA	NA	NA	NA	4.82 (2.18 to 10.64)	L	4.82 (2.18 to 10.64)	L	ROB, intransitivity
BUP-PTCH	BUP-Buccal	1.16 (0.57 to 2.37)	238	0	1	M	1.9 (0.7 to 5.14)	L	1.38 (0.78 to 2.44)	L	ROB, intransitivity, imprecision
COD-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.86 (0.88 to 9.25)	L	2.86 (0.88 to 9.25)	VL	ROB, intransitivity, imprecision
FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	NA	1.53 (0.77 to 3.07)	M	1.53 (0.77 to 3.07)	VL	ROB, imprecision
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.21 (1.12 to 4.35)	L	2.21 (1.12 to 4.35)	VL	ROB, intransitivity
HYD-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.05 (0.45 to 2.48)	VL	1.05 (0.45 to 2.48)	VL	ROB, intransitivity, imprecision
MPH-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.66 (1.36 to 5.19)	L	2.66 (1.36 to 5.19)	L	ROB, intransitivity
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.22 (1.08 to 4.59)	L	2.22 (1.08 to 4.59)	L	ROB, intransitivity
OXY-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.46 (1.31 to 4.6)	L	2.46 (1.31 to 4.6)	L	ROB, intransitivity
TPN-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.1 (0.58 to 2.09)	L	1.1 (0.58 to 2.09)	VL	ROB, intransitivity, imprecision
TPN-NR	BUP-Buccal	NA	NA	NA	NA	NA	0.74 (0.28 to 1.99)	L	0.74 (0.28 to 1.99)	VL	ROB, intransitivity, imprecision
TRA-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.74 (0.92 to 3.31)	L	1.74 (0.92 to 3.31)	VL	ROB, intransitivity, imprecision

TRA-NR	BUP-Buccal	NA	NA	NA	NA	NA	1.51 (0.68 to 3.32)	VL	1.51 (0.68 to 3.32)	VL	ROB, intransitivity, imprecision
OXY-NR	BUP-Buccal	NA	NA	NA	NA	NA	1.87 (0.76 to 4.6)	L	1.87 (0.76 to 4.6)	VL	ROB, intransitivity, imprecision
COD-ER	BUP-PTCH	NA	NA	NA	NA	NA	2.07 (0.7 to 6.11)	M	2.07 (0.7 to 6.11)	L	ROB, imprecision
FEN-PTCH	BUP-PTCH	NA	NA	NA	NA	NA	1.11 (0.66 to 1.87)	L	1.11 (0.66 to 1.87)	VL	ROB, intransitivity, imprecision
HMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.61 (0.98 to 2.63)	M	1.61 (0.98 to 2.63)	L	ROB, imprecision
HYD-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.76 (0.37 to 1.57)	M	0.76 (0.37 to 1.57)	L	ROB, imprecision
MPH-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.93 (1.19 to 3.14)	M	1.93 (1.19 to 3.14)	M	ROB
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.61 (0.92 to 2.82)	M	1.61 (0.92 to 2.82)	L	ROB, imprecision
OXY-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.78 (1.17 to 2.73)	M	1.78 (1.17 to 2.73)	M	ROB
TPN-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.8 (0.52 to 1.25)	M	0.8 (0.52 to 1.25)	L	ROB, imprecision
TPN-NR	BUP-PTCH	NA	NA	NA	NA	NA	0.54 (0.24 to 1.2)	L	0.54 (0.24 to 1.2)	VL	ROB, intransitivity, imprecision
TRA-ER	BUP-PTCH	0.68 (0.34 to 1.35)	414	60	2	L	1.77 (1.04 to 3.01)	M	1.27 (0.83 to 1.94)	L	ROB, imprecision, incoherence[¥,2]
TRA-NR	BUP-PTCH	NA	NA	NA	NA	NA	1.1 (0.58 to 2.06)	VL	1.1 (0.58 to 2.06)	VL	ROB, intransitivity, imprecision
OXY-NR	BUP-PTCH	1.35 (0.67 to 2.72)	660	0	1	M	NA	NA	1.36 (0.68 to 2.72)	L	ROB, imprecision

FEN-PTCH	COD-ER	NA	NA	NA	NA	NA	0.54 (0.18 to 1.57)	L	0.54 (0.18 to 1.57)	VL	ROB, intransitivity, imprecision
HMOR-ER	COD-ER	NA	NA	NA	NA	NA	0.77 (0.27 to 2.24)	M	0.77 (0.27 to 2.24)	VL	ROB, imprecision
HYD-ER	COD-ER	NA	NA	NA	NA	NA	0.37 (0.11 to 1.2)	VL	0.37 (0.11 to 1.2)	VL	ROB, intransitivity, imprecision
MPH-ER	COD-ER	NA	NA	NA	NA	NA	0.93 (0.32 to 2.68)	M	0.93 (0.32 to 2.68)	L	ROB, imprecision
OMOR-ER	COD-ER	NA	NA	NA	NA	NA	0.78 (0.26 to 2.32)	M	0.78 (0.26 to 2.32)	L	ROB, imprecision
OXY-ER	COD-ER	NA	NA	NA	NA	NA	0.86 (0.31 to 2.41)	M	0.86 (0.31 to 2.41)	L	ROB, imprecision
TPN-ER	COD-ER	NA	NA	NA	NA	NA	0.39 (0.14 to 1.09)	M	0.39 (0.14 to 1.09)	L	ROB, imprecision
TPN-NR	COD-ER	NA	NA	NA	NA	NA	0.26 (0.07 to 1)	L	0.26 (0.07 to 1)	VL	ROB, intransitivity, imprecision
TRA-ER	COD-ER	NA	NA	NA	NA	NA	0.61 (0.21 to 1.75)	M	0.61 (0.21 to 1.75)	L	ROB, imprecision
TRA-NR	COD-ER	NA	NA	NA	NA	NA	0.53 (0.17 to 1.66)	L	0.53 (0.17 to 1.66)	VL	ROB, imprecision
OXY-NR	COD-ER	NA	NA	NA	NA	NA	0.65 (0.18 to 2.36)	L	0.65 (0.18 to 2.36)	VL	ROB, intransitivity, imprecision
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.44 (0.9 to 2.3)	M	1.44 (0.9 to 2.3)	VL	ROB, imprecision
HYD-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.69 (0.34 to 1.39)	L	0.69 (0.34 to 1.39)	VL	ROB, imprecision
MPH-ER	FEN-PTCH	1.58 (1.22 to 2.04)	1168	0	2	M	3.74 (1.67 to 8.33)	L	1.73 (1.36 to 2.2)	L	ROB, intransitivity, incoherence*[,3]
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.45 (0.87 to 2.42)	L	1.45 (0.87 to 2.42)	VL	ROB, intransitivity, imprecision

OXY-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.6 (1.13 to 2.26)	L	1.6 (1.13 to 2.26)	VL	ROB, intransitivity
TPN-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.72 (0.49 to 1.05)	L	0.72 (0.49 to 1.05)	VL	ROB, intransitivity, imprecision
TPN-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.48 (0.18 to 1.26)	L	0.48 (0.18 to 1.26)	VL	ROB, intransitivity, imprecision
TRA-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.14 (0.72 to 1.8)	L	1.14 (0.72 to 1.8)	VL	ROB, intransitivity, imprecision
TRA-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.98 (0.52 to 1.87)	VL	0.98 (0.52 to 1.87)	VL	ROB, intransitivity, imprecision
OXY-NR	FEN-PTCH	NA	NA	NA	NA	NA	1.22 (0.51 to 2.9)	L	1.22 (0.51 to 2.9)	VL	ROB, intransitivity, imprecision
HYD-ER	HMOR-ER	NA	NA	NA	NA	NA	0.48 (0.24 to 0.95)	VL	0.48 (0.24 to 0.95)	VL	ROB, intransitivity, imprecision
MPH-ER	HMOR-ER	NA	NA	NA	NA	NA	1.2 (0.78 to 1.85)	M	1.2 (0.78 to 1.85)	VL	ROB, imprecision
OMOR-ER	HMOR-ER	NA	NA	NA	NA	NA	1.01 (0.6 to 1.68)	M	1.01 (0.6 to 1.68)	VL	ROB, imprecision
OXY-ER	HMOR-ER	0.8 (0.38 to 1.72)	138	0	1	M	1.34 (0.72 to 2.47)	M	1.11 (0.78 to 1.58)	L	ROB, imprecision
TPN-ER	HMOR-ER	NA	NA	NA	NA	NA	0.5 (0.34 to 0.73)	M	0.5 (0.34 to 0.73)	VL	ROB, imprecision
TPN-NR	HMOR-ER	NA	NA	NA	NA	NA	0.33 (0.13 to 0.86)	L	0.33 (0.13 to 0.86)	VL	ROB, intransitivity, imprecision
TRA-ER	HMOR-ER	NA	NA	NA	NA	NA	0.79 (0.51 to 1.21)	M	0.79 (0.51 to 1.21)	VL	ROB, imprecision
TRA-NR	HMOR-ER	NA	NA	NA	NA	NA	0.68 (0.37 to 1.27)	VL	0.68 (0.37 to 1.27)	VL	ROB, intransitivity, imprecision

OXY-NR	HMOR-ER	NA	NA	NA	NA	NA	0.84 (0.36 to 1.98)	L	0.84 (0.36 to 1.98)	VL	ROB, intransitivity, imprecision
MPH-ER	HYD-ER	NA	NA	NA	NA	NA	2.52 (1.27 to 5.01)	VL	2.52 (1.27 to 5.01)	VL	ROB, intransitivity
OMOR-ER	HYD-ER	NA	NA	NA	NA	NA	2.11 (1.01 to 4.42)	L	2.11 (1.01 to 4.42)	L	ROB, intransitivity
OXY-ER	HYD-ER	NA	NA	NA	NA	NA	2.33 (1.23 to 4.44)	L	2.33 (1.23 to 4.44)	L	ROB, intransitivity
TPN-ER	HYD-ER	NA	NA	NA	NA	NA	1.05 (0.55 to 2.02)	VL	1.05 (0.55 to 2.02)	VL	ROB, intransitivity, imprecision
TPN-NR	HYD-ER	NA	NA	NA	NA	NA	0.7 (0.24 to 2.07)	VL	0.7 (0.24 to 2.07)	VL	ROB, intransitivity, imprecision
TRA-ER	HYD-ER	NA	NA	NA	NA	NA	1.66 (0.84 to 3.26)	VL	1.66 (0.84 to 3.26)	VL	ROB, intransitivity, imprecision
TRA-NR	HYD-ER	NA	NA	NA	NA	NA	1.43 (0.63 to 3.24)	VL	1.43 (0.63 to 3.24)	VL	ROB, intransitivity, imprecision
OXY-NR	HYD-ER	NA	NA	NA	NA	NA	1.77 (0.65 to 4.83)	VL	1.77 (0.65 to 4.83)	VL	ROB, intransitivity, imprecision
OMOR-ER	MPH-ER	NA	NA	NA	NA	NA	0.84 (0.52 to 1.35)	M	0.84 (0.52 to 1.35)	L	ROB, imprecision
OXY-ER	MPH-ER	0.85 (0.48 to 1.51)	756	48	3	M	0.79 (0.43 to 1.47)	M	0.92 (0.7 to 1.23)	L	ROB, imprecision
TPN-ER	MPH-ER	NA	NA	NA	NA	NA	0.42 (0.3 to 0.57)	M	0.42 (0.3 to 0.57)	L	ROB, imprecision
TPN-NR	MPH-ER	NA	NA	NA	NA	NA	0.28 (0.11 to 0.71)	L	0.28 (0.11 to 0.71)	VL	ROB, intransitivity, imprecision
TRA-ER	MPH-ER	NA	NA	NA	NA	NA	0.66 (0.43 to 1)	M	0.66 (0.43 to 1)	L	ROB, imprecision

TRA-NR	MPH-ER	NA	NA	NA	NA	NA	0.57 (0.31 to 1.05)	L	0.57 (0.31 to 1.05)	VL	ROB, imprecision
OXY-NR	MPH-ER	NA	NA	NA	NA	NA	0.7 (0.3 to 1.64)	L	0.7 (0.3 to 1.64)	VL	ROB, intransitivity, imprecision
OXY-ER	OMOR-ER	0.98 (0.63 to 1.55)	366	0	1	M	1.7 (0.63 to 4.64)	M	1.1 (0.74 to 1.64)	L	ROB, imprecision
TPN-ER	OMOR-ER	NA	NA	NA	NA	NA	0.5 (0.32 to 0.76)	M	0.5 (0.32 to 0.76)	L	ROB, imprecision
TPN-NR	OMOR-ER	NA	NA	NA	NA	NA	0.33 (0.12 to 0.89)	L	0.33 (0.12 to 0.89)	VL	ROB, intransitivity, imprecision
TRA-ER	OMOR-ER	NA	NA	NA	NA	NA	0.78 (0.47 to 1.29)	M	0.78 (0.47 to 1.29)	L	ROB, imprecision
TRA-NR	OMOR-ER	NA	NA	NA	NA	NA	0.68 (0.35 to 1.33)	L	0.68 (0.35 to 1.33)	VL	ROB, imprecision
OXY-NR	OMOR-ER	NA	NA	NA	NA	NA	0.84 (0.34 to 2.05)	L	0.84 (0.34 to 2.05)	VL	ROB, intransitivity, imprecision
TPN-ER	OXY-ER	0.42 (0.35 to 0.5)	3099	0	4	M	0.82 (0.44 to 1.53)	M	0.45 (0.38 to 0.53)	L	ROB, imprecision, incoherence[*,2]
TPN-NR	OXY-ER	NA	NA	NA	NA	NA	0.3 (0.12 to 0.75)	L	0.3 (0.12 to 0.75)	VL	ROB, intransitivity, imprecision
TRA-ER	OXY-ER	NA	NA	NA	NA	NA	0.71 (0.5 to 1.01)	M	0.71 (0.5 to 1.01)	L	ROB, imprecision
TRA-NR	OXY-ER	NA	NA	NA	NA	NA	0.61 (0.35 to 1.09)	L	0.61 (0.35 to 1.09)	VL	ROB, imprecision
OXY-NR	OXY-ER	NA	NA	NA	NA	NA	0.76 (0.34 to 1.72)	L	0.76 (0.34 to 1.72)	VL	ROB, intransitivity, imprecision
TPN-NR	TPN-ER	NA	NA	NA	NA	NA	0.67 (0.27 to 1.68)	L	0.67 (0.27 to 1.68)	VL	ROB, intransitivity, imprecision

TRA-ER	TPN-ER	NA	NA	NA	NA	NA	1.58 (1.09 to 2.28)	M	1.58 (1.09 to 2.28)	M	ROB
TRA-NR	TPN-ER	NA	NA	NA	NA	NA	1.37 (0.76 to 2.45)	L	1.37 (0.76 to 2.45)	VL	ROB, imprecision
OXY-NR	TPN-ER	NA	NA	NA	NA	NA	1.69 (0.74 to 3.86)	L	1.69 (0.74 to 3.86)	VL	ROB, intransitivity, imprecision
TRA-ER	TPN-NR	NA	NA	NA	NA	NA	2.36 (0.95 to 5.87)	L	2.36 (0.95 to 5.87)	VL	ROB, intransitivity, imprecision
TRA-NR	TPN-NR	NA	NA	NA	NA	NA	2.04 (0.73 to 5.68)	VL	2.04 (0.73 to 5.68)	VL	ROB, intransitivity, imprecision
OXY-NR	TPN-NR	2.52 (1.68 to 3.78)	849	0	1	M	NA	NA	2.52 (1.68 to 3.79)	L	ROB, imprecision[1]
TRA-NR	TRA-ER	0.86 (0.28 to 2.67)	390	74	2	L	0.83 (0.28 to 2.38)	L	0.87 (0.53 to 1.42)	L	ROB, heterogeneity, imprecision
OXY-NR	TRA-ER	NA	NA	NA	NA	NA	1.07 (0.47 to 2.42)	L	1.07 (0.47 to 2.42)	VL	ROB, intransitivity, imprecision
OXY-NR	TRA-NR	NA	NA	NA	NA	NA	1.24 (0.48 to 3.17)	VL	1.24 (0.48 to 3.17)	VL	ROB, intransitivity, imprecision

Footnote: Results are Odds Ratio (95% CIs). Direct estimates are from DerSimonian and Laird random-effects meta-analysis.
Risk of bias (ROB), indirectness, publication bias, and heterogeneity were assessed for direct comparisons. Transitivity was checked for indirect estimates. Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of events- a total number of events less than the optimal information size [<300]).
Small-study effects were assessed when there were at least 10 studies using Harbord test.
* The best estimate of effect was obtained from direct evidence because there was incoherence.
¥ The best estimate of effect was obtained from indirect evidence because there was incoherence.
[1]Rated dwon on the basis of imprecision since did not meet OIS.
[2]Not rated down twice for imprecision and incoherence.
[3]Not rated down twice for intransitivity and incoherence.
H: high certainty of evidence; M: moderate; L: low; VL: very low.
MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch.

Appendix 3. 13: Direct, indirect, and NMA estimates for nausea with the GRADE certainty of evidence

Comparisons		Direct Estimates OR (95%CI)	# of Studies	I^{2} %	# of participants	Direct GRADE	Indirect Estimates OR (95%CI)	Indirect GRADE	NMA estimate OR (95%CI)	NMA GRADE	Reasons
BUP-Buccal	Placebo	1.19 (0.75 to 1.9)	2	0	971	M	5.85 (2.21 to 15.48)	VL	2.03 (1.1 to 3.75)	VL	ROB, intransitivity, imprecision, incoherence [1,2]
BUP-PTCH	Placebo	3.25 (1.69 to 6.24)	5	77	1332	L	2.41 (1.22 to 4.75)	M	2.89 (1.94 to 4.3)	L	ROB, imprecision[2]
FEN-PTCH	Placebo	2.49 (1.71 to 3.62)	3	70	729	L	6.86 (2.93 to 16.08)	M	3.03 (1.77 to 5.17)	L	ROB, imprecision, incoherence [2,3]
HMOR-ER	Placebo	3.21 (2.18 to 4.71)	2	85	1249	L	6.04 (1.96 to 18.58)	M	3.29 (1.77 to 6.14)	L	ROB, heterogeneity, imprecision[2]
HYD-ER	Placebo	1.56 (1.01 to 2.43)	3	0	1260	M	NA		1.62 (0.83 to 3.15)	L	ROB, imprecision
MPH-ER	Placebo	4.38 (2.24 to 8.58)	3	0	480	M	2.84 (1.48 to 5.47)	L	3.49 (2.09 to 5.84)	L	ROB, imprecision[2]
OMOR-ER	Placebo	6.35 (3.95 to 10.21)	3	88	347	L	8.64 (1.4 to 53.27)	M	5.1 (2.57 to 10.12)	L	ROB, heterogeneity, imprecision[2]
OXY-ER	Placebo	5.23 (3.9 to 7)	10	50	3715	M	2.86 (1.56 to 5.24)	M	4.43 (3.25 to 6.04)	M	ROB
TPN-ER	Placebo	3.04 (2.39 to 3.87)	8	7	3048	M	1.21 (0.56 to 2.65)	M	2.55 (1.79 to 3.62)	L	ROB, incoherence[¥]
TPN-NR	Placebo	NA	NA	NA	NA	NA	1.22 (0.3 to 5.05)	VL	1.22 (0.3 to 5.05)	VL	ROB, intransitivity, imprecision
TRA-ER	Placebo	3.16 (2.52 to 3.97)	10	0	4206	M	3.28 (1.64 to 6.6)	M	3.34 (2.41 to 4.61)	M	ROB
TRA-NR	Placebo	4.65 (2.23 to 9.7)	4	0	549	M	2.18 (0.95 to 5.04)	M	3.2 (1.75 to 5.86)	L	ROB, imprecision[2]

OXY-NR	Placebo	NA	NA	NA	NA	NA	2.26 (0.76 to 6.68)	VL	2.26 (0.76 to 6.68)	VL	ROB, intransitivity, imprecision
BUP-PTCH	BUP-Buccal	0.57 (0.34 to 0.96)	1		238	M	2.82 (1.27 to 6.24)	L	1.42 (0.74 to 2.72)	L	ROB, imprecision, incoherence¥
FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	NA	1.49 (0.66 to 3.36)	VL	1.49 (0.66 to 3.36)	VL	ROB, intransitivity, imprecision
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.62 (0.68 to 3.89)	VL	1.62 (0.68 to 3.89)	VL	ROB, intransitivity, imprecision
HYD-ER	BUP-Buccal	NA	NA	NA	NA	NA	0.8 (0.32 to 1.97)	M	0.8 (0.32 to 1.97)	L	ROB, imprecision
MPH-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.72 (0.77 to 3.83)	L	1.72 (0.77 to 3.83)	VL	ROB, intransitivity, imprecision
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.51 (1 to 6.29)	VL	2.51 (1 to 6.29)	VL	ROB, intransitivity, imprecision
OXY-ER	BUP-Buccal	NA	NA	NA	NA	NA	2.18 (1.1 to 4.34)	L	2.18 (1.1 to 4.34)	L	ROB, intransitivity
TPN-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.25 (0.62 to 2.55)	L	1.25 (0.62 to 2.55)	VL	ROB, intransitivity, imprecision
TPN-NR	BUP-Buccal	NA	NA	NA	NA	NA	0.6 (0.13 to 2.72)	VL	0.6 (0.13 to 2.72)	VL	ROB, intransitivity, imprecision
TRA-ER	BUP-Buccal	NA	NA	NA	NA	NA	1.64 (0.83 to 3.24)	L	1.64 (0.83 to 3.24)	VL	ROB, intransitivity, imprecision
TRA-NR	BUP-Buccal	NA	NA	NA	NA	NA	1.58 (0.67 to 3.71)	L	1.58 (0.67 to 3.71)	VL	ROB, intransitivity, imprecision
OXY-NR	BUP-Buccal	NA	NA	NA	NA	NA	1.11 (0.34 to 3.69)	VL	1.11 (0.34 to 3.69)	VL	ROB, intransitivity, imprecision

FEN-PTCH	BUP-PTCH	NA	NA	NA	NA	NA	1.05 (0.54 to 2.05)	L	1.05 (0.54 to 2.05)	VL	ROB, imprecision
HMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.14 (0.54 to 2.39)	L	1.14 (0.54 to 2.39)	VL	ROB, imprecision
HYD-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.56 (0.26 to 1.22)	L	0.56 (0.26 to 1.22)	VL	ROB, imprecision
MPH-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.21 (0.63 to 2.31)	VL	1.21 (0.63 to 2.31)	VL	ROB, intransitivity, imprecision
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.77 (0.8 to 3.92)	L	1.77 (0.8 to 3.92)	VL	ROB, imprecision
OXY-ER	BUP-PTCH	NA	NA	NA	NA	NA	1.54 (0.93 to 2.55)	VL	1.54 (0.93 to 2.55)	VL	ROB, intransitivity, imprecision
TPN-ER	BUP-PTCH	NA	NA	NA	NA	NA	0.88 (0.52 to 1.5)	VL	0.88 (0.52 to 1.5)	VL	ROB, intransitivity, imprecision
TPN-NR	BUP-PTCH	NA	NA	NA	NA	NA	0.42 (0.11 to 1.65)	VL	0.42 (0.11 to 1.65)	VL	ROB, intransitivity, imprecision
TRA-ER	BUP-PTCH	0.87 (0.55 to 1.36)	2	0	414	M	1.39 (0.79 to 2.43)	VL	1.16 (0.74 to 1.82)	L	ROB, intransitivity, imprecision
TRA-NR	BUP-PTCH	NA	NA	NA	NA	NA	1.11 (0.55 to 2.23)	L	1.11 (0.55 to 2.23)	VL	ROB, imprecision
OXY-NR	BUP-PTCH	0.78 (0.44 to 1.38)	1		660	M	NA	L	0.78 (0.29 to 2.15)	L	ROB, imprecision
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.09 (0.48 to 2.46)	L	1.09 (0.48 to 2.46)	VL	ROB, imprecision
HYD-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.53 (0.23 to 1.26)	VL	0.53 (0.23 to 1.26)	VL	ROB, intransitivity, imprecision
MPH-ER	FEN-PTCH	0.78 (0.61 to 1)	2	0	1165	M	2.66 (1.1 to 6.41)	L	1.15 (0.68 to 1.97)	L	ROB, imprecision, incoherence¥
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.69 (0.72 to 3.97)	L	1.69 (0.72 to 3.97)	VL	ROB, imprecision

OXY-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.47 (0.81 to 2.65)	L	1.47 (0.81 to 2.65)	VL	ROB, imprecision
TPN-ER	FEN-PTCH	NA	NA	NA	NA	NA	0.84 (0.45 to 1.59)	L	0.84 (0.45 to 1.59)	VL	ROB, imprecision
TPN-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.4 (0.09 to 1.84)	VL	0.4 (0.09 to 1.84)	VL	ROB, intransitivity, imprecision
TRA-ER	FEN-PTCH	NA	NA	NA	NA	NA	1.1 (0.59 to 2.07)	L	1.1 (0.59 to 2.07)	VL	ROB, imprecision
TRA-NR	FEN-PTCH	NA	NA	NA	NA	NA	1.06 (0.47 to 2.38)	L	1.06 (0.47 to 2.38)	VL	ROB, imprecision
OXY-NR	FEN-PTCH	NA	NA	NA	NA	NA	0.75 (0.22 to 2.51)	VL	0.75 (0.22 to 2.51)	VL	ROB, intransitivity, imprecision
HYD-ER	HMOR-ER	NA	NA	NA	NA	NA	0.49 (0.2 to 1.22)	VL	0.49 (0.2 to 1.22)	VL	ROB, intransitivity, imprecision
MPH-ER	HMOR-ER	NA	NA	NA	NA	NA	1.06 (0.48 to 2.35)	L	1.06 (0.48 to 2.35)	VL	ROB, imprecision
OMOR-ER	HMOR-ER	NA	NA	NA	NA	NA	1.55 (0.62 to 3.84)	L	1.55 (0.62 to 3.84)	VL	ROB, imprecision
OXY-ER	HMOR-ER	0.79 (0.38 to 1.6)	1		138	M	1.83 (0.83 to 4.04)	L	1.35 (0.7 to 2.58)	L	ROB, imprecision
TPN-ER	HMOR-ER	NA	NA	NA	NA	NA	0.77 (0.38 to 1.56)	L	0.77 (0.38 to 1.56)	VL	ROB, imprecision
TPN-NR	HMOR-ER	NA	NA	NA	NA	NA	0.37 (0.08 to 1.75)	VL	0.37 (0.08 to 1.75)	VL	ROB, intransitivity, imprecision
TRA-ER	HMOR-ER	NA	NA	NA	NA	NA	1.01 (0.5 to 2.05)	L	1.01 (0.5 to 2.05)	VL	ROB, imprecision
TRA-NR	HMOR-ER	NA	NA	NA	NA	NA	0.97 (0.41 to 2.32)	L	0.97 (0.41 to 2.32)	VL	ROB, imprecision
OXY-NR	HMOR-ER	NA	NA	NA	NA	NA	0.69 (0.2 to 2.4)	VL	0.69 (0.2 to 2.4)	VL	ROB, intransitivity, imprecision

MPH-ER	HYD-ER	NA	NA	NA	NA	NA	2.16 (0.93 to 5)	L	2.16 (0.93 to 5)	VL	ROB, intransitivity, imprecision
OMOR-ER	HYD-ER	NA	NA	NA	NA	NA	3.15 (1.21 to 8.21)	VL	3.15 (1.21 to 8.21)	VL	ROB, intransitivity
OXY-ER	HYD-ER	NA	NA	NA	NA	NA	2.74 (1.32 to 5.71)	L	2.74 (1.32 to 5.71)	L	ROB, intransitivity
TPN-ER	HYD-ER	NA	NA	NA	NA	NA	1.57 (0.74 to 3.34)	L	1.57 (0.74 to 3.34)	VL	ROB, intransitivity, imprecision
TPN-NR	HYD-ER	NA	NA	NA	NA	NA	0.76 (0.16 to 3.62)	VL	0.76 (0.16 to 3.62)	VL	ROB, intransitivity, imprecision
TRA-ER	HYD-ER	NA	NA	NA	NA	NA	2.06 (0.98 to 4.32)	L	2.06 (0.98 to 4.32)	VL	ROB, intransitivity, imprecision
TRA-NR	HYD-ER	NA	NA	NA	NA	NA	1.98 (0.81 to 4.86)	L	1.98 (0.81 to 4.86)	VL	ROB, intransitivity, imprecision
OXY-NR	HYD-ER	NA	NA	NA	NA	NA	1.39 (0.39 to 4.98)	L	1.39 (0.39 to 4.98)	VL	ROB, imprecision
OMOR-ER	MPH-ER	NA	NA	NA	NA	NA	1.46 (0.63 to 3.41)	VL	1.46 (0.63 to 3.41)	VL	ROB, intransitivity, imprecision
OXY-ER	MPH-ER	0.82 (0.43 to 1.58)	2	0	417	M	1.68 (0.86 to 3.29)	M	1.27 (0.73 to 2.2)	L	ROB, imprecision
TPN-ER	MPH-ER	NA	NA	NA	NA	NA	0.73 (0.4 to 1.33)	M	0.73 (0.4 to 1.33)	L	ROB, imprecision
TPN-NR	MPH-ER	NA	NA	NA	NA	NA	0.35 (0.08 to 1.58)	VL	0.35 (0.08 to 1.58)	VL	ROB, intransitivity, imprecision
TRA-ER	MPH-ER	NA	NA	NA	NA	NA	0.96 (0.52 to 1.75)	M	0.96 (0.52 to 1.75)	L	ROB, imprecision
TRA-NR	MPH-ER	NA	NA	NA	NA	NA	0.92 (0.42 to 2.02)	M	0.92 (0.42 to 2.02)	L	ROB, imprecision

OXY-NR	MPH-ER	NA	NA	NA	NA	NA	0.65 (0.19 to 2.15)	VL	0.65 (0.19 to 2.15)	VL	ROB, intransitivity, imprecision
OXY-ER	OMOR-ER	0.49 (0.32 to 0.77)	1	NA	365	M	1.8 (0.66 to 4.92)	L	0.87 (0.43 to 1.75)	L	ROB, imprecision, incoherence¥
TPN-ER	OMOR-ER	NA	NA	NA	NA	NA	0.5 (0.24 to 1.06)	L	0.5 (0.24 to 1.06)	VL	ROB, imprecision
TPN-NR	OMOR-ER	NA	NA	NA	NA	NA	0.24 (0.05 to 1.16)	VL	0.24 (0.05 to 1.16)	VL	ROB, intransitivity, imprecision
TRA-ER	OMOR-ER	NA	NA	NA	NA	NA	0.65 (0.31 to 1.4)	VL	0.65 (0.31 to 1.4)	VL	ROB, intransitivity, imprecision
TRA-NR	OMOR-ER	NA	NA	NA	NA	NA	0.63 (0.25 to 1.57)	L	0.63 (0.25 to 1.57)	VL	ROB, imprecision
OXY-NR	OMOR-ER	NA	NA	NA	NA	NA	0.44 (0.12 to 1.6)	VL	0.44 (0.12 to 1.6)	VL	ROB, intransitivity, imprecision
TPN-ER	OXY-ER	0.45 (0.38 to 0.54)	4	0	3097	M	0.91 (0.48 to 1.69)	M	0.57 (0.39 to 0.84)	M	ROB
TPN-NR	OXY-ER	NA	NA	NA	NA	NA	0.28 (0.06 to 1.18)	VL	0.28 (0.06 to 1.18)	VL	ROB, intransitivity, imprecision
TRA-ER	OXY-ER	NA	NA	NA	NA	NA	0.75 (0.48 to 1.18)	M	0.75 (0.48 to 1.18)	L	ROB, imprecision
TRA-NR	OXY-ER	NA	NA	NA	NA	NA	0.72 (0.37 to 1.43)	M	0.72 (0.37 to 1.43)	L	ROB, imprecision
OXY-NR	OXY-ER	NA	NA	NA	NA	NA	0.51 (0.16 to 1.57)	VL	0.51 (0.16 to 1.57)	VL	ROB, intransitivity, imprecision
TPN-NR	TPN-ER	NA	NA	NA	NA	NA	0.48 (0.11 to 2.07)	VL	0.48 (0.11 to 2.07)	VL	ROB, intransitivity, imprecision
TRA-ER	TPN-ER	NA	NA	NA	NA	NA	1.31 (0.81 to 2.11)	M	1.31 (0.81 to 2.11)	L	ROB, imprecision

TRA-NR	TPN-ER	NA	NA	NA	NA	NA	1.26 (0.63 to 2.53)	M	1.26 (0.63 to 2.53)	L	ROB, imprecision
OXY-NR	TPN-ER	NA	NA	NA	NA	NA	0.89 (0.28 to 2.77)	VL	0.89 (0.28 to 2.77)	VL	ROB, intransitivity, imprecision
TRA-ER	TPN-NR	NA	NA	NA	NA	NA	2.73 (0.65 to 11.47)	VL	2.73 (0.65 to 11.47)	VL	ROB, intransitivity, imprecision
TRA-NR	TPN-NR	NA	NA	NA	NA	NA	2.62 (0.57 to 12.13)	VL	2.62 (0.57 to 12.13)	VL	ROB, intransitivity, imprecision
OXY-NR	TPN-NR	1.84 (1.25 to 2.7)	1	NA	849	M	1.85 (0.74 to 4.61)		1.85 (0.74 to 4.61)	L	ROB, imprecision
TRA-NR	TRA-ER	0.69 (0.34 to 1.4)	2	45	390	M	1.49 (0.6 to 3.67)	M	0.96 (0.53 to 1.74)	L	ROB, imprecision
OXY-NR	TRA-ER	NA	NA	NA	NA	NA	0.68 (0.22 to 2.04)	VL	0.68 (0.22 to 2.04)	VL	ROB, intransitivity, imprecision
OXY-NR	TRA-NR	NA	NA	NA	NA	NA	0.7 (0.21 to 2.4)	VL	0.7 (0.21 to 2.4)	VL	ROB, intransitivity, imprecision

Footnote: Results are Odds Ratio (95% CIs). Direct estimates are from DerSimonian and Laird random-effects meta-analysis.
Transitivity was checked for indirect estimates. Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of events- a total number of events less than the optimal information size [<300]).
Small-study effects were assessed when there were at least 10 studies using Harbord test.
¥ The best estimate of effect was obtained from direct evidence because there was incoherence.
[1] Rated down twice because of simulatenous intransitivity, imprecision, and incoherence.
[2]Rated down on the basis of imprecision since did not meet OIS.
[3]Not rated down twice because of imprecision and incoherence.
[4]Not rated down twice because of intransitivity and incoherence.
H: high certainty of evidence; M: moderate; L: low; VL: very low.

Appendix 3. 14: Network meta-analysis results for Pain relief

Placebo													
-0.86 (-1.35 to -0.38)	BUPB												
-0.71 (-1 to -0.41)	0.16 (-0.38 to 0.69)	BUPP											
-2.03 (-3.28 to -0.78)	-1.17 (-2.51 to 0.18)	**-1.32 (-2.61 to -0.03)**	COD-ER										
-0.78 (-1.18 to -0.39)	0.08 (-0.54 to 0.7)	-0.08 (-0.54 to 0.39)	1.25 (-0.07 to 2.56)	FENP									
-0.52 (-0.88 to -0.16)	0.35 (-0.25 to 0.95)	0.19 (-0.27 to 0.66)	**1.51 (0.21 to 2.82)**	0.27 (-0.26 to 0.8)	HMOR-ER								
-0.53 (-0.97 to -0.09)	0.33 (-0.32 to 0.98)	0.18 (-0.35 to 0.71)	**1.5 (0.17 to 2.83)**	0.25 (-0.34 to 0.84)	-0.02 (-0.59 to 0.55)	HYD-ER							
-0.86 (-1.17 to -0.56)	0 (-0.57 to 0.57)	-0.15 (-0.57 to 0.27)	1.17 (-0.12 to 2.46)	-0.08 (-0.51 to 0.36)	-0.34 (-0.8 to 0.12)	-0.33 (-0.86 to 0.21)	MPH-ER						
-1.47 (-2.03 to -0.91)	-0.6 (-1.34 to 0.13)	**-0.76 (-1.39 to -0.13)**	0.56 (-0.81 to 1.93)	-0.68 (-1.37 to 0)	**-0.95 (-1.62 to -0.29)**	**-0.94 (-1.65 to -0.22)**	-0.61 (-1.25 to 0.03)	OMOR-ER					
-0.66 (-0.89 to -0.44)	0.2 (-0.33 to 0.73)	0.05 (-0.32 to 0.41)	**1.37 (0.09 to 2.64)**	0.12 (-0.32 to 0.56)	-0.15 (-0.52 to 0.23)	-0.13 (-0.62 to 0.36)	0.2 (-0.14 to 0.53)	**0.81 (0.2 to 1.41)**	OXY-ER				
-0.81 (-1.08 to -0.53)	0.06 (-0.5 to 0.61)	-0.1 (-0.5 to 0.31)	1.22 (-0.06 to 2.51)	-0.02 (-0.5 to 0.46)	-0.29 (-0.73 to 0.15)	-0.27 (-0.79 to 0.25)	0.05 (-0.34 to 0.45)	**0.66 (0.04 to 1.29)**	-0.14 (-0.44 to 0.16)	TPN-ER			
-1.09 (-2.22 to 0.04)	-0.22 (-1.44 to 0.99)	-0.38 (-1.47 to 0.71)	0.94 (-0.75 to 2.63)	-0.3 (-1.49 to 0.88)	-0.57 (-1.76 to 0.61)	-0.56 (-1.77 to 0.65)	-0.23 (-1.39 to 0.94)	0.38 (-0.88 to 1.64)	-0.43 (-1.57 to 0.72)	-0.28 (-1.44 to 0.88)	TPN-NR		
-0.8 (-1.05 to -0.55)	0.06 (-0.47 to 0.6)	-0.09 (-0.44 to 0.26)	1.23 (-0.05 to 2.51)	-0.02 (-0.48 to 0.45)	-0.28 (-0.72 to 0.15)	-0.27 (-0.77 to 0.24)	0.06 (-0.33 to 0.45)	0.67 (0.06 to 1.28)	-0.14 (-0.47 to 0.19)	0.01 (-0.36 to 0.38)	0.29 (-0.85 to 1.43)	TRA-ER	
-1.09 (-1.54 to -0.65)	-0.23 (-0.88 to 0.43)	-0.38 (-0.91 to 0.15)	0.94 (-0.39 to 2.27)	-0.31 (-0.9 to 0.29)	-0.57 (-1.15 to 0)	-0.56 (-1.18 to 0.07)	-0.23 (-0.77 to 0.31)	0.38 (-0.34 to 1.09)	-0.43 (-0.92 to 0.07)	-0.28 (-0.81 to 0.24)	0 (-1.21 to 1.21)	-0.29 (-0.78 to 0.19)	TRA-NR
-0.99 (-1.81 to -0.17)	-0.12 (-1.05 to 0.81)	-0.28 (-1.04 to 0.48)	1.04 (-0.46 to 2.54)	-0.2 (-1.1 to 0.69)	-0.47 (-1.36 to 0.42)	-0.46 (-1.38 to 0.47)	-0.13 (-1 to 0.74)	0.48 (-0.51 to 1.47)	-0.33 (-1.17 to 0.52)	-0.18 (-1.04 to 0.68)	0.1 (-0.68 to 0.88)	-0.19 (-1.03 to 0.65)	0.1 (-0.82 to 1.03)	OXY-NR

Results are mean difference (95%CI). MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch. For each comparison (column vs. row) a mean difference > 0 indicates the intervention in the column is superior to the comparator in the row. Numbers in bold represent statistically significant. Scores range from 0 to 10 cm; lower is better (MID is 1 cm).

Appendix 3. 15: Network meta-analysis results for physical functioning

Placebo											
3.67 (-0.02,7.37)	_BUPB_										
2.16 (-0.60,4.92)	-1.51 (-6.12,3.09)	BUPP									
17.76 (7.35,28.17)	**14.09 (3.04,25.13)**	**15.60 (4.83,26.37)**	COD-ER								
1.53 (-0.60,3.65)	-2.15 (-6.41,2.11)	-0.63 (-4.01,2.74)	**-16.23 (-26.86,-5.61)**	FEN-PTCH							
3.45 (1.28,5.61)	-0.23 (-4.51,4.05)	1.29 (-2.22,4.79)	**-14.31 (-24.94,-3.68)**	1.92 (-1.09,4.93)	HMOR-ER						
-1.13 (-6.23,3.97)	-4.80 (-11.10,1.49)	-3.29 (-9.09,2.51)	**-18.89 (-30.48,-7.30)**	-2.66 (-8.18,2.87)	-4.58 (-10.11,0.96)	HYD-ER					
1.98 (-0.30,4.26)	-1.70 (-6.04,2.65)	-0.18 (-3.71,3.34)	**-15.78 (-26.44,-5.13)**	0.45 (-1.88,2.79)	-1.47 (-4.57,1.63)	3.11 (-2.48,8.69)	MPH-ER				
1.67 (-1.40,4.75)	-2.00 (-6.81,2.81)	-0.48 (-4.61,3.65)	**-16.09 (-26.94,-5.23)**	0.15 (-3.56,3.86)	-1.77 (-5.48,1.94)	2.80 (-3.15,8.76)	-0.30 (-4.06,3.46)	OMOR-ER			
1.21 (0.01,2.40)	-2.47 (-6.35,1.42)	-0.95 (-3.95,2.05)	**-16.55 (-27.03,-6.08)**	-0.32 (-2.67,2.03)	-2.24 (-4.54,0.06)	2.34 (-2.90,7.57)	-0.77 (-3.11,1.56)	-0.47 (-3.56,2.62)	OXY-ER		
2.13 (0.67,3.59)	-1.54 (-5.51,2.43)	-0.03 (-3.14,3.09)	**-15.63 (-26.14,-5.12)**	0.61 (-1.95,3.16)	-1.31 (-3.88,1.26)	3.26 (-2.04,8.57)	0.16 (-2.47,2.79)	0.46 (-2.89,3.81)	0.93 (-0.72,2.57)	TPN-ER	
1.81 (-0.32,3.95)	-1.86 (-6.13,2.41)	-0.35 (-3.83,3.14)	**-15.95 (-26.57,-5.33)**	0.29 (-2.72,3.29)	-1.64 (-4.70,1.42)	2.94 (-2.59,8.47)	-0.17 (-3.22,2.89)	0.14 (-3.60,3.87)	0.61 (-1.79,3.00)	-0.32 (-2.87,2.23)	TRA-ER

Results are mean difference (95%CI). MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch. For each comparison (column vs. row) a mean difference > 0 indicates the intervention in the column is superior to the comparator in the row. Numbers in bold represent statistically significant. scores range from 0 to 100 point; higher is better (MID is 5 point).

Appendix 3. 16: Network meta-analysis for constipation

Placebo													
2.58 (1.42 to 4.69)	BUP-Buccal												
3.55 (2.43 to 5.19)	1.38 (0.78 to 2.44)	BUP-PTCH											
7.37 (2.68 to 20.29)	2.86 (0.88 to 9.25)	2.07 (0.7 to 6.11)	COD-ER										
3.96 (2.78 to 5.65)	1.53 (0.77 to 3.07)	1.11 (0.66 to 1.87)	0.54 (0.18 to 1.57)	FEN-PTCH									
5.71 (4.15 to 7.85)	**2.21 (1.12 to 4.35)**	1.61 (0.98 to 2.63)	0.77 (0.27 to 2.24)	1.44 (0.9 to 2.3)	HMOR-ER								
2.72 (1.47 to 5.01)	1.05 (0.45 to 2.48)	0.76 (0.37 to 1.57)	0.37 (0.11 to 1.2)	0.69 (0.34 to 1.39)	0.48 (0.24 to 0.95)	HYD-ER							
6.86 (5.05 to 9.31)	**2.66 (1.36 to 5.19)**	**1.93 (1.19 to 3.14)**	0.93 (0.32 to 2.68)	**1.73 (1.36 to 2.2)**	1.2 (0.78 to 1.85)	**2.52 (1.27 to 5.01)**	MPH-ER						
5.74 (3.81 to 8.65)	**2.22 (1.08 to 4.59)**	1.61 (0.92 to 2.82)	0.78 (0.26 to 2.32)	1.45 (0.87 to 2.42)	1.01 (0.6 to 1.68)	**2.11 (1.01 to 4.42)**	0.84 (0.52 to 1.35)	OMOR-ER					
6.34 (5.21 to 7.71)	**2.46 (1.31 to 4.6)**	**1.78 (1.17 to 2.73)**	0.86 (0.31 to 2.41)	**1.6 (1.13 to 2.26)**	1.11 (0.78 to 1.58)	**2.33 (1.23 to 4.44)**	0.92 (0.7 to 1.23)	1.1 (0.74 to 1.64)	OXY-ER				
2.85 (2.27 to 3.57)	1.1 (0.58 to 2.09)	0.8 (0.52 to 1.25)	0.39 (0.14 to 1.09)	0.72 (0.49 to 1.05)	0.5 (0.34 to 0.73)	1.05 (0.55 to 2.02)	**0.42 (0.3 to 0.57)**	**0.5 (0.32 to 0.76)**	**0.45 (0.38 to 0.53)**	TPN-ER			
1.91 (0.78 to 4.65)	0.74 (0.28 to 1.99)	0.54 (0.24 to 1.2)	0.26 (0.07 to 1)	0.48 (0.18 to 1.26)	0.33 (0.13 to 0.86)	0.7 (0.24 to 2.07)	**0.28 (0.11 to 0.71)**	**0.33 (0.12 to 0.89)**	**0.3 (0.12 to 0.75)**	0.67 (0.27 to 1.68)	TPN-NR		
4.5 (3.37 to 6)	1.74 (0.92 to 3.31)	1.27 (0.83 to 1.94)	0.61 (0.21 to 1.75)	1.14 (0.72 to 1.8)	0.79 (0.51 to 1.21)	1.66 (0.84 to 3.26)	0.66 (0.43 to 1)	0.78 (0.47 to 1.29)	0.71 (0.5 to 1.01)	**1.58 (1.09 to 2.28)**	2.36 (0.95 to 5.87)	TRA-ER	
3.89 (2.28 to 6.66)	1.51 (0.68 to 3.32)	1.1 (0.58 to 2.06)	0.53 (0.17 to 1.66)	0.98 (0.52 to 1.87)	0.68 (0.37 to 1.27)	1.43 (0.63 to 3.24)	0.57 (0.31 to 1.05)	0.68 (0.35 to 1.33)	0.61 (0.35 to 1.09)	1.37 (0.76 to 2.45)	2.04 (0.73 to 5.68)	0.87 (0.53 to 1.42)	TRA-NR
4.82 (2.18 to 10.64)	1.87 (0.76 to 4.6)	1.36 (0.68 to 2.72)	0.65 (0.18 to 2.36)	1.22 (0.51 to 2.9)	0.84 (0.36 to 1.98)	1.77 (0.65 to 4.83)	0.7 (0.3 to 1.64)	0.84 (0.34 to 2.05)	0.76 (0.34 to 1.72)	1.69 (0.74 to 3.86)	**2.52 (1.68 to 3.79)**	1.07 (0.47 to 2.42)	1.24 (0.48 to 3.17)	OXY-NR

Results are Odds ratio (95%CI). MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch. For each comparison (column vs. row) an OR> 1 indicates the intervention in the column is less harmful than the comparator in the row. Numbers in bold represent statistically significant.

Appendix 3. 17: Network meta-analysis for vomiting

Placebo												
5.28 (2.95 to 9.45)	BUP-Buccal											
3.59 (2.33 to 5.54)	0.68 (0.4 to 1.15)	BUPPTCH										
9.83 (5.9 to 16.38)	1.86 (0.86 to 4.04)	**2.74 (1.4 to 5.35)**	FENPTCH									
4.75 (2.77 to 8.14)	0.9 (0.41 to 1.99)	1.32 (0.66 to 2.64)	0.48 (0.23 to 1)	HMORER								
1.94 (1.04 to 3.61)	0.37 (0.16 to 0.86)	0.54 (0.25 to 1.15)	**0.2 (0.09 to 0.44)**	**0.41 (0.18 to 0.93)**	HYDER							
8.77 (5.4 to 14.25)	1.66 (0.78 to 3.54)	**2.44 (1.27 to 4.68)**	0.89 (0.67 to 1.19)	1.85 (0.91 to 3.74)	**4.52 (2.05 to 9.95)**	MPHER						
19.57 (10.68 to 35.86)	**3.71 (1.6 to 8.59)**	**5.45 (2.59 to 11.47)**	1.99 (0.94 to 4.21)	**4.12 (1.87 to 9.08)**	**10.09 (4.23 to 24.04)**	**2.23 (1.08 to 4.61)**	OMORER					
7.12 (5.42 to 9.35)	1.35 (0.71 to 2.56)	**1.98 (1.19 to 3.31)**	0.72 (0.44 to 1.19)	1.5 (0.85 to 2.64)	**3.67 (1.86 to 7.24)**	0.81 (0.51 to 1.28)	**0.36 (0.21 to 0.64)**	OXYER				
2.85 (2.11 to 3.84)	0.54 (0.28 to 1.04)	0.79 (0.47 to 1.34)	0.29 (0.17 to 0.49)	0.6 (0.33 to 1.08)	1.47 (0.74 to 2.93)	**0.32 (0.2 to 0.54)**	**0.15 (0.08 to 0.27)**	**0.4 (0.32 to 0.5)**	TPNER			
1.93 (0.7 to 5.33)	0.37 (0.13 to 1.05)	0.54 (0.21 to 1.35)	**0.2 (0.06 to 0.61)**	0.41 (0.13 to 1.28)	1 (0.3 to 3.28)	**0.22 (0.07 to 0.68)**	**0.1 (0.03 to 0.32)**	**0.27 (0.09 to 0.78)**	0.68 (0.24 to 1.95)	TPNNR		
4.04 (2.57 to 6.34)	0.76 (0.39 to 1.51)	1.12 (0.67 to 1.9)	**0.41 (0.21 to 0.81)**	0.85 (0.42 to 1.72)	2.08 (0.96 to 4.49)	**0.46 (0.24 to 0.89)**	**0.21 (0.1 to 0.44)**	**0.57 (0.33 to 0.96)**	1.42 (0.82 to 2.43)	2.09 (0.73 to 6.01)	TRAER	
4.28 (1.87 to 9.78)	0.81 (0.31 to 2.15)	1.19 (0.5 to 2.85)	0.44 (0.16 to 1.15)	0.9 (0.34 to 2.42)	2.21 (0.78 to 6.21)	0.49 (0.19 to 1.27)	**0.22 (0.08 to 0.61)**	0.6 (0.25 to 1.44)	**1.5 (0.62 to 3.62)**	2.21 (0.62 to 7.85)	1.06 (0.52 to 2.15)	TRANR
4.06 (1.59 to 10.39)	0.77 (0.29 to 2.06)	1.13 (0.49 to 2.6)	0.41 (0.14 to 1.2)	0.86 (0.29 to 2.53)	2.09 (0.68 to 6.46)	0.46 (0.16 to 1.33)	**0.21 (0.07 to 0.63)**	0.57 (0.21 to 1.52)	1.43 (0.53 to 3.82)	**2.1 (1.43 to 3.09)**	1.01 (0.38 to 2.69)	0.95 (0.28 to 3.17)	OXYNR

Results are Odds ratio (95%CI). MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch. For each comparison (column vs. row) an OR> 1 indicates the intervention in the column is less harmful than the comparator in the row. Numbers in bold represent statistically significant.

Appendix 3. 18: Network meta-analysis for nausea

Placebo													
2.03 (1.1 to 3.75)	BUPBuccal												
2.89 (1.94 to 4.3)	1.42 (0.74 to 2.72)	BUP-Ptch											
3.03 (1.77 to 5.17)	1.49 (0.66 to 3.36)	1.05 (0.54 to 2.05)	FEN-Ptch										
3.29 (1.77 to 6.14)	1.62 (0.68 to 3.89)	1.14 (0.54 to 2.39)	1.09 (0.48 to 2.46)	HMOR-ER									
1.62 (0.83 to 3.15)	0.8 (0.32 to 1.97)	0.56 (0.26 to 1.22)	0.53 (0.23 to 1.26)	0.49 (0.2 to 1.22)	HYD-ER								
3.49 (2.09 to 5.84)	1.72 (0.77 to 3.83)	1.21 (0.63 to 2.31)	1.15 (0.68 to 1.97)	1.06 (0.48 to 2.35)	2.16 (0.93 to 5)	MPH-ER							
5.1 (2.57 to 10.12)	**2.51 (1 to 6.29)**	1.77 (0.8 to 3.92)	1.69 (0.72 to 3.97)	1.55 (0.62 to 3.84)	**3.15 (1.21 to 8.21)**	1.46 (0.63 to 3.41)	OMOR-ER						
4.43 (3.25 to 6.04)	**2.18 (1.1 to 4.34)**	1.54 (0.93 to 2.55)	1.47 (0.81 to 2.65)	1.35 (0.7 to 2.58)	**2.74 (1.32 to 5.71)**	1.27 (0.73 to 2.2)	0.87 (0.43 to 1.75)	OXY-ER					
2.55 (1.79 to 3.62)	1.25 (0.62 to 2.55)	0.88 (0.52 to 1.5)	0.84 (0.45 to 1.59)	0.77 (0.38 to 1.56)	1.57 (0.74 to 3.34)	0.73 (0.4 to 1.33)	0.5 (0.24 to 1.06)	**0.57 (0.39 to 0.84)**	TPN-ER				
1.22 (0.3 to 5.05)	0.6 (0.13 to 2.72)	0.42 (0.11 to 1.65)	0.4 (0.09 to 1.84)	0.37 (0.08 to 1.75)	0.76 (0.16 to 3.62)	0.35 (0.08 to 1.58)	0.24 (0.05 to 1.16)	0.28 (0.06 to 1.18)	0.48 (0.11 to 2.07)	TPN-NR			
3.34 (2.41 to 4.61)	1.64 (0.83 to 3.24)	1.16 (0.74 to 1.82)	1.1 (0.59 to 2.07)	1.01 (0.5 to 2.05)	2.06 (0.98 to 4.32)	0.96 (0.52 to 1.75)	0.65 (0.31 to 1.4)	0.75 (0.48 to 1.18)	1.31 (0.81 to 2.11)	2.73 (0.65 to 11.47)	TRA-ER		
3.2 (1.75 to 5.86)	1.58 (0.67 to 3.71)	1.11 (0.55 to 2.23)	1.06 (0.47 to 2.38)	0.97 (0.41 to 2.32)	1.98 (0.81 to 4.86)	0.92 (0.42 to 2.02)	0.63 (0.25 to 1.57)	0.72 (0.37 to 1.43)	1.26 (0.63 to 2.53)	2.62 (0.57 to 12.13)	0.96 (0.53 to 1.74)	TRA-NR	
2.26 (0.76 to 6.68)	1.11 (0.34 to 3.69)	0.78 (0.29 to 2.15)	0.75 (0.22 to 2.51)	0.69 (0.2 to 2.4)	1.39 (0.39 to 4.98)	0.65 (0.19 to 2.15)	0.44 (0.12 to 1.6)	0.51 (0.16 to 1.57)	0.89 (0.28 to 2.77)	1.85 (0.74 to 4.61)	0.68 (0.22 to 2.04)	0.7 (0.21 to 2.4)	OXY-NR

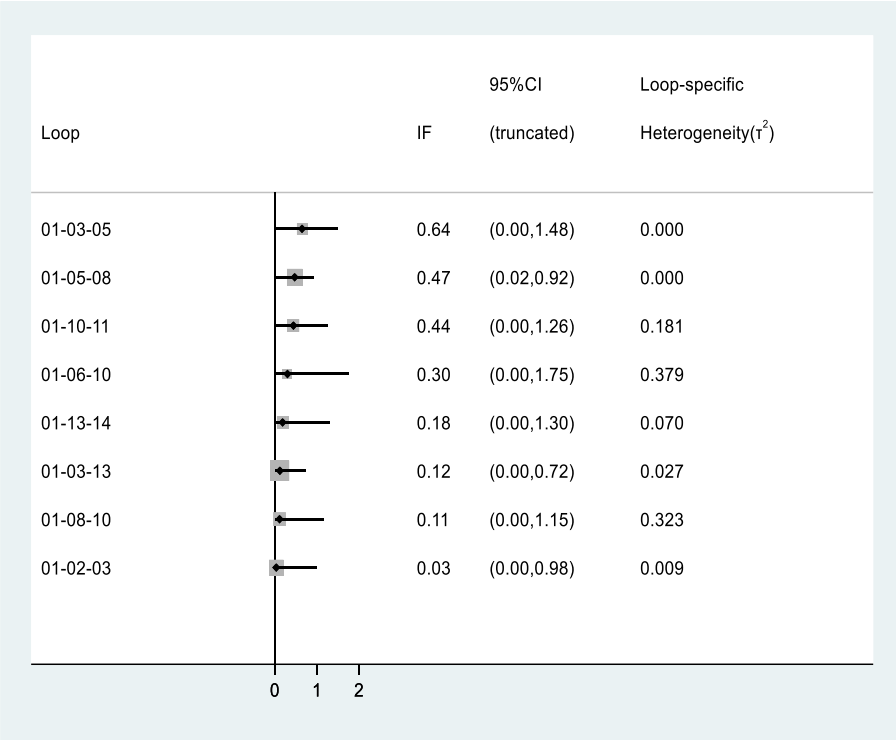
Results are Odds ratio (95%CI). MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released; PTCH: patch. For each comparison (column vs. row) an OR> 1 indicates the intervention in the column is less harmful than the comparator in the row. Numbers in bold represent statistically significant.

Appendix 3. 19: node-splitting Results-Pain relief

Comparisons	**Indirect and direct difference**		**P-value**
	Estimate	**SE**	
BUP-Buccal vs PLC[£]	0.07	0.66	0.91
BUP-PTCH vs PLC	0.13	0.33	0.69
FEN-PTCH vs PLC	0.08	0.42	0.84
HMOR-ER vs PLC	0.19	0.40	0.62
MPH-ER vs PLC	-0.18	0.32	0.64
OXY-ER vs PLC	0.697	-0.1	0.26
TPN-ER vs PLC	0.231	0.47	0.39
TRA-ER vs PLC	0.679	0.15	0.35
TRA-NR vs PLC	0.796	-0.16	0.6
BUP-PTCH vs BUP-Buccal	0.909	0.08	0.66
FEN-PTCH vs BUP-PTCH	0.196	0.77	0.59
TRA-ER vs BUP-PTCH	0.761	-0.12	0.41
MPH-ER vs FEN-PTCH	0.214	0.58	0.47
OXY-ER vs HMOR-ER	0.628	0.2	0.41
OXY-ER vs MPH-ER	0.746	0.12	0.36
TPN-ER vs OXY-ER	0.392	-0.28	0.33
TRA-NR vs TRA-ER	0.796	0.16	0.6

[£] MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone; PLC: placebo. ER: Extended-released; NR: Normal-released; PTCH: patch.

Appendix 3. 20: Incoherence plot for Pain Relief

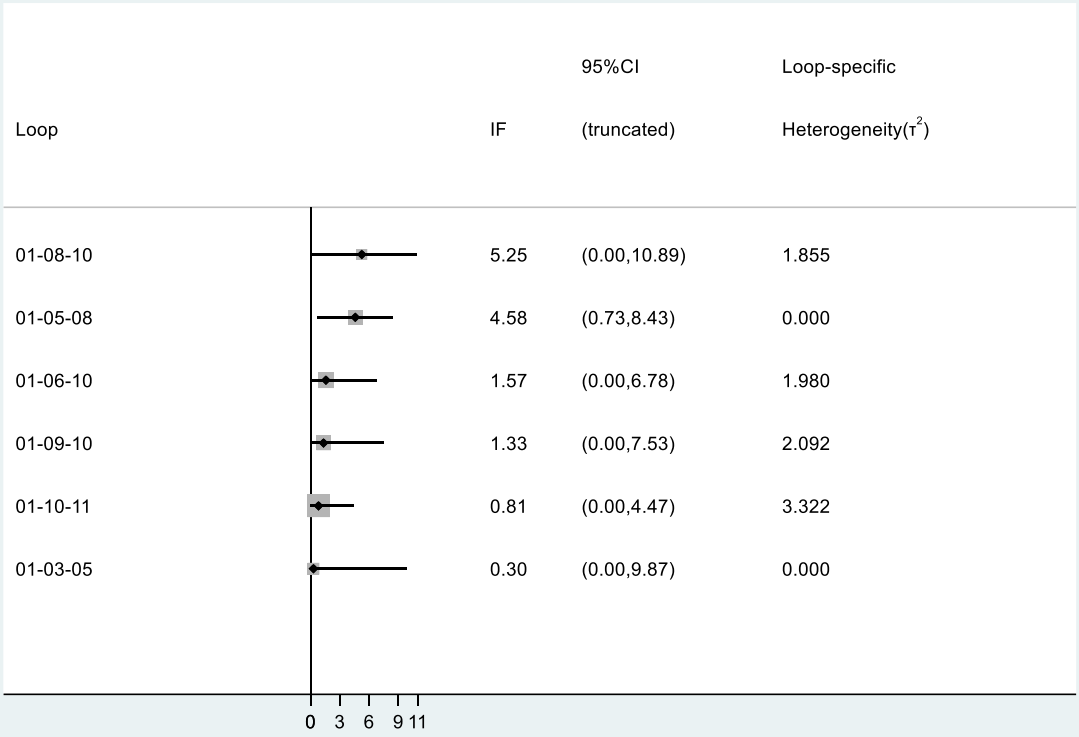


Incoherance factors (IF) along with 95% confidence intervals (CI) are displayed. IFs are calculated as the absolute difference between direct and indirect estimates. Comparisons in which the lower CI limit does not reach the zero line are considered to present statistically significant inconsistency.

01-03-05=Placebo-BUP_PATCH-FEN_PATCH.
01-05-08=PLACEBO-FEN_PATCH-MPH-ER.
01-10-11= PLACEBO-OXY_ER-TPN_ER.
01-06-10= PLACEBO-HMOR_ER-OXY_ER.
01-13-14=PLACEBO-TRA_ER-TRA_NR.
01-03-13=PLACEBO-BUP_PATCH-TRA_ER.
01-08-10= PLACEBO-MPH_ER-OXY_ER.
01-02-03=PLACEBO-BUP_BUCCAL-BUP_PATCH.

Global test of incoherence=0.640.

Appendix 3. 21: incoherence plot for physical function

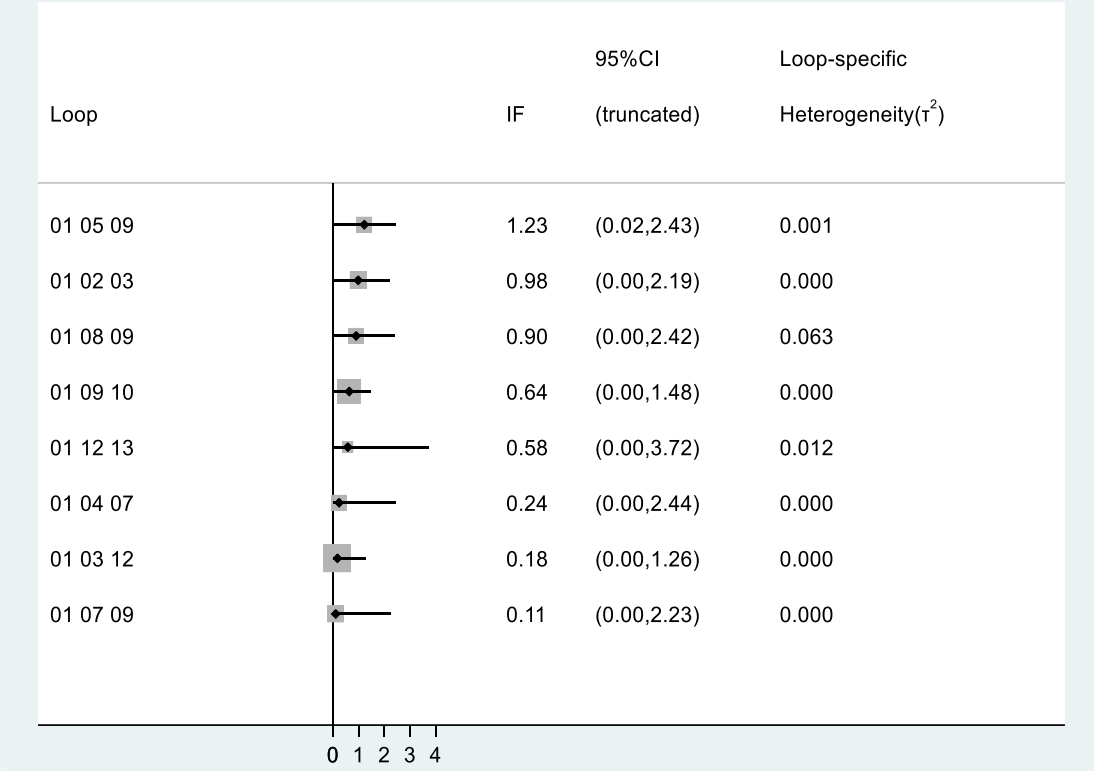


Incoherance factors (IF) along with 95% confidence intervals (CI) are displayed. IFs are calculated as the absolute difference between direct and indirect estimates. Comparisons in which the lower CI limit does not reach the zero line are considered to present statistically significant inconsistency.

01-08-10=Placebo-morphine-ER-oxycodone-ER.
01-05-08= placebo-fentanyl-patch- morphine-ER.
01-06-10= placebo-hydromorphone-ER-oxycodone-ER
01-09-10= placebo-oxymorphone-ER- oxycodone-ER.
01-10-11= placebo- oxycodone-ER- tapentadol-ER.
01-03-05=placebo- buprenorphine-patch- fentanyl-patch.

Global test of incoherence=0.620.

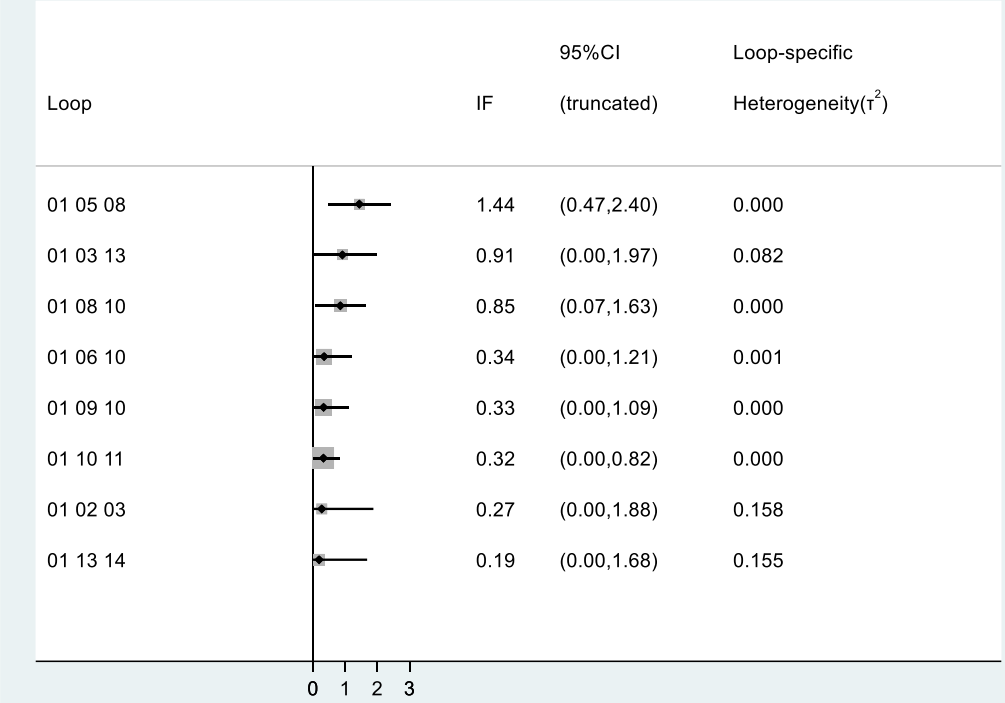
Appendix 3. 22: incoherence plot for vomiting



The inconsistency plot (IF) that presents for each loop the estimated inconsistency factor and its confidence interval (truncated to 0) are displayed.

01 05 09=placebo_HMOR-ER_OXY-ER
01 02 03= placebo_BUP-buccal_BUP-patch
01 08 09=placebo_OMOR-ER_OXY-ER
01 09 10= placebo_OXY-ER_TPN-ER
01 12 13=placebo_TRA-ER_TRA-NR
01 04 07= placebo_FEN-patch_MPH-ER
01 03 12=placebo_BUP-patch_TRA-ER
01 07 09=placebo_MPH-ER_OXY-ER
Comparisons in which the lower CI limit does not reach the zero line are considered to present statistically significant inconsistency. The within-loop heterogeneities have been estimated using the method of moments estimator.

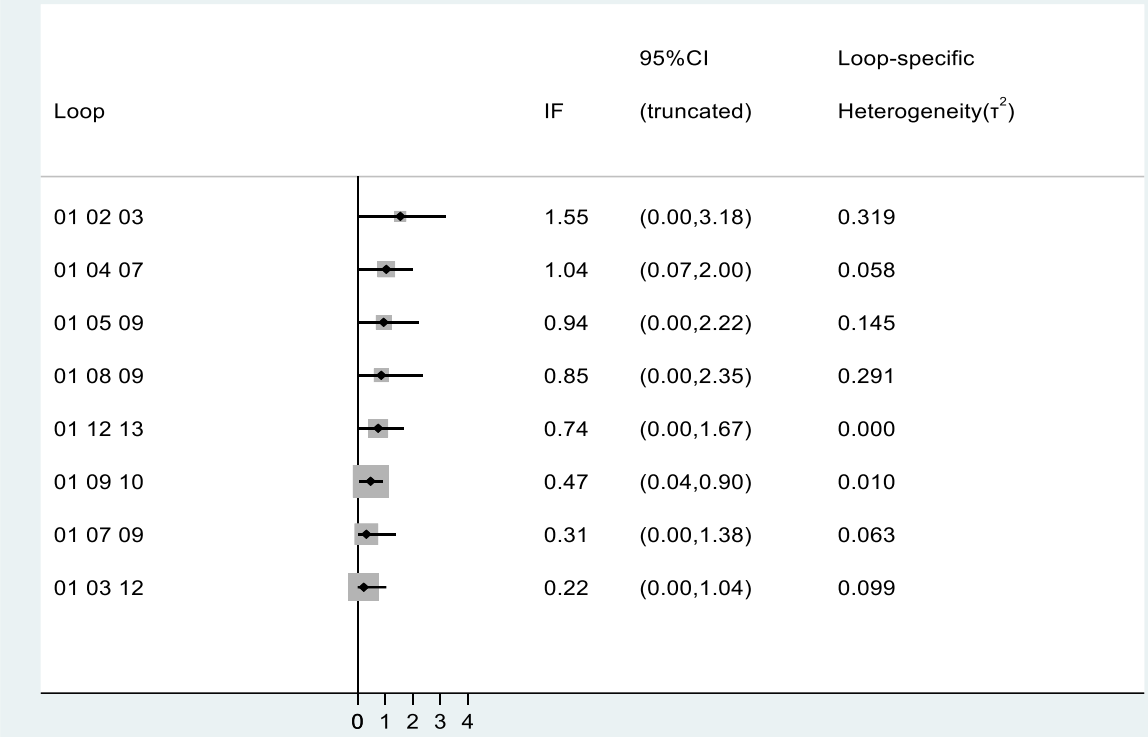
Appendix 3. 23: incoherence plot for constipation



The inconsistency plot (IF) that presents for each loop the estimated inconsistency factor and its confidence interval (truncated to 0) are displayed.

01 05 08=placebo_FEN-patch_ MPH-ER
01 03 13=placebo_BUP-patch_TRA-ER
01 08 10=placebo_MPH-ER_OXY-ER
01 06 10=placebo_HMOR-ER_OXY-ER
01 09 10=placebo_OMOR-ER_OXY-ER
01 10 11=placebo_OXY-ER_TPN-ER
01 02 03=placebo_BUP-Buccal_BUP-patch
01 13 14=placebo_TRA-ER_TRA-NR
Comparisons in which the lower CI limit does not reach the zero line are considered to present statistically significant inconsistency. The within-loop heterogeneities have been estimated using the method of moments estimator.

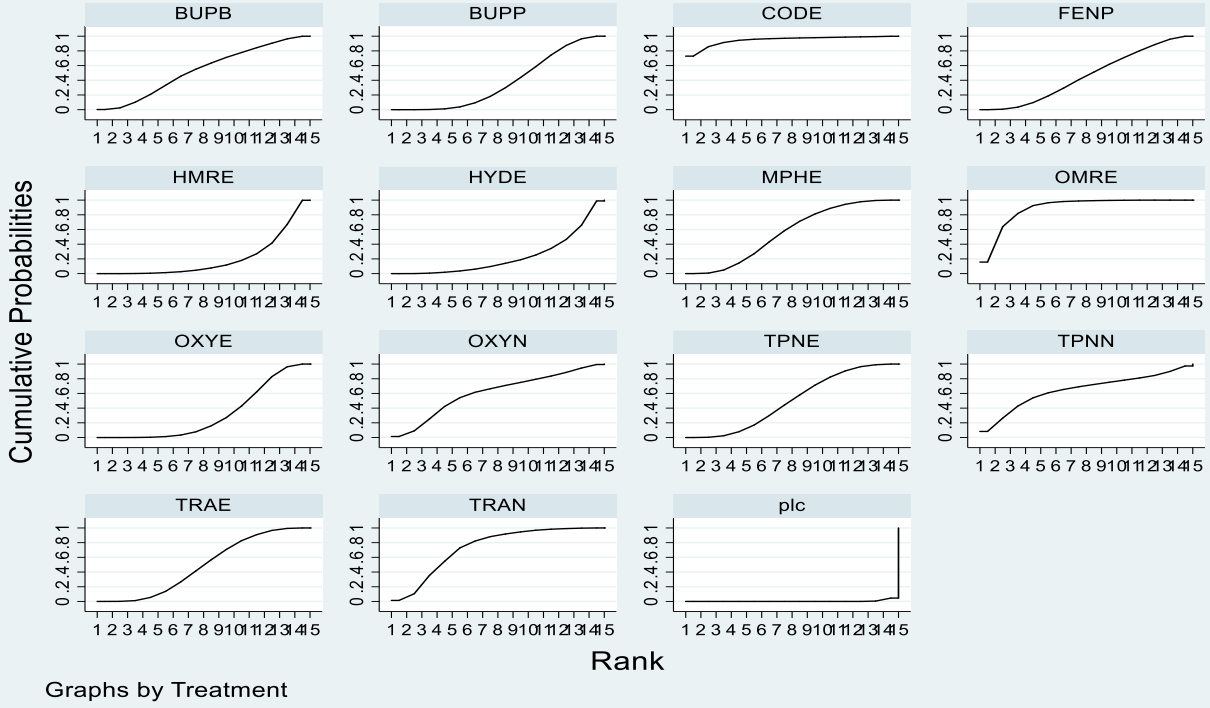
Appendix 3. 24: Incoherence plot for nausea



The inconsistency plot (IF) that presents for each loop the estimated inconsistency factor and its confidence interval (truncated to 0) are displayed.

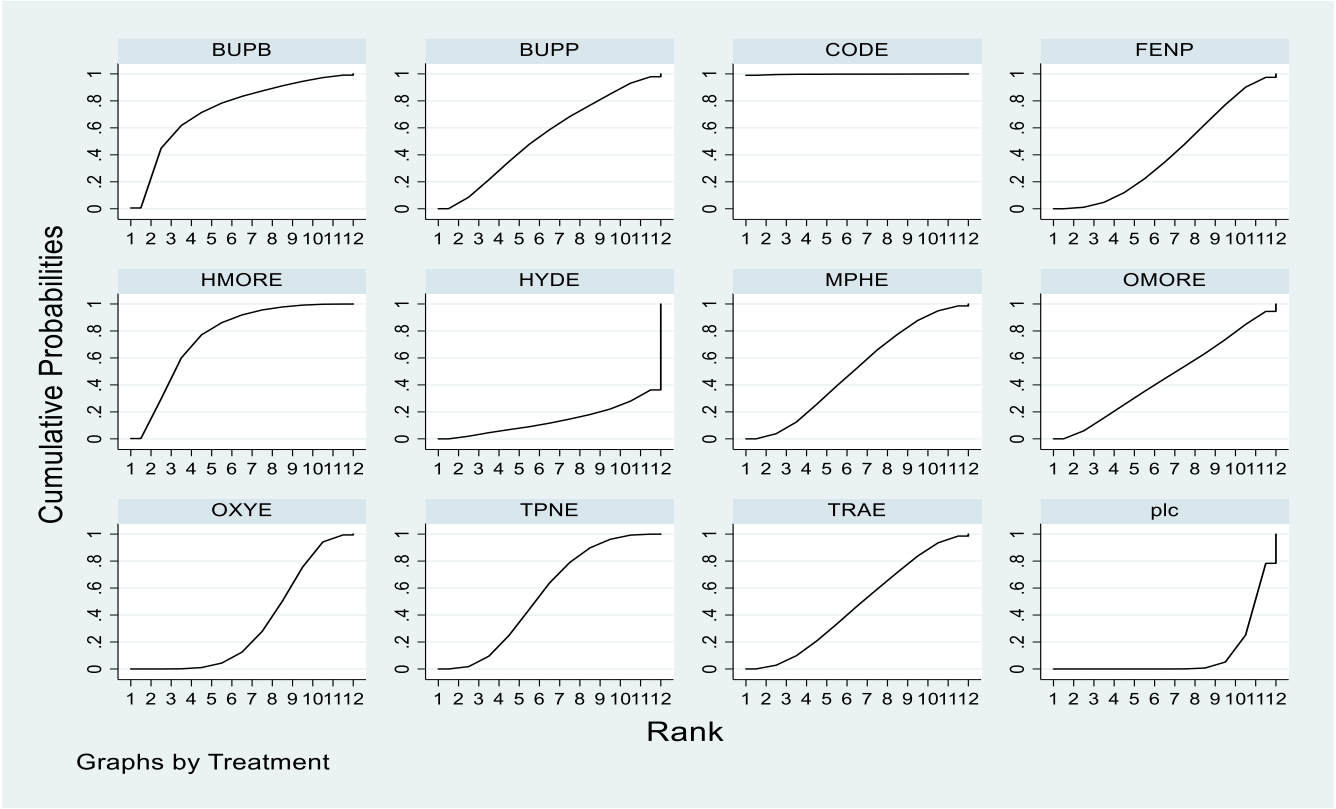
01 02 03= placebo_BUP-buccal_BUP-patch
01 04 07= placebo_FEN-patch_MPH-ER
01 05 09=placebo_HMOR-ER_OXY-ER
01 08 09=placebo_OMOR-ER_OXY-ER
01 12 13=placebo_TRA-ER_TRA-NR
01 09 10= placebo_OXY-ER_TPN-ER
01 07 09=placebo_MPH-ER_OXY-ER
01 03 12=placebo_BUP-patch_TRA-ER
Comparisons in which the lower CI limit does not reach the zero line are considered to present statistically significant inconsistency. The within-loop heterogeneities have been estimated using the method of moments estimator.

Appendix 3. 25: The surface under the cumulative ranking (SUCRA) values for all treatments for pain relief.

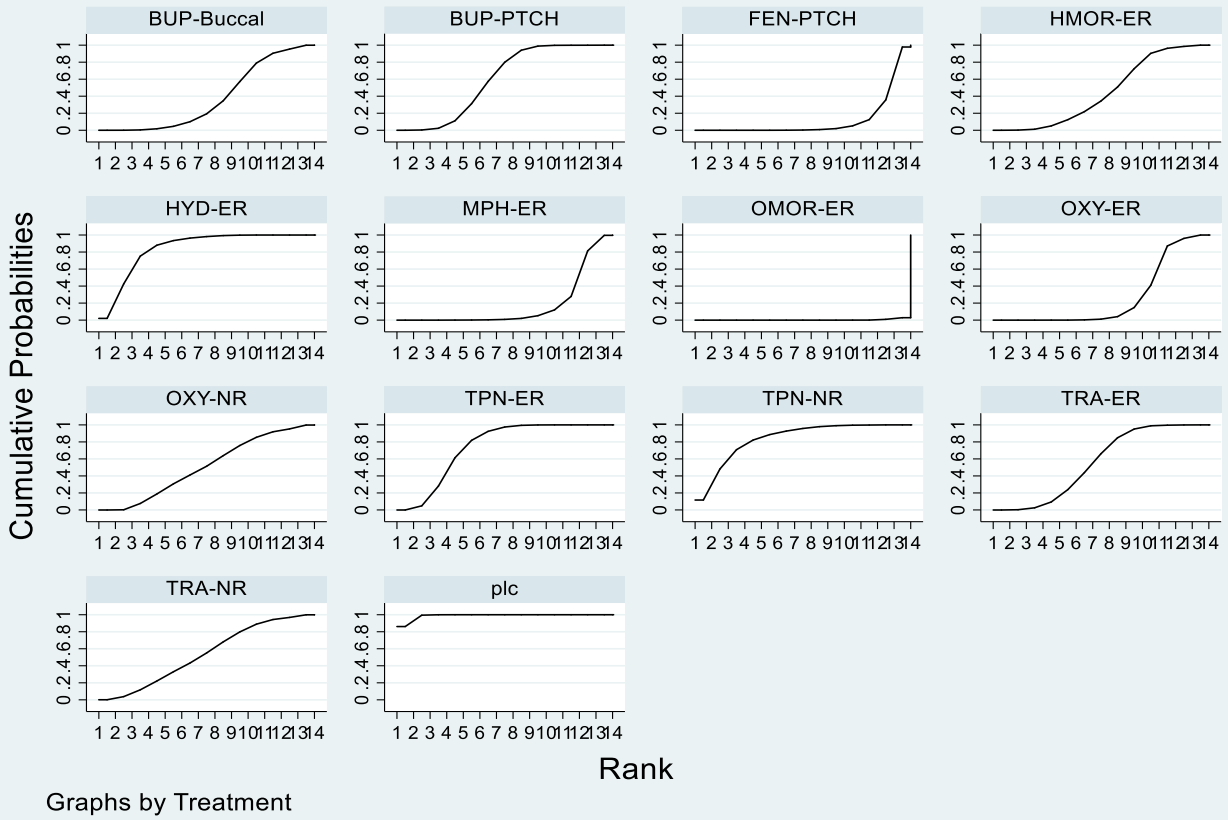


MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone; PLC: placebo. ER: Extended-released; NR: Normal-released; PTCH: patch.

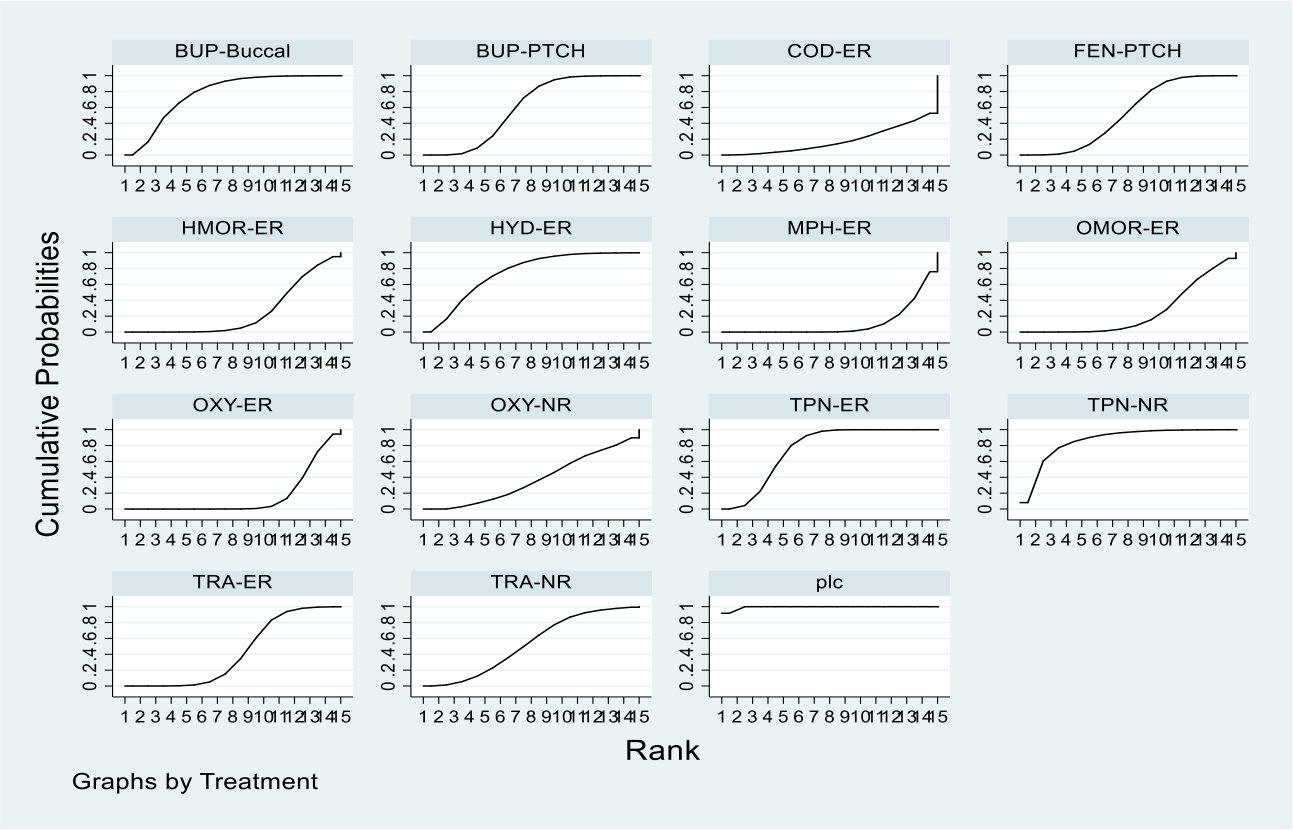
Appendix 3. 26: The surface under the cumulative ranking (SUCRA) values for all treatments for physical function



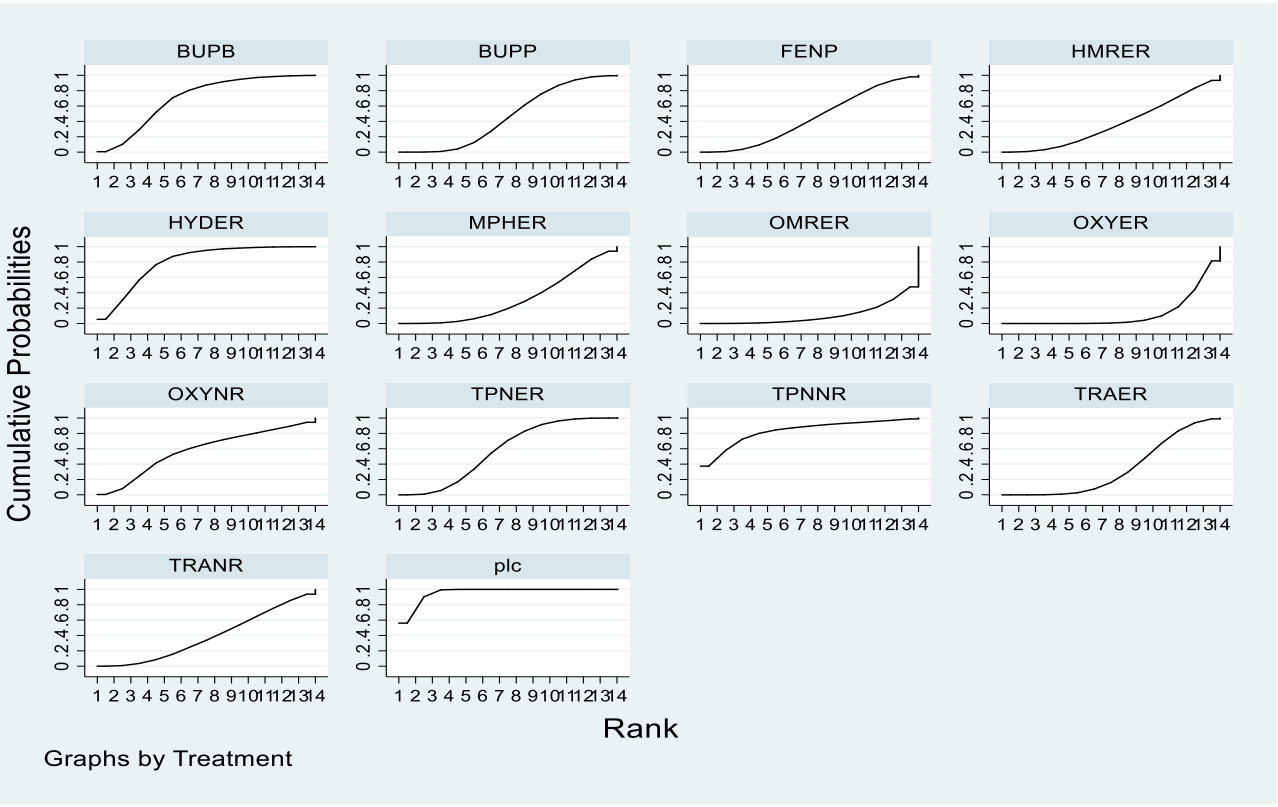
Appendix 3. 27: The surface under the cumulative ranking (SUCRA) values for all treatments for vomiting



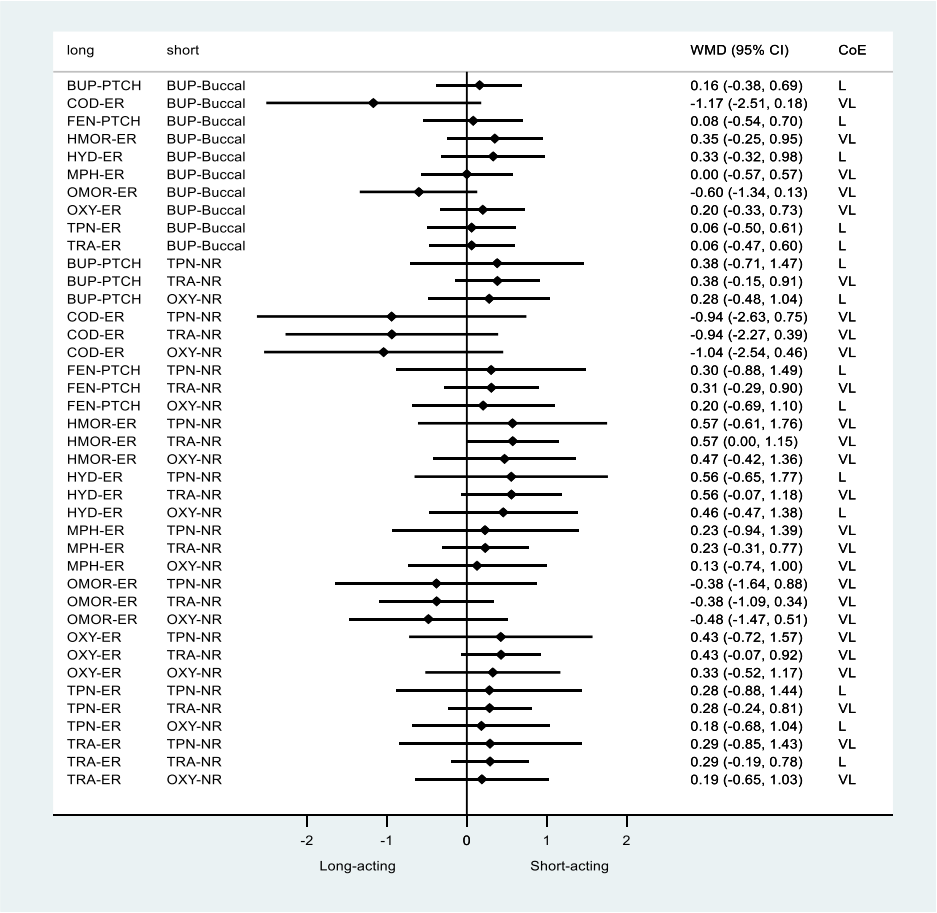
Appendix 3. 28: The surface under the cumulative ranking (SUCRA) values for all treatments for constipation



Appendix 3. 29: The surface under the cumulative ranking (SUCRA) values for all treatments for nausea

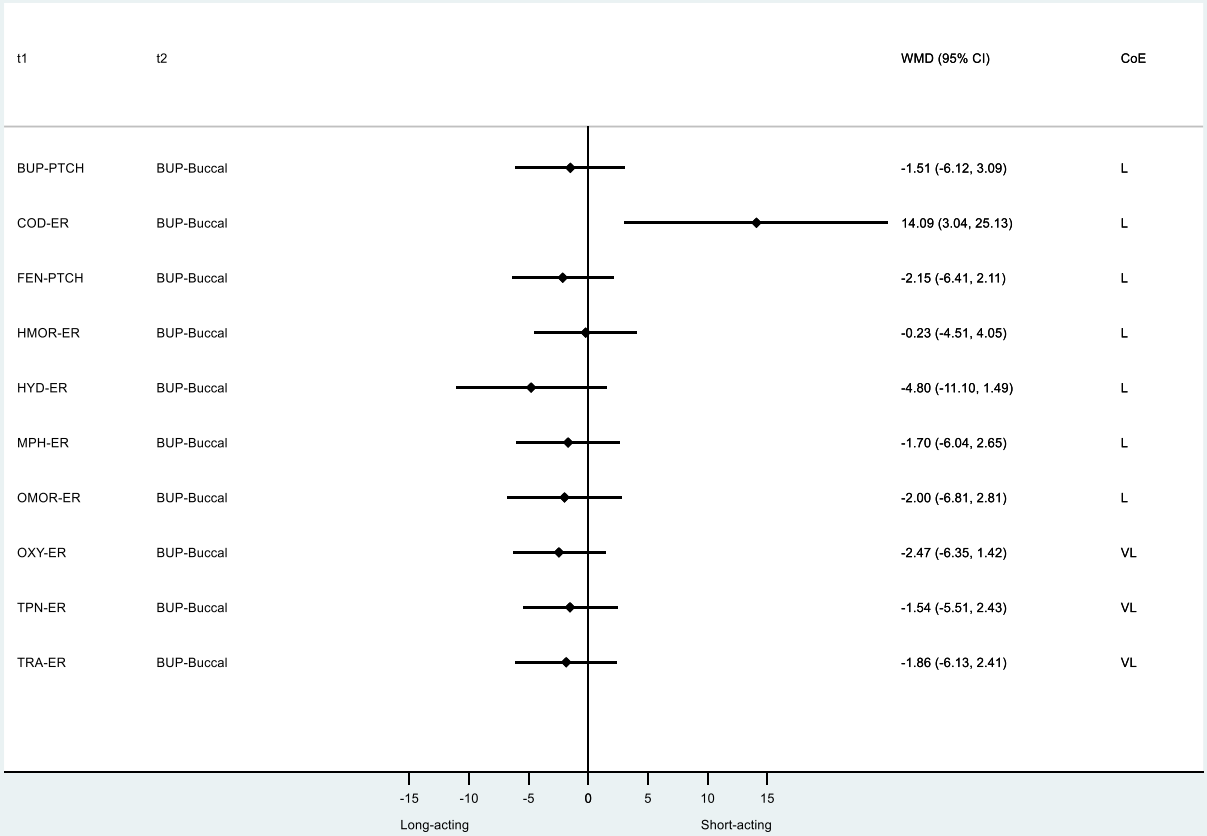


Appendix 3. 30: LA vs SA opioids for pain relief*



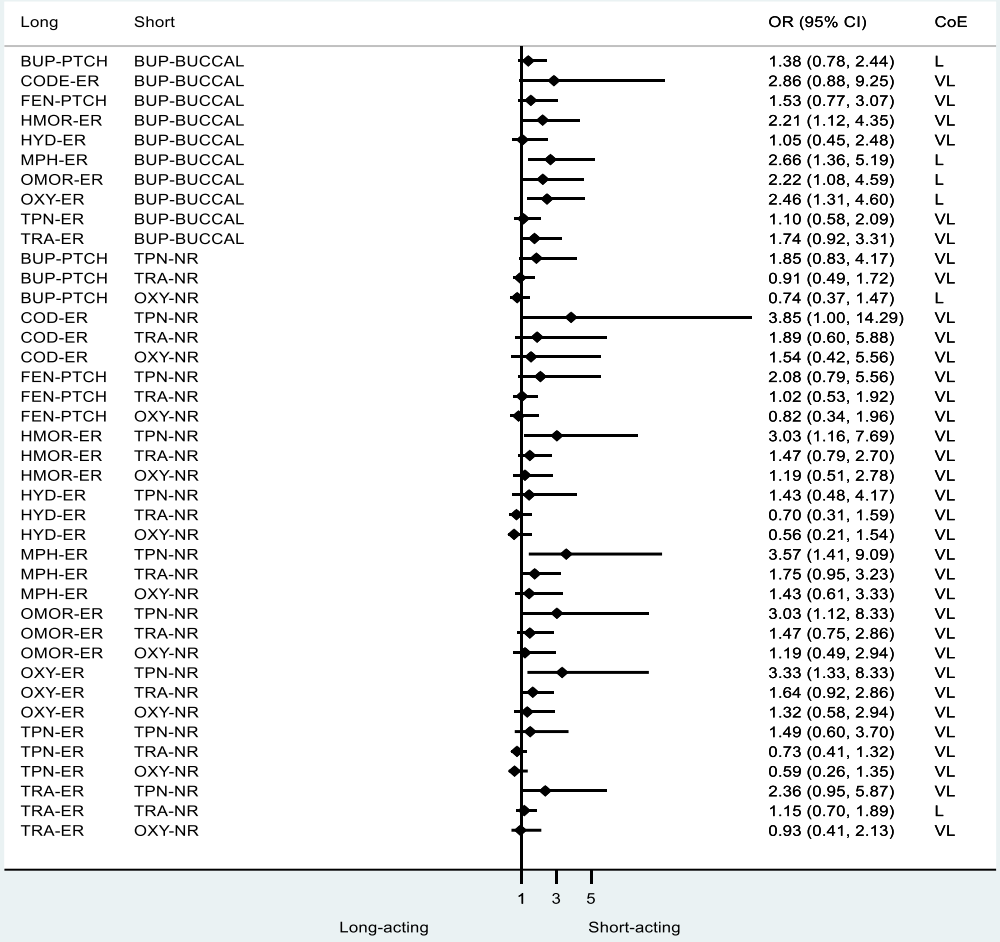
*All comparisons supported by “low to very low” certainty evidence (CoE).

Appendix 3. 31: LA vs SA opioids for physical function*



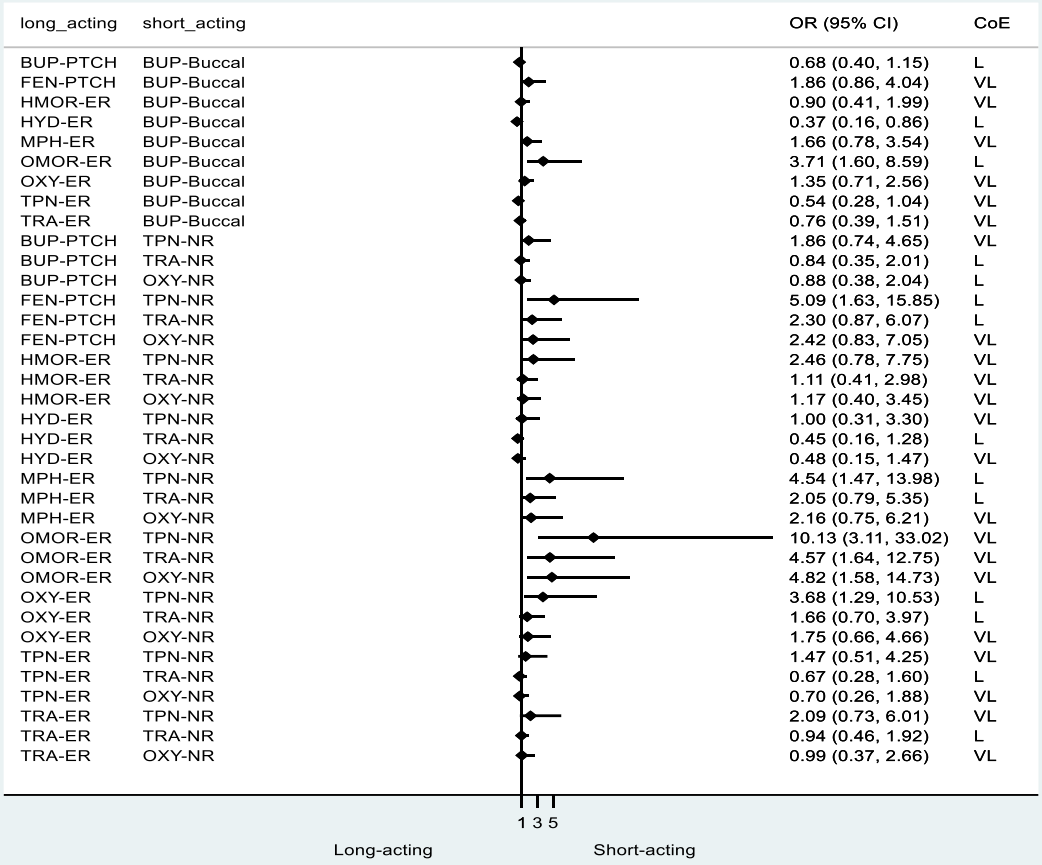
*All comparisons supported by “low to very low” certainty evidence.

Appendix 3. 32: LA vs SA opioids for constipation*



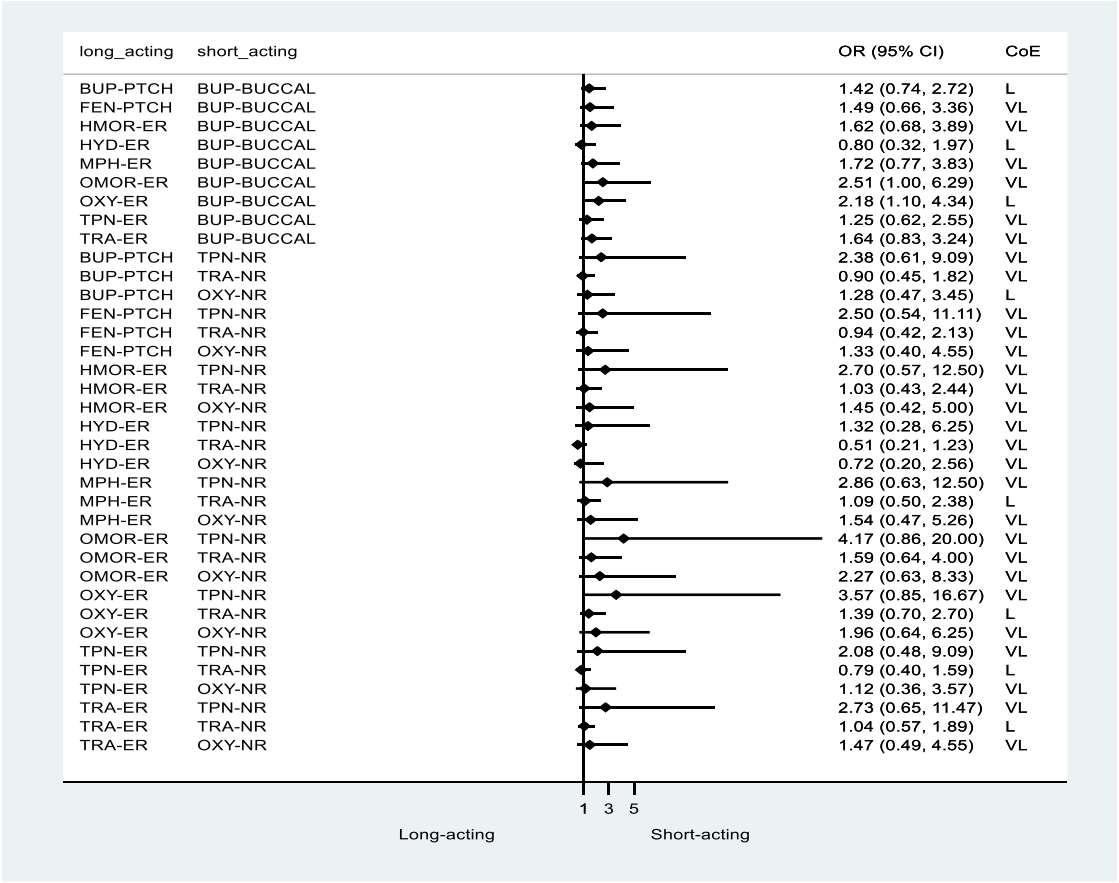
*All comparisons supported by “low to very low” certainty evidence.

Appendix 3. 33: LA vs SA opioids for vomiting*



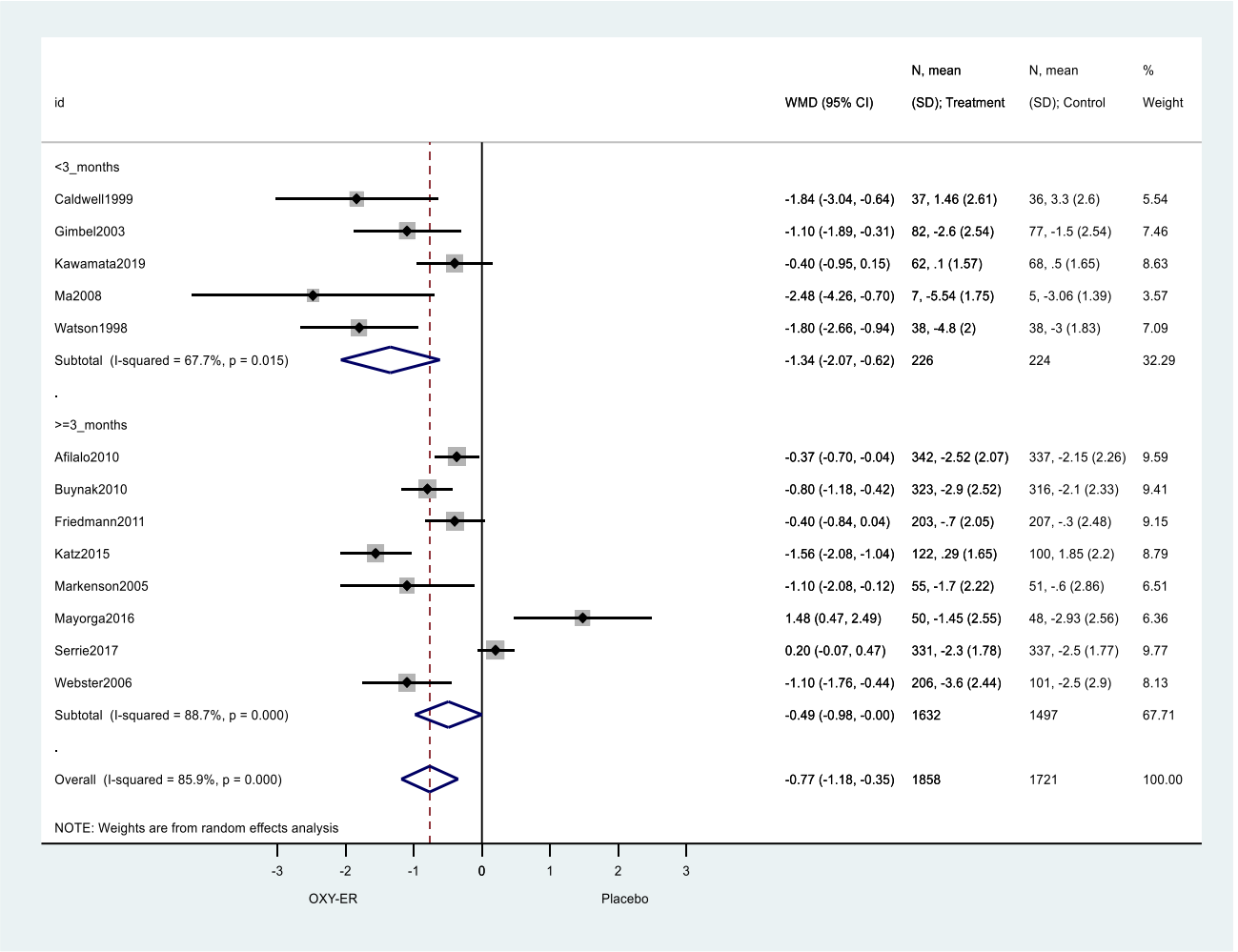
*****All comparisons supported by "low to very low certainty" evidence.

Appendix 3. 34: LA vs SA opioids for nausea*



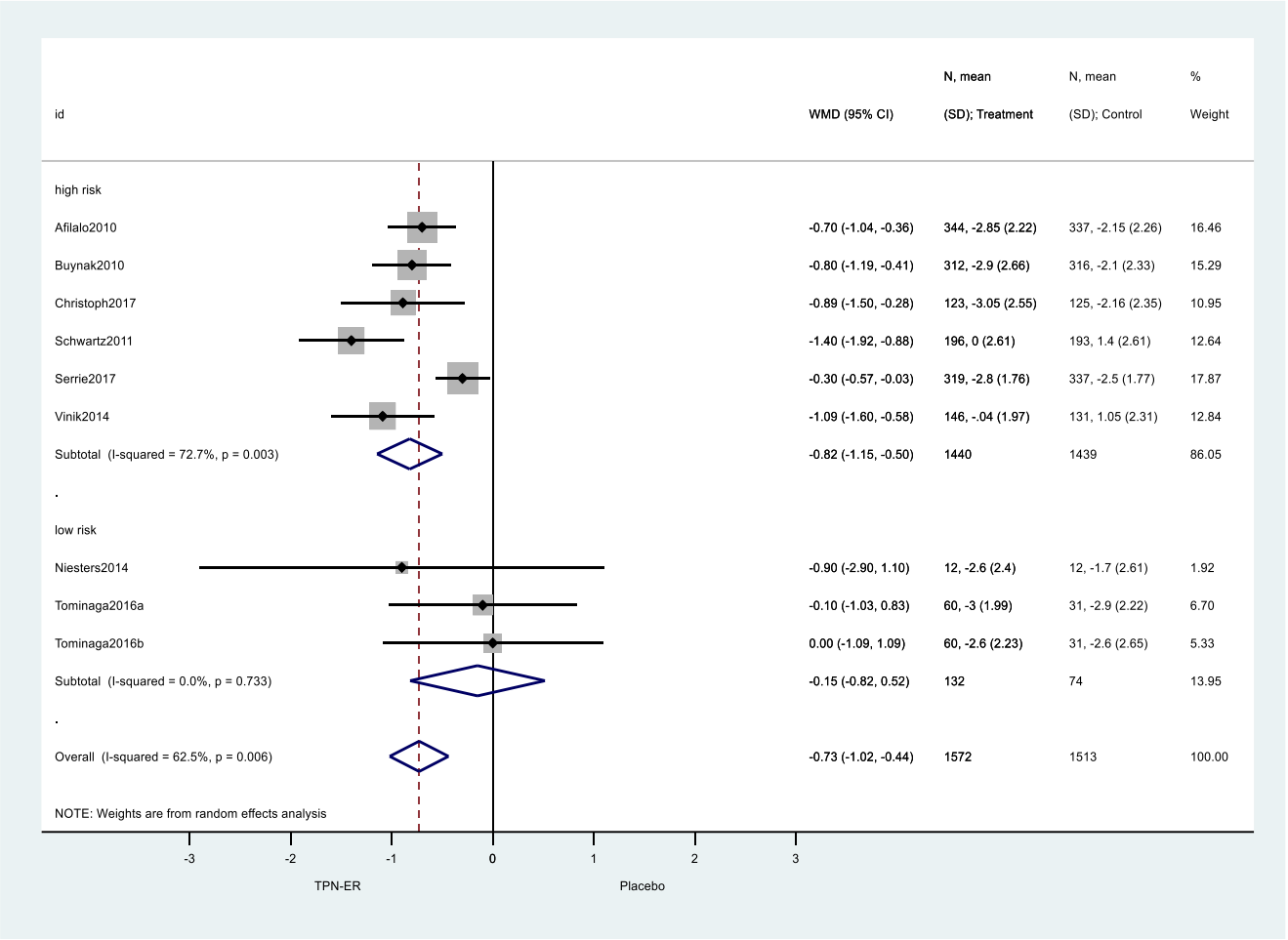
*All comparisons supported by “low to very low” certainty evidence.

Appendix 3. 35: Sub-group analysis based on duration of follow-up for pain relief.



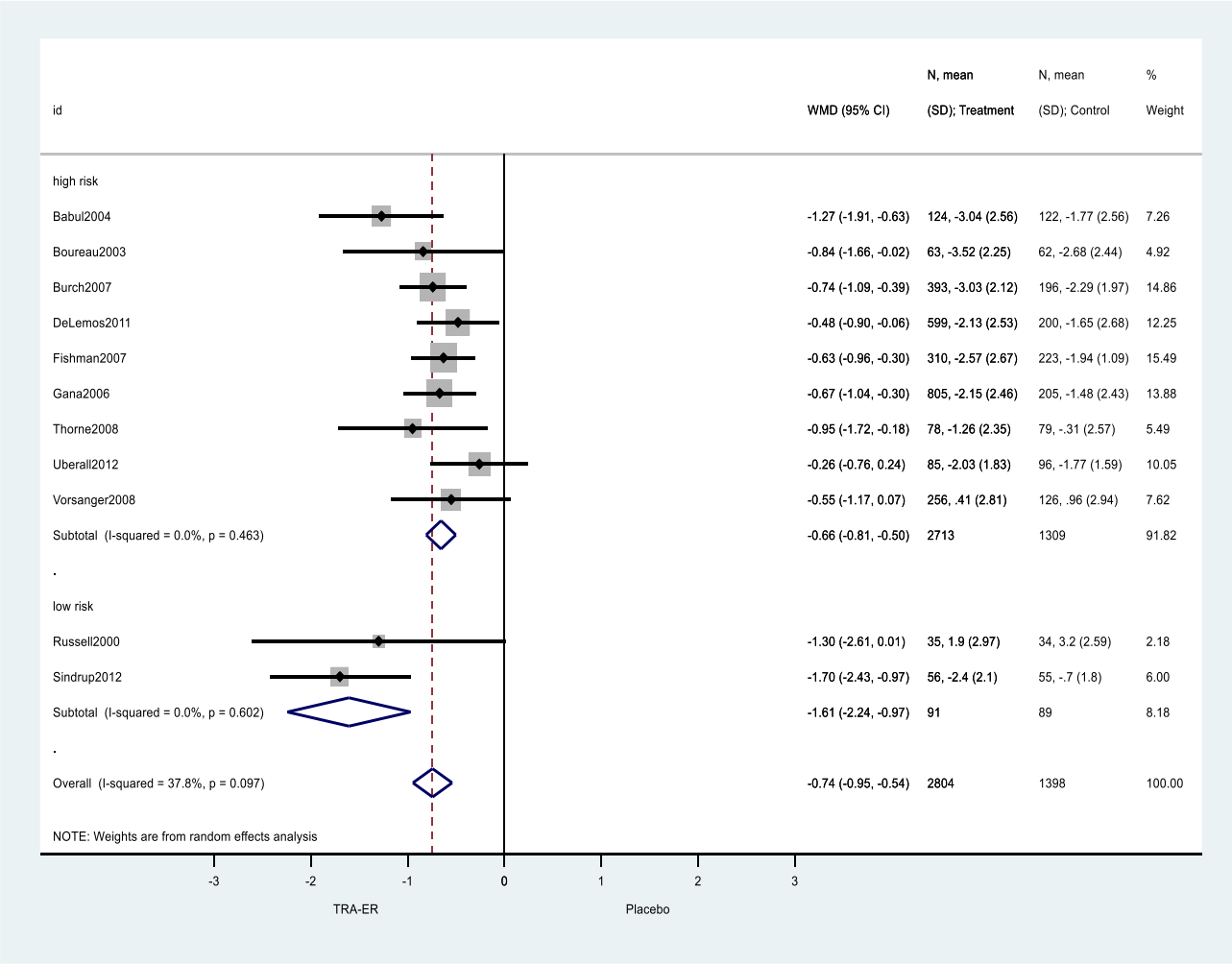
Oxycodone-ER vs placebo. Tau-square decreased, P-value of interaction was not statistically significant (P=0.110).

Appendix 3. 36: Sub-group analysis based on loss to follow-up (≤20% vs ≥20%) for pain relief



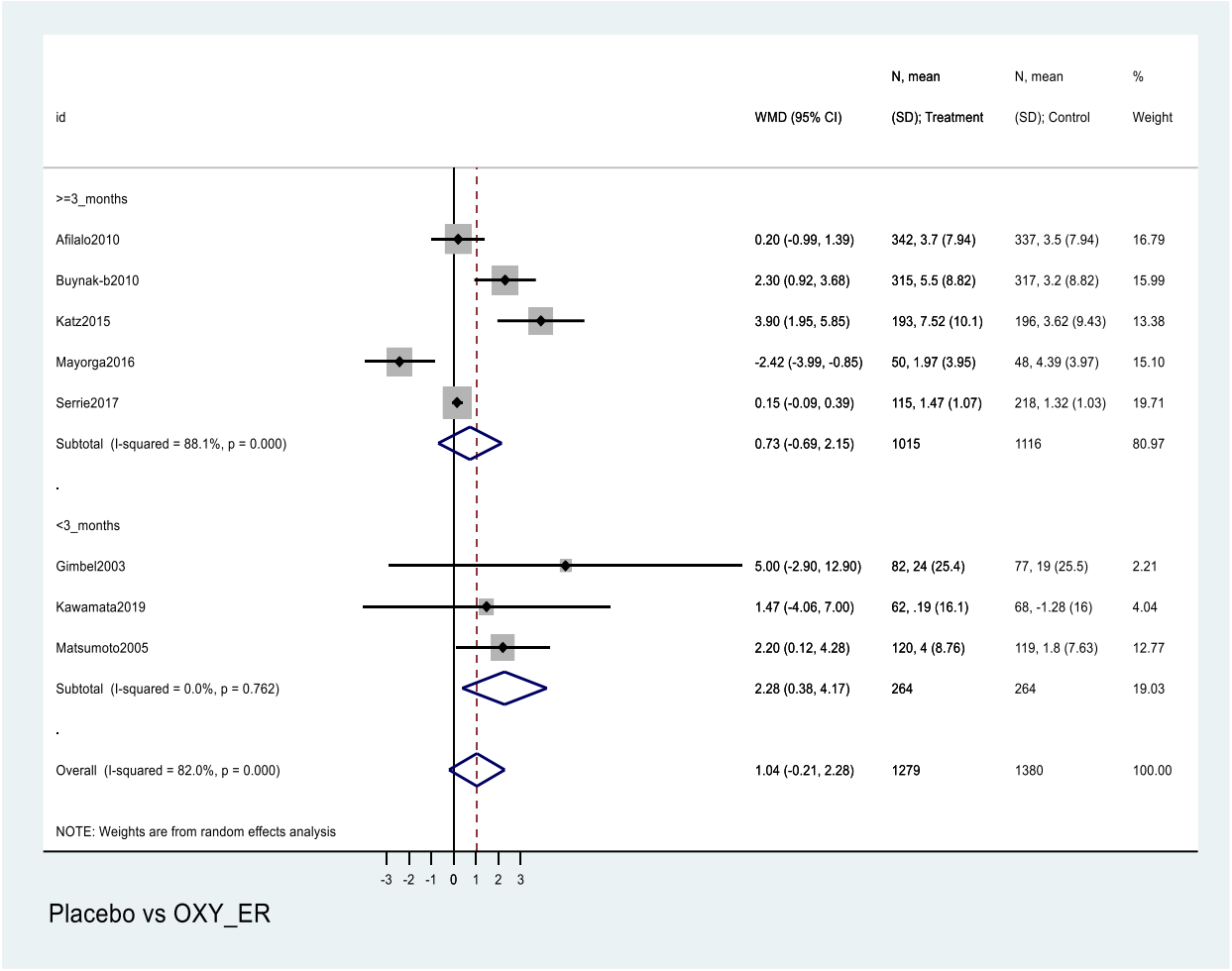
Tapentadol-ER vs placebo. Tau-square decreased, but P-value of interaction was not statistically significant (p= 0.168).

Appendix 3. 37: Sub-group analysis based on loss to follow-up (≤20% vs ≥20%) for pain relief



Tramadol-ER vs placebo. P-value of interaction=0.019.

Appendix 3. 38: Sub-group analysis based on duration of follow-up for physical function



Oxycodone-ER vs placebo. P-value of interaction was not statistically significant (p= 0.429).

Appendix 3. 39: Sensitivity analysis by using DerSimonian-Laird method vs. Knapp-Hartung modification for random effects meta-analysis

Outcome	**Comparison**	**D-L method**	**Knapp-Hartung**
Pain	Oxycodone-ER vs placebo	-0.76(-1.18 to-0.35)	-0.78 (-1.35 to -0.21)
	Morphine-ER vs placebo	-0.93 (-1.23 to -0.63)	-0.93 (-1.29 to -0.58)
	Tapentadol-ER vs placebo	-0.73 (-1.02 to -0.43)	-0.72 (-1.07 to -0.38)
	Tramadol-ER vs placebo	-0.74 (-0.94 to -0.54)	-0.73 (-0.97 to -0.49)
Physical Function			
	Oxycodone-ER vs placebo	1.03 (-0.20 to 2.28)	1.13 (-0.76 to 3.02)
	Tapentadol-ER vs placebo	1.93 (0.36 to 3.5)	1.84 (0.08 to 3.61)

Appendix 3. 40: Nausea- direct, indirect and network estimates

	OR			RR		
Comparison	Direct Estimates (95%CI)	Indirect Estimates (95%CI)	NMA estimate (95%CI)	Direct estimates (95%CI)	Indirect estimates (95%CI)	NMA estimate (95%CI)
BUP-Buccal vs. Placebo	1.19 (0.75 to 1.9)	5.85 (2.21 to 15.48)	2.03 (1.1 to 3.75)	1.18 (0.76 to 1.90)	3.53 (1.83 to 6.83)	1.84 (1.15 to 2.92)
BUP-PTCH vs. Placebo	3.25 (1.69 to 6.24)	2.41 (1.22 to 4.75)	2.89 (1.94 to 4.3)	2.44 (1.53 to 3.88)	2.15 (1.3 to 3.57)	2.31 (1.72 to 3.11)
FEN-PTCH vs placebo	2.49 (1.71 to 3.62)	6.86 (2.93 to 16.08)	3.03 (1.77 to 5.17)	1.60 (0.87 to 2.92)	4.71 (2.43 to 9.11)	2.43 (1.61 to 3.66)
HMOR-ER vs placebo	3.21 (2.18 to 4.71)	6.04 (1.96 to 18.58)	3.29 (1.77 to 6.14)	2.07 (0.82 to 5.24)	4.11 (1.84 to 9.19)	2.78 (1.74 to 4.44)
MPH-ER vs placebo	4.38 (2.24 to 8.58)	2.84 (1.48 to 5.47)	3.49 (2.09 to 5.84)	3.57 (2 to 6.34)	2.26 (1.36 to 3.75)	1.55 (0.9 to 2.67)
OMOR-ER vs placebo	6.35 (3.95 to 10.21)	8.64 (1.4 to 53.27)	5.1 (2.57 to 10.12)	2.66 (0.76 to 9.25)	5.14 (1.38 to 19.22)	2.71 (1.79 to 4.08)
OXY-ER vs placebo	5.23 (3.9 to 7)	2.86 (1.56 to 5.24)	4.43 (3.25 to 6.04)	3.84 (3 to 5)	2.41 (1.51 to 3.86)	3.51 (2.1 to 5.87)
TPN-ER vs placebo	3.04 (2.39 to 3.87)	1.21 (0.56 to 2.65)	2.55 (1.79 to 3.62)	2.6 (2 to 3.31)	1.18 (0.65 to 2.13)	3.36 (2.65 to 4.26)
TRA-ER vs placebo	3.16 (2.52 to 3.97)	3.28 (1.64 to 6.6)	3.34 (2.41 to 4.61)	2.61 (2.12 to 3.21)	2.5 (1.47 to 4.24)	2.2 (1.68 to 2.88)
TRA-NR vs placebo	4.65 (2.23 to 9.7)	2.18 (0.95 to 5.04)	3.2 (1.75 to 5.86)	3.6 (1.72 to 7.43)	1.97 (1.05 to 3.67)	1.16 (0.4 to 3.37)
BUP-PTCH vs BUP-Buccal	0.57 (0.34 to 0.96)	2.82 (1.27 to 6.24)	1.42 (0.74 to 2.72)	0.73 (0.54 to 0.98)	2.2 (1.17 to 4.14)	1.26 (0.78 to 2.03)
TRA-ER vs BUP-PTCH	0.87 (0.55 to 1.36)	1.39 (0.79 to 2.43)	1.16 (0.74 to 1.82)	0.90 (0.64 to 1.24)	1.39 (0.9 to 2.15)	1.16 (0.83 to 1.63)
MPH-ER vs FEN-PTCH	0.78 (0.61 to 1)	2.66 (1.1 to 6.41)	1.15 (0.68 to 1.97)	0.85 (0.68 to 1)	2.3 (1.13 to 4.66)	1.11 (0.75 to 1.65)

OXY-ER vs HMOR-ER	0.79 (0.38 to 1.6)	1.83 (0.83 to 4.04)	1.35 (0.7 to 2.58)	0.85 (0.52 to 1.37)	1.53 (0.82 to 2.86)	1.21 (0.74 to 1.96)
OXY-ER vs MPH-ER	0.82 (0.43 to 1.58)	1.68 (0.86 to 3.29)	1.27 (0.73 to 2.2)	0.84 (0.47 to 1.51)	1.55 (0.9 to 2.65)	1.24 (0.8 to 1.93)
OXY-ER vs OMOR-ER	0.49 (0.32 to 0.77)	1.8 (0.66 to 4.92)	0.87 (0.43 to 1.75)	0.71 (0.57 to 0.90)	1.65 (0.71 to 3.84)	0.96 (0.57 to 1.6)
TPN-ER vs OXY-ER	0.45 (0.38 to 0.54)	0.91 (0.48 to 1.69)	0.57 (0.39 to 0.84)	0.56 (0.50 to 0.64)	0.99 (0.6 to 1.64)	0.65 (0.5 to 0.86)
TRA-NR vs TRA-ER	0.69 (0.34 to 1.4)	1.49 (0.6 to 3.67)	0.96 (0.53 to 1.74)	0.76 (0.41 to 1.40)	1.38 (0.65 to 2.95)	0.69 (0.29 to 1.62)

Appendix 3. 41: Constipation- direct, indirect and network estimates using different models

Comparison		OR			RR		
		Direct Estimates (95%CI)	Indirect Estimates (95%CI)	NMA estimate (95%CI)	Direct estimates (95%CI)	Indirect estimates (95%CI)	NMA estimate (95%CI)
BUP-Buccal	Placebo	2.06 (0.87 to 4.86)	3.29 (1.36 to 7.94)	2.58 (1.42 to 4.69)	1.95 (0.83 to 4.57)	2.77 (1.18 to 6.48)	2.37 (1.28 to 4.37)
BUP-PTCH	Placebo	3.21 (1.71 to 6.01)	5 (2.64 to 9.47)	3.55 (2.43 to 5.19)	2.84 (1.49 to 5.45)	4.32 (2.29 to 8.15)	3.02 (2.04 to 4.46)
COD-ER	Placebo	7.37 (2.67 to 20.29)	NA	7.37 (2.68 to 20.29)	4.24 (1.90 to 9.50)	NA	4.25 (1.73 to 10.44)
FEN-PTCH	Placebo	2.54 (0.78 to 8.21)	5.31 (2.8 to 10.04)	3.96 (2.78 to 5.65)	2.39 (0.76 to 7.45)	4.31 (2.6 to 7.12)	3.34 (2.27 to 4.9)
HMOR-ER	Placebo	4.01 (1.48 to 10.8)	8.08 (3.35 to 19.68)	5.71 (4.15 to 7.85)	3.36 (2.11 to 5.36)	5.35 (2.55 to 11.2)	3.86 (2.62 to 5.69)
HYD-ER	Placebo	3.12 (1.01 to 9.62)	NA	2.72 (1.47 to 5.01)	2.87 (1 to 8.21)	NA	2.57 (1.35 to 4.9)
MPH-ER	Placebo	14.79 (7.57 to 28.9)	5.58 (3.97 to 7.89)	6.86 (5.05 to 9.31)	7.75 (4.32 to 13.92)	4.01 (3 to 5.36)	4.84 (3.39 to 6.92)
OMOR-ER	Placebo	4.6 (2.6 to 8.15)	9.68 (3.45 to 27.05)	5.74 (3.81 to 8.65)	3.38 (2.07 to 5.54)	6.4 (2.11 to 19.38)	4.14 (2.62 to 6.53)
OXY-ER	Placebo	6.07 (4.85 to 7.61)	7.1 (4.37 to 11.43)	6.34 (5.21 to 7.71)	4.28 (3.52 to 5.20)	4.65 (2.99 to 7.23)	4.43 (3.57 to 5.5)
TPN-ER	Placebo	3.19 (2.33 to 4.38)	2.41 (1.32 to 4.41)	2.85 (2.27 to 3.57)	2.83 (2.09 to 3.85)	2.08 (1.19 to 3.63)	2.58 (1.93 to 3.46)
TRA-ER	Placebo	5.01 (3.63 to 6.92)	2.59 (1.32 to 5.07)	4.5 (3.37 to 6)	4.31 (3.20 to 5.82)	1.94 (1.08 to 3.5)	3.73 (2.75 to 5.05)
TRA-NR	Placebo	4.64 (0.78 to 27.51)	3.97 (2.02 to 7.88)	3.89 (2.28 to 6.66)	3.97 (0.60 to 25.8)	3.57 (1.94 to 6.59)	3.08 (1.88 to 5.06)

BUP-PTCH	BUP-Buccal	1.16 (0.57 to 2.37)	1.9 (0.7 to 5.14)	1.38 (0.78 to 2.44)	1.14 (0.62 to 2.07)	1.58 (0.58 to 4.31)	1.27 (0.71 to 2.3)
TRA-ER	BUP-PTCH	0.68 (0.34 to 1.35)	1.77 (1.04 to 3.01)	1.27 (0.83 to 1.94)	0.70 (0.37 to 1.32)	1.71 (1.03 to 2.84)	1.24 (0.8 to 1.9)
OXY-NR	BUP-PTCH	1.35 (0.67 to 2.72)	NA	1.36 (0.68 to 2.72)	1.33 (0.70 to 2.57)	NA	1.33 (0.62 to 2.88)
MPH-ER	FEN-PTCH	1.58 (1.22 to 2.04)	3.74 (1.67 to 8.33)	1.73 (1.36 to 2.2)	1.25 (1.10 to 1.42)	2.69 (1.29 to 5.57)	1.45 (1.01 to 2.08)
OXY-ER	HMOR-ER	0.8 (0.38 to 1.72)	1.34 (0.72 to 2.47)	1.11 (0.78 to 1.58)	0.85 (0.50 to 1.48)	1.37 (0.79 to 2.39)	1.15 (0.76 to 1.73)
OXY-ER	MPH-ER	0.85 (0.48 to 1.51)	0.79 (0.43 to 1.47)	0.92 (0.7 to 1.23)	0.90 (0.58 to 1.36)	0.89 (0.51 to 1.53)	0.92 (0.66 to 1.26)
OXY-ER	OMOR-ER	0.98 (0.63 to 1.55)	1.7 (0.63 to 4.64)	1.1 (0.74 to 1.64)	0.99 (0.74 to 1.32)	1.42 (0.5 to 4.04)	1.07 (0.69 to 1.67)
TPN-ER	OXY-ER	0.42 (0.35 to 0.5)	0.82 (0.44 to 1.53)	0.45 (0.38 to 0.53)	0.54 (0.47 to 0.61)	1.06 (0.58 to 1.94)	0.58 (0.46 to 0.74)
TRA-NR	TRA-ER	0.86 (0.28 to 2.67)	0.83 (0.28 to 2.38)	0.87 (0.53 to 1.42)	0.87 (0.40 to 2.24)	0.61 (0.25 to 1.48)	0.83 (0.52 to 1.31)
OXY-NR	TPN-NR	2.52 (1.68 to 3.78)	NA	2.52 (1.68 to 3.79)	2.11 (1.54 to 2.90)	NA	2.11 (1.27 to 3.52)

Appendix 3. 42: Meta-regression for enrichment design

Outcome	Comparison	# of studies	P-value	95% CI
Nausea	BUP-Buccal vs. Placebo	2	-	-
	BUP-PTCH vs. Placebo	5	*0.027*	0.09 to 0.75
	FEN-PTCH vs placebo	3	0.236	0.001 to 80
	HMOR-ER vs placebo	2		
	HYD-ER vs placebo	3	All enrichment design	
	MPH-ER vs placebo	3	All non-enrichment design	
	OMOR-ER vs placebo	3	0.151	0 to 102
	OXY-ER vs placebo	10	*0.005*	0.19 to 0.66
	TPN-ER vs placebo	9	0.342	0.35 to 1.5
	TRA-ER vs placebo	11	0.489	0.43 to 1.53
	TRA-NR vs placebo	4	0.801	0.01 to 33.95
	BUP-PTCH vs BUP-Buccal	1	-	-
	TRA-ER vs BUP-PTCH	2	-	-
	OXY-NR vs BUP-PTCH	1	-	-
	MPH-ER vs FEN-PTCH	2	-	-
	OXY-ER vs HMOR-ER	1	-	-
	OXY-ER vs MPH-ER	2	-	-
	OXY-ER vs OMOR-ER	1	-	-
	TPN-ER vs OXY-ER	4	All with enrichment design	
	OXY-NR vs TPN-NR	1	-	-
	TRA-NR vs TRA-ER	2	-	-
Constipation				
	BUP-Buccal vs placebo	2	-	
	BUP-PTCH vs placebo	5	0.964	0.049 to 22.29
	COD-ER vs placebo	1	-	
	FEN-PTCH vs placebo	3	0.262*	0 to 211
	HMOR-ER vs placebo	2	-	
	HYD-ER vs placebo	3	All enrichment design	
	MPH-ER vs placebo	5	All non-enrichment design	
	OMOR-ER vs placebo	3	0.835	0 to 5484
	OXY-ER vs placebo	10	0.594	0.33 to 1.95
	TPN-ER vs placebo	8	0.214	0.47 to 14.74
	TRA-ER vs placebo	9	0.641	0.31 to 2.14
	TRA-NR vs placebo	3	All non-enrichment design	

*Visually enrichment design probably was one source of the heterogeneity, however not enough power for meta-regression. Other comparisons were with only one or two studies or without variability.

Appendix 3. 43: Network meta-regression for enrichment design

Outcome	Opioid	Coefficient (95% CI)	P-value
Vomiting	BUP-patch vs placebo	-0.64 (-1.83 to 0.50)	0.291
	FEN-patch vs placebo	-0.92 (-2.5 to 0.72)	0.272
	HMOR-ER vs Placebo	-1.69 (-2.94 to -0.43)	*0.008*
	OMOR-ER plc	-2.12 (-3.99 to -0.24)	*0.026*
	OXY-ER vs Placebo	-0.35 (-1.30 to 0.59)	0.465
	TPN-ER plc	0.20 (-0.63 to 1.03)	0.638
Nausea	BUP-patch vs placebo	-1.29 (-1.90 to -0.69)	*<0.0001*
	FEN-patch vs placebo	-1.44 (-2.24 to -0.65)	*<0.0001*
	HMOR-ER vs Placebo	-1.46 (-2.41 to -0.52)	*0.002*
	OMOR-ER plc	-2.20 (-3.15 to -1.25)	*<0.0001*
	OXY-ER vs Placebo	-0.93 (-1.45 to -0.43)	*<0.0001*
	TPN-ER plc	-0.18 (-0.71 to 0.35)	0.497
Constipation	BUP-patch vs placebo	-0.11 (-1.50 to 1.27)	0.874
	FEN-patch vs placebo	-1.35 (-2.31 to -0.40)	*0.005*
	HMOR-ER vs Placebo	-1.11 (-2.27 to 0.04)	0.06
	OMOR-ER plc	-0.07 (-1.66 to 1.51)	0.927
	OXY-ER vs Placebo	-0.29 (-1.04 to 0.44)	0.434
	TPN-ER plc	0.98 (-0.34 t7 to 2.34)	0.157

Appendix 3. 44: Full references of included studies

(N=80; 2 studies reported 2 separate trials in one paper: Arai et al. 2015, and Tominaga et al 2016.)

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Chapter 4: Concordance of certainty of evidence between the GRADE Working Group framework and CINeMA approach for a network meta-analysis of opioids for chronic noncancer pain

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Authors contribution

A. Noori, J.W. Busse, G.H. Guyatt conceived and designed the study. A. Noori drafted the manuscript. Interpretation of results: A. Noori, J.W. Busse, R. A. Siemieniuk, B. Sadegigirad, L. Thabane, M. Bhandari. All authors reviewed or critically revised the manuscript. Study supervision: J.W. Busse, G.H. Guyatt.

Concordance of certainty of evidence between the GRADE Working Group framework and CINeMA approach for a network meta-analysis of opioids for chronic noncancer pain

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Abstract

Objective: Assessment of the certainty of evidence (CoE) from network meta-analysis is critical to convey the strength of inferences for clinical decision-making. Two approaches that are applying GRADE principals are GRADE Working Group (GWG) and the CINeMA framework; we applied both effect estimates from the same network meta-analysis to explore for concordance of results.

Study design and setting: We assessed the certainty of evidence for pain relief and physical functioning from a network meta-analysis of individual opioids for chronic noncancer pain using the GWG approach and the CINeMA framework. We quantified the number of comparisons per outcome, the proportion of discrepant CoE ratings between approaches, and the magnitude of the difference (i.e., 1-level, 2-levels, or 3-levels).

Results: Across 105 comparisons among individual opioids for pain relief, the GWG and CINeMA approaches provided different CoE ratings in 40% of cases (42 of 105). Across 66 comparisons among individual opioids for physical functioning, there was discordance between approaches in 32% of cases (21 of 66). All discrepancies were separated by 1-level (e.g., very low vs. low).

Conclusion: Our findings suggest there are differences between the CoE ratings provided by the GWG and CINeMA approaches when applied to network meta-analyses. Further research is needed to replicate or refute our findings in other network meta-analyses and assess the implications for clinical decision-making.

Background

Network Meta-Analysis (NMA), an extension of conventional meta-analysis, explores the relative effectiveness of multiple treatments by combining direct and indirect evidence.[1, 2] With several available competing interventions and different outcomes to consider, the results of NMAs are often complex and challenging to interpret.[3] Typically, competing interventions are ranked using the SUCRA approach; however, this system only considers the point estimates of effect and not the certainty of evidence (CoE). Recent guidance recommends a minimally contextualized approach to ranking competing interventions that considers both the magnitude of effects and CoE.[4]

The Cochrane Collaboration has endorsed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate CoE for network meta-analyses.[5] Another approach is the Confidence in Network Meta-Analysis (CINeMA) framework.[6] There are several conceptual differences between GRADE and CINeMA and in the current study we investigated the concordance of CoE ratings between these competing systems in a NMA of opioids for chronic noncancer pain.

Methods

Full methodologic details of our NMA are described in the published protocol.[7] In brief, we included clinical trials that enrolled patients with chronic noncancer pain, randomized them to receive an opioid vs placebo, or another opioid, and followed them for ≥4 weeks. Our primary outcome was pain relief, and pain instruments among all eligible trials were

transformed to a 10cm visual analogue scale (VAS) for pain. Physical functioning was a secondary outcome, and all instruments reporting this domain were transformed to the 100-point short form-36 (SF-36) physical component summary (PCS) score. We used DerSimonian–Laird random-effects models to calculate the weighted mean differences (WMDs) and associated 95% CIs for all pairwise comparisons. We performed all analysis in Stata using the *mvmeta* command [8] and illustrated network plots using the *networkplot* command (StataCorp, Release 15.1, College Station, Texas). We used the *netweight* command to calculate the contribution matrix which shows the percentage contribution of each study to the estimation of each relative effect in the network.

Application of the GRADE principals for NMA output

We used GWG approach[9] and CINeMA framework to evaluate the CoE for all network effect estimates for pain and physical functioning (Appendix 4.9). The principals of both approaches are similar, but the items that comprise the basis for judgements are not identical (Table 4.1). Using GWG, we assessed four components including, risk of bias (ROB),[10] heterogeneity,[11] indirectness,[12] and publication bias[13] for each comparison informed by direct evidence. To assess the CoE from indirect estimates, we visually examined the network map to find the first-order loop (one intervention connecting to two interventions, also called a single common comparator) available for indirect comparison. We then used the lower CoE of the two contributed direct estimates to the first-order loop for the CoE of indirect estimates.[5] If there were more than one first-order loop available,

we used the one that contributed the most weight to the comparison. When a first-order loop was not available, we used the highest order loop (more than one interventions connecting to the two interventions) to rate the CoE (the lowest of the ratings of certainty for the direct estimates contributing to the loop was used). Finally, we rated the certainty of the network estimate when both direct and indirect evidence was available based on the higher certainty rating if they both contributed importantly to the network estimate, or the direct or indirect evidence that most contributed to the network estimate (at least 60%). We rated the network estimate as imprecise if the associated 95% confidence interval (95%CI) included 0.5cm for pain or 2.5 points for physical function (½ the minimally important difference [MID]).[14] We either rated down the certainty of network by one level if there was incoherence between the direct and indirect evidences or used only the direct or indirect evidence if one was higher certainty of evidence.

In the CINeMA framework, the CoE is not summarized across domains to rate its certainty for direct comparisons.[6] Instead, all available comparisons from direct and indirect evidence with their contribution to the combined estimation (network) are considered. For example, the percentage of each study contributing to each NMA estimate along with risk of bias and indirectness assessments are considered to evaluate within-study limitations and indirectness and results are presented in bar charts (Appendix 4.2). The rule for imprecision is based on the overlap of 95%CI with null effect and MID. For instance, if the 95%CI includes the null effect (zero for continuous outcomes) and the MID, ‘major concern’ is assigned. For assessing heterogeneity of network estimates, CINeMA considers the agreement between the 95%CI and the

prediction interval, which is a range of values in which the true effect of a new study is likely to lie. For evidence with both direct and indirect estimates available, incoherence is judged based on the agreement of direct and indirect 95%CIs and the p-value from side-splitting test.[6]

Transitivity assumption

In the GWG approach for assessing the CoE of effect estimates from a NMA, indirect effect estimates may be rated down for intransitivity; the transitivity assumption requires similarity across the contributing direct comparisons in terms of the population, intervention and control and trial methodology. For example, two direct comparisons that inform the indirect evidence might be different with respect to the percentage of duration of follow-up, which was a significant effect modifier for pain and physical function in our NMA of opioids for chronic pain. As such, we set a rule that if the percentage of duration of follow-up≥3 months was 50% or more different in the two direct comparisons, we downgraded the CoE of indirect evidence one level due to intransitivity .[15]

In CINeMA, the transitivity check is assessed as part of the consideration of indirectness based on the network structure and amount of available evidence. For example, we rated down the CoE for opioids that were assessed in a single study or only compared vs. the reference without connection with other opioids.

Overall judgments across the six domains in CINeMA

CINeMA assigns three possible judgments to each of six domains (i.e., no concerns, some concerns, or major concerns) and then the same reviewer that assigned GRADE ratings summarized the results to determine the CoE for each network estimate as high, moderate, low or very-low (Appendix 4.3). We rated down the CoE one level for each domain with 'major concern' or two domains with 'some concern'. We also downgraded the certainty by two levels if simultaneously we had 'major concern' in one domain and 'some concern' in another domain. The CoE was further reduced by 1 level in the presence of intransitivity.

RESULTS

A total of 78 trials, involving 21,906 participants, contributed to our NMA and assessed the effect of 14 individual opioids. Most studies (88% [72 of 82]) were at risk of bias due to frequent missing (≥20%) outcome data or unblinding of patients; only nine studies were judged at low risk of bias across all domains.

Our network was informed by 22 direct comparisons (Figure 4.1). The design by-treatment interaction model showed no evidence of incoherence for either network (pain or physical function). Further, side-splitting showed no evidence of incoherence for all comparisons informed by both direct and indirect evidence.

Comparing CoEs between CINeMA framework and GWG system

Across 105 comparisons among individual opioids for pain relief, the GWG and CINeMA approaches provided different CoE ratings in 40% of cases (42 of 105). Each discrepancy was separated by 1-level (e.g., very low vs. low). Among these 42 discripancies, 16 were related to intransitivity assessment (38%), 16 out of 42 were due to heterogeneity consideration (38%), and 10 out of 42 were due to imprecsion consideration (24%). Overall, GWG resulted in higher certainty ratings compare with CINeMA framework (all low vs very-low).

Across 66 comparisons among individual opioids for physical functioning, there was discordance between approaches in 29% of cases (19 of 66); all discrepancies were separated by 1-level (Table 4.2, Appendix 4.1, Appendix 4.9). 12 out of 19 diffrences were due to imprecision consideration (63%), six were related to heterogeneity assessment (32%), and one was due to intransitivity consideration (5%).

For pain relief there was more than one first-order loop available for five comparisons, including buprenorphine patches, fentanyl patches, extended release (ER) tramadol, ER morphine, and ER oxycodone vs placebo. For these comparisons, to rate the CoE for indirect evidence using GRADE, we selected the most dominant loop with the greatest percentage contribution based on the network contribution matrix or by comparing the width of the confidence intervals (Appendix 4.4-8).

For physical functioning there were 3 comparisons for which more than one first-order loop was available (fentanyl patches vs. placebo, ER morphine vs. placebo, and ER

oxycodone vs. placebo). For ER oxycodone vs. placebo, two of the first-order loops had almost similar weights, however, both loops were low CoE (Appendix 4.11).

Intransitivity

Using the CINeMA framework, all comparisons involving ER codeine, ER hydrocodone, ER oxymorphone, normal release (NR) oxycodone, and NR tapentadol were downgraded for intransitivity, as they were informed by a single study or were not connected to other opioids in the network (Table 4.2, Appendix 4.1). But some of these comparisons rated down with the GWG approach if violated the transitivity assumption based on the duration of follow-up.

Imprecision

Using the GWG approach for pain relief, we rated down the network estimates for buprenorphine patches, fentanyl patches, ER hydromorphone, ER hydrocodone, ER oxycodone, and NR oxycodone vs placebo for imprecision, as the associated 95%CI included half the MID. Further, for the comparison of ER codeine vs placebo, the GWG approach rated the CoE down one level due to imprecision, as the direct evidence was informed by less than 300 observations. These comparisons were not rated down in CINeMA.

DISCUSSION

In the current study, we explored the concordance of CoEs between the GWG system and CINeMA approach in a NMA of opioids for chronic noncancer pain. We found that GWG and CINeMA differ appreciably in their assessment of CoE for network effect estimates, in all cases by 1 level of magnitude (e.g., very low vs. low).

In our analysis, differences in CoE ratings between systems were predominantly due to considerations around imprecision and intransitivity. Regarding the assessment of imprecision, CINeMA only assigns 'major concern' when the 95%CI simultaneously includes the null effect and the MID. For example, the network estimation of the comparison between buprenorphine patches vs. placebo was -0.71cm (95%CI -1 to -0.40cm on a 10-cm VAS for pain); the network estimate was not rated down in CINeMA because the 95%CI did not include the null effect ("0") and the MID of 1cm. However, in GWG we downgraded one level for imprecision since the 95%CI included ½ the MID. Specifically, the CINeMA framework considers any effect as potentially important, whereas the GWG approach we used required a difference that was likely to be important to patients. In this case, a 10% risk difference in achieving the MID for pain relief (which equates to ½ the MID) has been found to be important to chronic pain patients, whereas smaller effects were unlikely to be important.[16, 17]

The baseline CoE for the network estimate (before intransitivity, incoherence and imprecision are assessed) was not a source of inconsistency between rating systems, likely because of very limited variability; however, GWG and CINeMA do use different approaches. The baseline CoE of some network estimates are informed by only indirect evidence, and others are informed by both direct and indirect evidence. Generally, in

complex networks, there are multiple comparisons informing indirect evidence, including first-order loops and higher. GWG focuses on the most dominant first-order loop which usually contributes the most information to the indirect estimate. If there are more than one first order loop, then GWG uses the lowest CoE among them to inform the CoE for the indirect evidence (which then becomes the baseline CoE of the network estimate).

In cases in which the network estimate is informed by both direct and indirect evidence, GWG uses the higher CoE of the two to inform the baseline network CoE. The rationale is two-fold: first, the higher rated evidence is typically more precise, second, in the absence of serious incoherence, the evidence (direct or indirect) associated with lower CoE is not likely to reduce the confidence of the network estimate.[5] The CINeMA approach does not choose a source of evidence to inform the baseline CoE estimate for the network estimate. Instead, CINeMA considers the CoE of all contributing evidence to inform the baseline network estimate. Ours is the first study to compare the concordance of CoEs between GWG and CINeMA approaches for network estimates, but there are limitations to our study. First, both approaches were applied by the same reviewer. Second, most of the evidence in our NMA of opioids for chronic pain was rated as low or very-low certainty and this limited variability may have attenuated differences between the GWG and CINeMA approaches. The interpretation and effect of using weights for rating the CoE in different NMA may change according to the network geometry, the amount of direct evidence available, and the degree of differences in risk of bias or indirectness across the comparisons of the network.

Conclusion

Our findings suggest there are important differences between the CoE ratings provided by the GWG and CINeMA approaches when applied to network meta-analyses. Further research, ideally with greater variability in CoE ratings, is needed to replicate our findings in other network meta-analyses and assess the implications for clinical decision-making.

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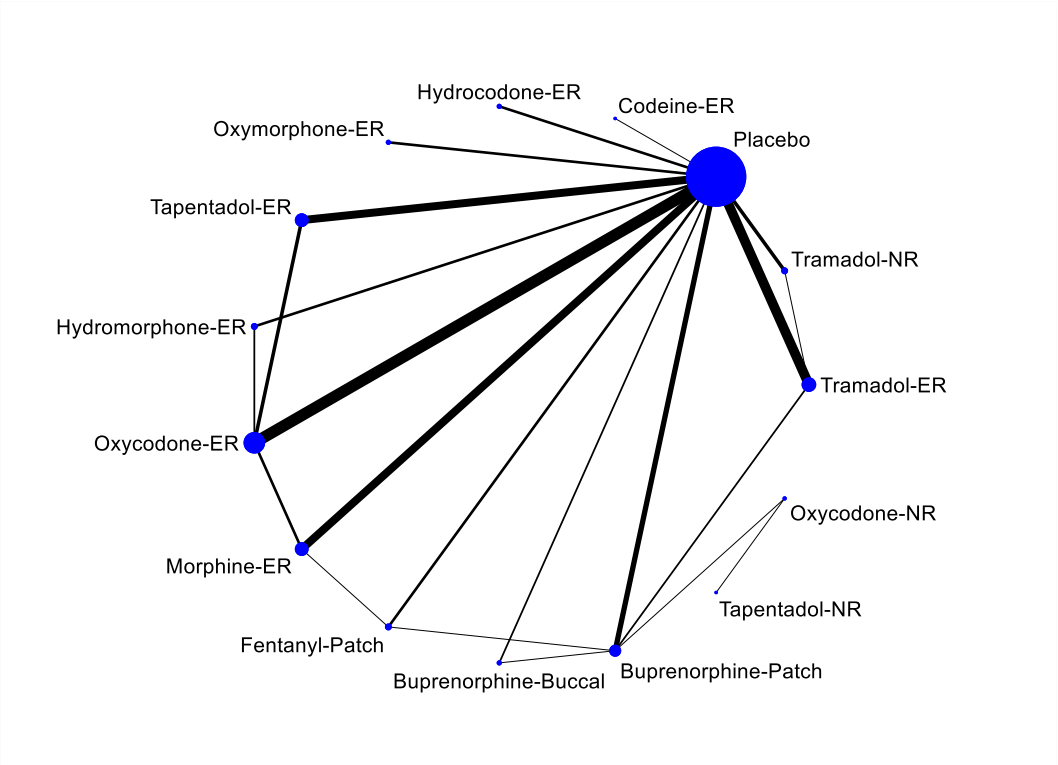


Figure 4. 1: Network plot for pain relief

The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.

Table 4. 1: Comparison between GRADE Working Group (GWG) system and CINeMA framework to obtain the overall certainty of evidence

Domain assessment	**Direct evidence**		**Indirect evidence**		**Network evidence**	
	GWG	**CINeMA framework**	**GWG**	**CINeMA framework**	**GWG**	**CINeMA framework**
Study limitations	Yes	Yes	No	Yes	-	-
Indirectness	Yes	Yes	No	Yes	-	-
Inconsistency	Yes	Yes	No	Yes	-	-
Publication bias	Yes	Yes	No	Yes	-	-
Intransitivity[1]	No	No	Yes	No	-	-
Imprecision	-	-	-	-	Yes	Yes
Incoherence	-	-	-	-	Yes	Yes
Overall rating across domains	*Yes*	No	*Yes*	No	*Yes*	*Yes*

[1]Intransitivity is assessed as a part of the consideration of indirectness in CINeMA.

Table 4. 2: Direct, indirect, and network estimates based on GRADE Working Group system (GWG) and CINeMA framework for pain relief (VAS 0 to 10cm)

GWG system									CINeMA framework		
Comparison	**Direct Estimates MD (95%CI)**	**# of Studies**	**I^2 (p-value)**	**Direct CoE**	**Indirect Estimates MD (95%CI)**	**Indirect CoE**	**NMA estimate MD (95%CI)**	**NMA CoE**	**NMA estimate**	**NMA CoE**	**Reasons**
BUP-Buccal vs Placebo	-0.87 (-1.11 to -0.63)	2	59 (0.118)	M[a]	-0.92 (-2.09 to 0.24)	L[b]	-0.86 (-1.35 to -0.38)[¥]	M[c]	-0.86 (-1.37 to -0.35)	M	ROB Heterogeneity
BUP-PTCH vs Placebo	-0.61 (-0.78 to -0.45)	6	0	M[a]	-0.8 (-1.35 to -0.25)	L	-0.71 (-1 to -0.41)	L[c]	-0.71 (-1.02 to -0.40)	L	ROB Heterogeneity
COD-ER vs Placebo	-2.03 (-3.09 to -0.97)	1	NA	M[a]	NA	NA	-2.03 (-3.28 to -0.78)	L[c]	-2.03 (-3.31 to -0.74)	L	ROB Intransitivity[1]
FEN-PTCH vs Placebo	-0.73 (-1.06 to -0.39)	3	0	M[a]	-0.83 (-1.47 to -0.19)	L[b]	-0.78 (-1.18 to -0.39)	L[c]	-0.78 (-1.19 to -0.36)	L	ROB Heterogeneity
HMOR-ER vs Placebo	-0.41 (-1.1 to 0.27)	3	90 (<0.001)	L[a, d]	-0.64 (-1.29 to 0)	L	-0.52 (-0.88 to -0.16)	VL[c]	-0.51 (-0.89 to -0.13)	L	ROB Heterogeneity
HYD-ER vs Placebo	-0.53 (-0.74 to -0.32)	3	0	M[a]	NA	NA	-0.53 (-0.97 to -0.09)	L[c]	-0.53 (-0.99 to -0.06)	VL	ROB Heterogeneity Intransitivity[1]
MPH-ER vs Placebo	-0.93 (-1.23 to -0.62)	9	0	M[a]	-0.75 (-1.25 to -0.25)	M	-0.86 (-1.17 to -0.56)	M	-0.86 (-1.18 to -0.55)	M	ROB
OMOR-ER vs Placebo	-1.51 (-2.3 to -0.72)	3	73 (0.024)	L[a, d]	NA	NA	-1.47 (-2.03 to -0.91)	L	-1.68 (-2.18 to -1.18)	L	ROB Intransitivity[1]
OXY-ER vs Placebo	-0.76 (-1.18 to -0.35)	13	85 (<0.001)	L[a, d]	-0.6 (-1.03 to -0.16)	M	-0.66 (-0.89 to -0.44)	L[c]	-0.66 (-0.89 to -0.43)	L	ROB Heterogeneity

TPN-ER vs Placebo	-0.73 (-1.02 to -0.43)	9	62 (0.005)	M[a]	-1.2 (-1.9 to -0.49)	L	-0.81 (-1.08 to -0.53)	M	-0.80 (-1.09 to -0.51)	M	ROB
TPN-NR vs Placebo	NA	NA	NA	NA	-1.09 (-2.22 to 0.04)	M	-1.09 (-2.22 to 0.04)	L[c]	-1.09 (-2.28 to 0.09)	VL	ROB Imprecision, Intransitivity[1]
TRA-ER vs Placebo	-0.74 (-0.94 to -0.54)	11	37 (0.097)	M[a]	-0.93 (-1.56 to -0.3)	L	-0.8 (-1.05 to -0.55)	M	-0.80 (-1.06 to -0.54)	M	ROB
TRA-NR vs Placebo	-1.13 (-1.76 to -0.5)	4	66 (0.030)	M[a]	-0.97 (-2.03 to 0.1)	L[b]	-1.09 (-1.54 to -0.65)	M	-1.09 (-1.55 to -0.63)	M	ROB
OXY-NR vs Placebo	NA	NA	NA	NA	-0.99 (-1.81 to -0.17)	M	-0.99 (-1.81 to -0.17)	L[c]	-0.99 (-1.85 to -0.13)	VL	ROB Heterogeneity Intransitivity[1]

-Direct estimations rated down if there were risk of bias (ROB), indirectness, publication bias, or heterogeneity.
-Indirect estimations rated down if there was intransitivity.
-Network estimates rated down if there were incoherence (node-splitting results) or imprecision (either due to inclusion of the half MID in 95%CI, or because the evidence is provided by a small number of participants- a total number of observation less than the optimal information size [≤300]).
-Small-study effects were assessed when there were at least 10 studies using Egger test.
[a] Direct estimate rated down one time for ROB.
[b] Indirect estimate rated down for intransitivity (based on the comparability of duration of follow-up between two direct comparisons constituted the indirect estimation).
[c] Network estimate rated down one time for imprecision.
[d] Direct estimate rated down for heterogeneity.
[¥] Used the direct estimation as the best evidence because of the inflated 95%CI of network estimation.
[1]Downgraded one more time due to intransitivity concern as this opioid was poorly connected to the network or assessed in a single study.
H: high certainty of evidence; M: moderate; L: low; VL: very low. MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-release

Appendix 4. 1: Direct, indirect, and network estimates based on GRADE Working Group system and CINeMA framework for pain reduction (VAS 0 to 10cm)

GWG system											CINeMA framework					
Comparison		**Direct MD (95%CI)**	**# of Studies**	**I^2 %**	**Direct CoE**	**Indirect MD (95%CI)**	**Indirect CoE**	**NMA MD (95%CI)**	**NMA CoE**	**Reasons**	**NMA MD (95%CI)**	**NMA CoE**		**Reasons**		
													ROB	**Imprecision**	**Heterogeneity**	**Intransitivity**
BUP-Buccal	Placebo	-0.87 (-1.11 to -0.63)	2	59	M	-0.92 (-2.09 to 0.24)	L	-0.86 (-1.35 to -0.38)	M*	ROB, intransitivity	-0.86 (-1.37, -0.35)	M	Some concerns	No concerns	Some concerns	No
BUP-PTCH	Placebo	-0.61 (-0.78 to -0.45)	6	0	L	-0.8 (-1.35 to -0.25)	M	-0.71 (-1 to -0.41)	L*	ROB[¥], imprecision	-0.71 (-1.02, -0.40)	L	Major concerns	No concerns	Some concerns	No
COD-ER	Placebo	-2.03 (-3.09 to -0.97)	1	NA	M	NA	NA	-2.03 (-3.28 to -0.78)	L	ROB, imprecision[1]	-2.03 (-3.31, -0.74)	L	Major concerns	No concerns	No concerns	Yes
FEN-PTCH	Placebo	-0.73 (-1.06 to -0.39)	3	0	M	-0.83 (-1.47 to -0.19)	L	-0.78 (-1.18 to -0.39)	L	ROB, intransitivity, imprecision	-0.78 (-1.19, -0.36)	L	Major concerns	No concerns	Some concerns	No
HMOR-ER	Placebo	-0.41 (-1.1 to 0.27)	3	90	L	-0.64 (-1.29 to 0)	L	-0.52 (-0.88 to -0.16)	VL	ROB, heterogeneity, imprecision	-0.51 (-0.89, -0.13)	L	Major concerns	No concerns	Some concerns	No
HYD-ER	Placebo	-0.53 (-0.74 to -0.32)	3	0	M	NA	NA	-0.53 (-0.97 to -0.09)	L	ROB, imprecision	-0.53 (-0.99, -0.06)	VL	Major concerns	No concerns	Some concerns	Yes
MPH-ER	Placebo	-0.93 (-1.23 to -0.62)	9	0	M	-0.75 (-1.25 to -0.25)	M	-0.86 (-1.17 to -0.56)	M	ROB	-0.86 (-1.18, -0.55)	M	Major concerns	No concerns	No concerns	No
OMOR-ER	Placebo	-1.51 (-2.3 to -0.72)	3	73	L	NA	NA	-1.47 (-2.03 to -0.91)	L	ROB, heterogeneity	-1.68 (-2.18, -1.18)	L	Major concerns	No concerns	No concerns	Yes
OXY-ER	Placebo	-0.76 (-1.18 to -0.35)	13	85	L	-0.6 (-1.03 to -0.16)	M	-0.66 (-0.89 to -0.44)	L	ROB, heterogeneity, imprecision	-0.66 (-0.89, -0.43)	L	Major concerns	No concerns	Some concerns	No

TPN-ER	Placebo	-0.73 (-1.02 to -0.43)	9	62	M	-1.2 (-1.9 to -0.49)	L	-0.81 (-1.08 to -0.53)	M	ROB	-0.80 (-1.09, -0.51)	M	Major concerns	No concerns	No concerns	No
TPN-NR	Placebo	NA	NA	NA	NA	-1.09 (-2.22 to 0.04)	M	-1.09 (-2.22 to 0.04)	L	ROB, imprecision	-1.09 (-2.28, 0.09)	VL	Major concerns	Some concerns	No concerns	Yes
TRA-ER	Placebo	-0.74 (-0.94 to -0.54)	11	37	M	-0.93 (-1.56 to -0.3)	L	-0.80 (-1.05 to -0.55)	M	ROB	-0.80 (-1.06, -0.54)	M	Major concerns	No concerns	No concerns	No
TRA-NR	Placebo	-1.13 (-1.76 to -0.5)	4	66	M	-0.97 (-2.03 to 0.1)	L	-1.09 (-1.54 to -0.65)	M	ROB, intransitivity	-1.09 (-1.55, -0.63)	M	Major concerns	No concerns	No concerns	No
OXY-NR	Placebo	NA	NA	NA	NA	-0.99 (-1.81 to -0.17)	M	-0.99 (-1.81 to -0.17)	L	ROB, imprecision	-0.99 (-1.85, -0.13)	VL	Major concerns	No concerns	Some concerns	Yes
BUP-PTCH	BUP-Buccal	0.21 (-0.65 to 1.07)	1	NA	M	0.13 (-0.51 to 0.78)	L	0.16 (-0.38 to 0.69)	L	ROB, imprecision	0.15 (-0.408, 0.714)	VL	Major concerns	Some concerns	Some concerns	No
COD-ER	BUP-Buccal	NA	NA	NA	NA	-1.17 (-2.51 to 0.18)	L	-1.17 (-2.51 to 0.18)	VL	ROB, intransitivity, imprecision	-1.16 (-2.543, 0.214)	VL	Major concerns	Some concerns	No concerns	Yes
FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	0.08 (-0.54 to 0.7)	M	0.08 (-0.54 to 0.7)	L	ROB, imprecision	0.08 (-0.564, 0.735)	VL	Major concerns	Major concerns	No concerns	No
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	0.35 (-0.25 to 0.95)	L	0.35 (-0.25 to 0.95)	VL	ROB, imprecision	0.35 (-0.284, 0.985)	VL	Major concerns	Some concerns	Some concerns	No
HYD-ER	BUP-Buccal	NA	NA	NA	NA	0.33 (-0.32 to 0.98)	M	0.33 (-0.32 to 0.98)	L	ROB, imprecision	0.33 (-0.357, 1.021)	L	Some concerns	Some concerns	Some concerns	Yes
MPH-ER	BUP-Buccal	NA	NA	NA	NA	0 (-0.57 to 0.57)	L	0 (-0.57 to 0.57)	VL	ROB, intransitivity, imprecision	-0.002 (-0.59, 0.59)	L	Some concerns	Major concerns	No concerns	No
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	-0.6 (-1.34 to 0.13)	L	-0.6 (-1.34 to 0.13)	VL	ROB, imprecision	-0.82 (-1.53, -0.107)	VL	Major concerns	No concerns	Some concerns	Yes
OXY-ER	BUP-Buccal	NA	NA	NA	NA	0.2 (-0.33 to 0.73)	L	0.2 (-0.33 to 0.73)	VL	ROB, imprecision	0.19 (-0.36, 0.75)	VL	Major concerns	Some concerns	Some concerns	No

TPN-ER	BUP-Buccal	NA	NA	NA	NA	0.06 (-0.5 to 0.61)	M	0.06 (-0.5 to 0.61)	L	ROB, imprecision	0.06 (-0.525, 0.644)	VL	Major concerns	Major concerns	No concerns	No
TPN-NR	BUP-Buccal	NA	NA	NA	NA	-0.22 (-1.44 to 0.99)	L	-0.22 (-1.44 to 0.99)	VL	ROB, intransitivity, imprecision	-0.22 (-1.506, 1.052)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	BUP-Buccal	NA	NA	NA	NA	0.06 (-0.47 to 0.6)	M	0.06 (-0.47 to 0.6)	L	ROB, imprecision	0.06 (-0.503, 0.624)	L	Some concerns	Major concerns	No concerns	No
TRA-NR	BUP-Buccal	NA	NA	NA	NA	-0.23 (-0.88 to 0.43)	VL	-0.23 (-0.88 to 0.43)	VL	ROB, intransitivity, imprecision	-0.23 (-0.914, 0.457)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	BUP-Buccal	NA	NA	NA	NA	-0.12 (-1.05 to 0.81)	L	-0.12 (-1.05 to 0.81)	VL	ROB, intransitivity, imprecision	-0.12 (-1.109, 0.855)	VL	Major concerns	Major concerns	No concerns	Yes
COD-ER	BUP-PTCH	NA	NA	NA	NA	-1.32 (-2.61 to -0.03)	L	-1.32 (-2.61 to -0.03)	VL	ROB, intransitivity, imprecision	-1.31 (-2.636, 0.000)	VL	Major concerns	Some concerns	No concerns	Yes
FEN-PTCH	BUP-PTCH	0.53 (-0.22 to 1.28)	1	NA	M	-0.24 (-0.78 to 0.3)	L	-0.08 (-0.54 to 0.39)	L	ROB, imprecision[1]	-0.06 (-0.553, 0.418)	VL	Major concerns	Some concerns	Some concerns	No
HMOR-ER	BUP-PTCH	NA	NA	NA	NA	0.19 (-0.27 to 0.66)	L	0.19 (-0.27 to 0.66)	VL	ROB, imprecision	0.19 (-0.292, 0.688)	VL	Major concerns	Some concerns	Some concerns	No
HYD-ER	BUP-PTCH	NA	NA	NA	NA	0.18 (-0.35 to 0.71)	L	0.18 (-0.35 to 0.71)	VL	ROB, imprecision	0.18 (-0.38, 0.73)	VL	Major concerns	Some concerns	Some concerns	Yes
MPH-ER	BUP-PTCH	NA	NA	NA	NA	-0.15 (-0.57 to 0.27)	L	-0.15 (-0.57 to 0.27)	L	ROB, intransitivity, imprecision	-0.15 (-0.58, 0.28)	VL	Major concerns	Some concerns	Some concerns	No
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	-0.76 (-1.39 to -0.13)	L	-0.76 (-1.39 to -0.13)	VL	ROB, imprecision	-0.97 (-1.56, -0.38)	L	Major concerns	No concerns	No concerns	Yes
OXY-ER	BUP-PTCH	NA	NA	NA	NA	0.05 (-0.32 to 0.41)	L	0.05 (-0.32 to 0.41)	L	ROB	0.04 (-0.34, 0.42)	VL	Major concerns	No concerns	Major concerns	No
TPN-ER	BUP-PTCH	NA	NA	NA	NA	-0.1 (-0.5 to 0.31)	L	-0.1 (-0.5 to 0.31)	VL	ROB, imprecision	-0.09 (-0.51, 0.32)	VL	Major concerns	Some concerns	Some concerns	No

TPN-NR	BUP-PTCH	NA	NA	NA	NA	-0.38 (-1.47 to 0.71)	L	-0.38 (-1.47 to 0.71)	VL	ROB, imprecision	-0.38 (-1.53, 0.77)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	BUP-PTCH	-0.23 (-0.65 to 0.19)	2	46	L	-0.06 (-0.49 to 0.38)	L	-0.09 (-0.44 to 0.26)	L	ROB¥	-0.09 (-0.45, 0.27)	VL	Major concerns	No concerns	Major concerns	No
TRA-NR	BUP-PTCH	NA	NA	NA	NA	-0.38 (-0.91 to 0.15)	L	-0.38 (-0.91 to 0.15)	VL	ROB, imprecision	-0.38 (-0.93, 0.16)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	BUP-PTCH	-0.28 (-0.64 to 0.08)	1	NA	M	NA	NA	-0.28 (-1.04 to 0.48)	L	ROB, imprecision	-0.28 (-1.08, 0.52)	VL	Major concerns	Major concerns	No concerns	Yes
FEN-PTCH	COD-ER	NA	NA	NA	NA	1.25 (-0.07 to 2.56)	M	1.25 (-0.07 to 2.56)	L	ROB, imprecision	1.25 (-0.09, 2.59)	L	Major concerns	Some concerns	No concerns	No
HMOR-ER	COD-ER	NA	NA	NA	NA	1.51 (0.21 to 2.82)	VL	1.51 (0.21 to 2.82)	VL	ROB, intransitivity, imprecision	1.51 (0.17, 2.85)	VL	Major concerns	No concerns	Some concerns	Yes
HYD-ER	COD-ER	NA	NA	NA	NA	1.5 (0.17 to 2.83)	L	1.5 (0.17 to 2.83)	VL	ROB, intransitivity, imprecision	1.5 (0.13, 2.86)	VL	Major concerns	No concerns	Some concerns	Yes
MPH-ER	COD-ER	NA	NA	NA	NA	1.17 (-0.12 to 2.46)	M	1.17 (-0.12 to 2.46)	L	ROB, imprecision	1.16 (-0.15, 2.48)	VL	Major concerns	Some concerns	No concerns	Yes
OMOR-ER	COD-ER	NA	NA	NA	NA	0.56 (-0.81 to 1.93)	VL	0.56 (-0.81 to 1.93)	VL	ROB, intransitivity, imprecision	0.34 (-1.03, 1.72)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	COD-ER	NA	NA	NA	NA	1.37 (0.09 to 2.64)	VL	1.37 (0.09 to 2.64)	VL	ROB, intransitivity, imprecision	1.361 (0.05, 2.66)	VL	Major concerns	No concerns	Some concerns	Yes
TPN-ER	COD-ER	NA	NA	NA	NA	1.22 (-0.06 to 2.51)	L	1.22 (-0.06 to 2.51)	VL	ROB, intransitivity, imprecision	1.22 (-0.08, 2.53)	VL	Major concerns	Some concerns	No concerns	Yes
TPN-NR	COD-ER	NA	NA	NA	NA	0.94 (-0.75 to 2.63)	L	0.94 (-0.75 to 2.63)	VL	ROB, intransitivity, imprecision	0.93 (-0.81, 2.68)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	COD-ER	NA	NA	NA	NA	1.23 (-0.05 to 2.51)	L	1.23 (-0.05 to 2.51)	VL	ROB, intransitivity, imprecision	1.22 (-0.08, 2.53)	VL	Major concerns	Some concerns	No concerns	Yes

TRA-NR	COD-ER	NA	NA	NA	NA	0.94 (-0.39 to 2.27)	L	0.94 (-0.39 to 2.27)	VL	ROB, imprecision	0.93 (-0.42, 2.29)	VL	Major concerns	Some concerns	Some concerns	Yes
OXY-NR	COD-ER	NA	NA	NA	NA	1.04 (-0.46 to 2.54)	L	1.04 (-0.46 to 2.54)	VL	ROB, intransitivity, imprecision	1.03 (-0.50, 2.58)	VL	Major concerns	Major concerns	No concerns	Yes
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	0.27 (-0.26 to 0.8)	L	0.27 (-0.26 to 0.8)	VL	ROB, imprecision	0.26 (-0.29, 0.82)	VL	Major concerns	Some concerns	Some concerns	No
HYD-ER	FEN-PTCH	NA	NA	NA	NA	0.25 (-0.34 to 0.84)	M	0.25 (-0.34 to 0.84)	L	ROB, imprecision	0.24 (-0.37, 0.86)	VL	Major concerns	Some concerns	Some concerns	Yes
MPH-ER	FEN-PTCH	0.26 (0.24 to 0.28)	1	NA	M	-0.32 (-0.9 to 0.26)	M	-0.08 (-0.51 to 0.36)	L	ROB, imprecision	-0.087 (-0.54, 0.36)	VL	Major concerns	Some concerns	Some concerns	No
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	-0.68 (-1.37 to 0)	L	-0.68 (-1.37 to 0)	VL	ROB, imprecision	-0.90 (-1.55, -0.25)	L	Major concerns	No concerns	Some concerns	No
OXY-ER	FEN-PTCH	NA	NA	NA	NA	0.12 (-0.32 to 0.56)	L	0.12 (-0.32 to 0.56)	VL	ROB, imprecision	0.11 (-0.35, 0.57)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	FEN-PTCH	NA	NA	NA	NA	-0.02 (-0.5 to 0.46)	M	-0.02 (-0.5 to 0.46)	L	ROB, imprecision	-0.02 (-0.52, 0.47)	VL	Major concerns	Some concerns	Some concerns	No
TPN-NR	FEN-PTCH	NA	NA	NA	NA	-0.3 (-1.49 to 0.88)	M	-0.3 (-1.49 to 0.88)	L	ROB, imprecision	-0.31 (-1.56, 0.93)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	FEN-PTCH	NA	NA	NA	NA	-0.02 (-0.50 to 0.45)	M	-0.02 (-0.50 to 0.45)	L	ROB, imprecision	-0.02 (-0.50, 0.45)	VL	Major concerns	Some concerns	Some concerns	No
TRA-NR	FEN-PTCH	NA	NA	NA	NA	-0.31 (-0.9 to 0.29)	L	-0.31 (-0.9 to 0.29)	VL	ROB, imprecision	-0.31 (-0.93, 0.30)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	FEN-PTCH	NA	NA	NA	NA	-0.2 (-1.1 to 0.69)	M	-0.2 (-1.1 to 0.69)	L	ROB, imprecision	-0.21 (-1.15, 0.72)	VL	Major concerns	Major concerns	No concerns	Yes
HYD-ER	HMOR-ER	NA	NA	NA	NA	-0.02 (-0.59 to 0.55)	L	-0.02 (-0.59 to 0.55)	VL	ROB, imprecision	-0.01 (-0.62, 0.58)	VL	Major concerns	Major concerns	No concerns	Yes

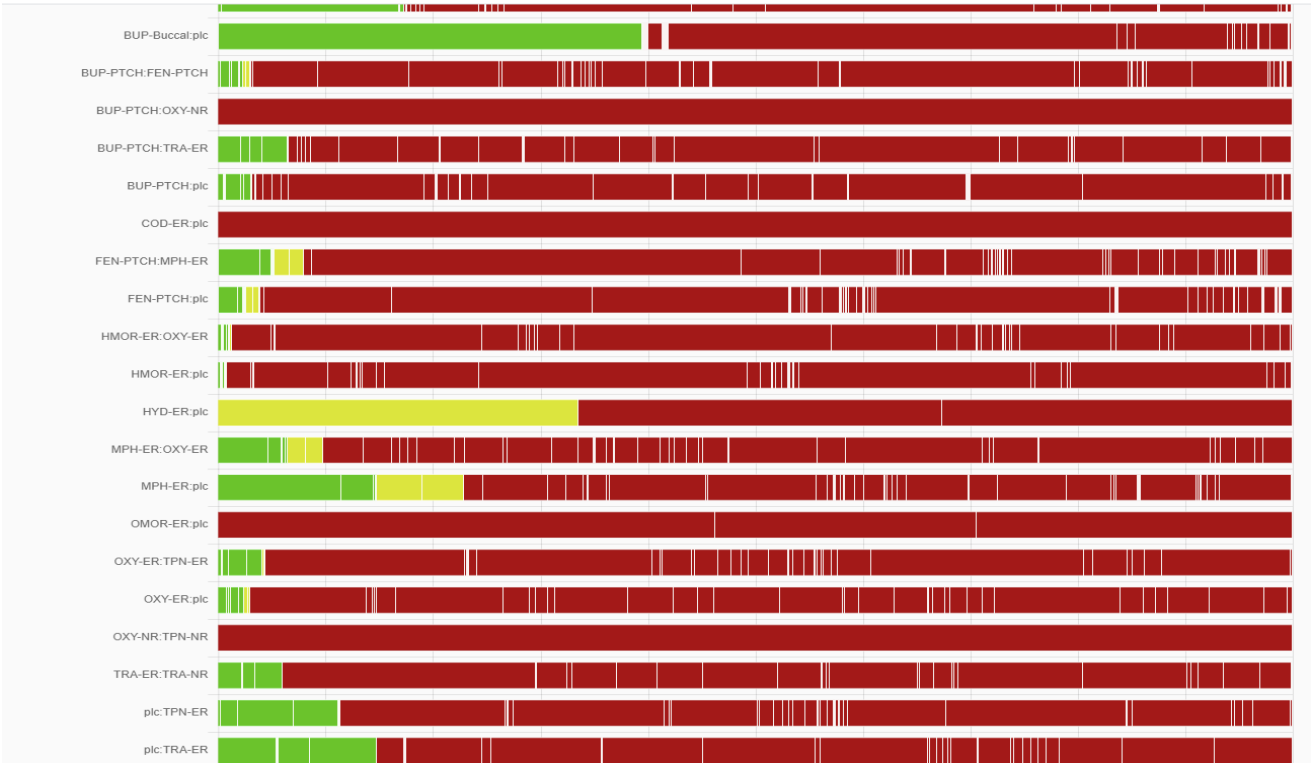
MPH-ER	HMOR-ER	NA	NA	NA	NA	-0.34 (-0.8 to 0.12)	VL	-0.34 (-0.8 to 0.12)	VL	ROB, intransitivity, imprecision	-0.35 (-0.83, 0.12)	VL	Major concerns	Some concerns	Some concerns	No
OMOR-ER	HMOR-ER	NA	NA	NA	NA	-0.95 (-1.62 to -0.29)	L	-0.95 (-1.62 to -0.29)	VL	ROB, imprecision	-1.17 (-1.80, -0.54)	L	Major concerns	No concerns	No concerns	Yes
OXY-ER	HMOR-ER	-0.01 (-0.31 to 0.28)	2	0	M	-0.24 (-0.78 to 0.29)	L	-0.15 (-0.52 to 0.23)	L	ROB, imprecision	-0.15 (-0.55, 0.24)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	HMOR-ER	NA	NA	NA	NA	-0.29 (-0.73 to 0.15)	L	-0.29 (-0.73 to 0.15)	VL	ROB, imprecision	-0.29 (-0.75, 0.17)	VL	Major concerns	Some concerns	Some concerns	No
TPN-NR	HMOR-ER	NA	NA	NA	NA	-0.57 (-1.76 to 0.61)	L	-0.57 (-1.76 to 0.61)	VL	ROB, imprecision	-0.57 (-1.82, 0.67)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	HMOR-ER	NA	NA	NA	NA	-0.28 (-0.72 to 0.15)	L	-0.28 (-0.72 to 0.15)	VL	ROB, imprecision	-0.29 (-0.74, 0.16)	VL	Major concerns	Some concerns	Some concerns	No
TRA-NR	HMOR-ER	NA	NA	NA	NA	-0.57 (-1.15 to 0)	VL	-0.57 (-1.15 to 0)	VL	ROB, intransitivity, imprecision	-0.57 (-1.17, 0.01)	L	Major concerns	Some concerns	No concerns	No
OXY-NR	HMOR-ER	NA	NA	NA	NA	-0.47 (-1.36 to 0.42)	L	-0.47 (-1.36 to 0.42)	VL	ROB, imprecision	-0.47 (-1.42, 0.46)	VL	Major concerns	Some concerns	Some concerns	Yes
MPH-ER	HYD-ER	NA	NA	NA	NA	-0.33 (-0.86 to 0.21)	L	-0.33 (-0.86 to 0.21)	VL	ROB, intransitivity, imprecision	0.33 (-0.22, 0.89)	VL	Major concerns	Some concerns	Some concerns	Yes
OMOR-ER	HYD-ER	NA	NA	NA	NA	-0.94 (-1.65 to -0.22)	L	-0.94 (-1.65 to -0.22)	VL	ROB, imprecision	-1.15 (-1.83, -0.47)	L	Major concerns	No concerns	No concerns	Yes
OXY-ER	HYD-ER	NA	NA	NA	NA	-0.13 (-0.62 to 0.36)	L	-0.13 (-0.62 to 0.36)	VL	ROB, imprecision	-0.13 (-0.65, 0.38)	VL	Major concerns	Some concerns	Some concerns	Yes
TPN-ER	HYD-ER	NA	NA	NA	NA	-0.27 (-0.79 to 0.25)	M	-0.27 (-0.79 to 0.25)	L	ROB, imprecision	-0.27 (-0.82, 0.27)	VL	Major concerns	Some concerns	Some concerns	Yes
TPN-NR	HYD-ER	NA	NA	NA	NA	-0.56 (-1.77 to 0.65)	M	-0.56 (-1.77 to 0.65)	L	ROB, imprecision	-0.56 (-1.83, 0.71)	VL	Major concerns	Major concerns	No concerns	Yes

TRA-ER	HYD-ER	NA	NA	NA	NA	-0.27 (-0.77 to 0.24)	M	-0.27 (-0.77 to 0.24)	L	ROB, imprecision	-0.27 (-0.80, 0.26)	VL	Major concerns	Some concerns	Some concerns	Yes
TRA-NR	HYD-ER	NA	NA	NA	NA	-0.56 (-1.18 to 0.07)	VL	-0.56 (-1.18 to 0.07)	VL	ROB, intransitivity, imprecision	-0.56 (-1.21, 0.09)	VL	Major concerns	Some concerns	No concerns	Yes
OXY-NR	HYD-ER	NA	NA	NA	NA	-0.46 (-1.38 to 0.47)	M	-0.46 (-1.38 to 0.47)	L	ROB, imprecision	-0.46 (-1.44, 0.52)	VL	Major concerns	Major concerns	No concerns	Yes
OMOR-ER	MPH-ER	NA	NA	NA	NA	-0.61 (-1.25 to 0.03)	VL	-0.61 (-1.25 to 0.03)	VL	ROB, intransitivity, imprecision	-0.81 (-1.41, -0.22)	VL	Major concerns	No concerns	Some concerns	Yes
OXY-ER	MPH-ER	0.23 (-0.12 to 0.58)	3	0	M	0.15 (-0.29 to 0.59)	VL	0.2 (-0.14 to 0.53)	L	ROB, intransitivity, imprecision	0.19 (-0.15, 0.54)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	MPH-ER	NA	NA	NA	NA	0.05 (-0.34 to 0.45)	L	0.05 (-0.34 to 0.45)	L	ROB, intransitivity	0.06 (-0.35, 0.47)	VL	Major concerns	No concerns	Major concerns	No
TPN-NR	MPH-ER	NA	NA	NA	NA	-0.23 (-1.39 to 0.94)	L	-0.23 (-1.39 to 0.94)	VL	ROB, intransitivity, imprecision	-0.22 (-1.45, 1.004)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	MPH-ER	NA	NA	NA	NA	0.06 (-0.33 to 0.45)	L	0.06 (-0.33 to 0.45)	L	ROB, intransitivity	0.06 (-0.34, 0.46)	VL	Major concerns	No concerns	Major concerns	No
TRA-NR	MPH-ER	NA	NA	NA	NA	-0.23 (-0.77 to 0.31)	L	-0.23 (-0.77 to 0.31)	VL	ROB, imprecision	-0.22 (-0.78, 0.33)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	MPH-ER	NA	NA	NA	NA	-0.13 (-1 to 0.74)	L	-0.13 (-1 to 0.74)	VL	ROB, intransitivity, imprecision	-0.12 (-1.04, 0.79)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	OMOR-ER	NA	NA	NA	NA	0.81 (0.2 to 1.41)	L	0.81 (0.2 to 1.41)	VL	ROB, imprecision	1.01 (0.46, 1.56)	L	Major concerns	No concerns	No concerns	Yes
TPN-ER	OMOR-ER	NA	NA	NA	NA	0.66 (0.04 to 1.29)	L	0.66 (0.04 to 1.29)	VL	ROB, imprecision	0.88 (0.30, 1.45)	VL	Major concerns	No concerns	Some concerns	Yes
TPN-NR	OMOR-ER	NA	NA	NA	NA	0.38 (-0.88 to 1.64)	L	0.38 (-0.88 to 1.64)	VL	ROB, imprecision	0.59 (-0.69, 1.885)	VL	Major concerns	Major concerns	No concerns	Yes

TRA-ER	OMOR-ER	NA	NA	NA	NA	0.67 (0.06 to 1.28)	L	0.67 (0.06 to 1.28)	VL	ROB, imprecision	0.88 (0.31, 1.44)	VL	Major concerns	No concerns	Some concerns	Yes
TRA-NR	OMOR-ER	NA	NA	NA	NA	0.38 (-0.34 to 1.09)	L	0.38 (-0.34 to 1.09)	VL	ROB, imprecision	0.59 (-0.09, 1.27)	VL	Major concerns	Some concerns	No concerns	Yes
OXY-NR	OMOR-ER	NA	NA	NA	NA	0.48 (-0.51 to 1.47)	L	0.48 (-0.51 to 1.47)	VL	ROB, imprecision	0.69 (-0.30, 1.69)	VL	Major concerns	Some concerns	Some concerns	Yes
TPN-ER	OXY-ER	-0.27 (-0.5 to -0.05)	4	40	L	0.04 (-0.47 to 0.54)	L	-0.14 (-0.44 to 0.16)	L	ROB, heterogeneity	-0.13 (-0.45, 0.17)	VL	Major concerns	No concerns	Major concerns	No
TPN-NR	OXY-ER	NA	NA	NA	NA	-0.43 (-1.57 to 0.72)	L	-0.43 (-1.57 to 0.72)	VL	ROB, imprecision	-0.42 (-1.63, 0.79)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	OXY-ER	NA	NA	NA	NA	-0.14 (-0.47 to 0.19)	L	-0.14 (-0.47 to 0.19)	L	ROB	-0.13 (-0.48, 0.20)	VL	Major concerns	No concerns	Major concerns	No
TRA-NR	OXY-ER	NA	NA	NA	NA	-0.43 (-0.92 to 0.07)	L	-0.43 (-0.92 to 0.07)	VL	ROB, imprecision	-0.42 (-0.94, 0.09)	L	Major concerns	Some concerns	No concerns	No
OXY-NR	OXY-ER	NA	NA	NA	NA	-0.33 (-1.17 to 0.52)	L	-0.33 (-1.17 to 0.52)	VL	ROB, imprecision	-0.32 (-1.21, 0.57)	VL	Major concerns	Major concerns	No concerns	Yes
TPN-NR	TPN-ER	NA	NA	NA	NA	-0.28 (-1.44 to 0.88)	M	-0.28 (-1.44 to 0.88)	L	ROB, imprecision	-0.28 (-1.51, 0.93)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	TPN-ER	NA	NA	NA	NA	0.01 (-0.36 to 0.38)	L	0.01 (-0.36 to 0.38)	L	ROB, intransitivity	0.001 (-0.38, 0.38)	VL	Major concerns	No concerns	Major concerns	No
TRA-NR	TPN-ER	NA	NA	NA	NA	-0.28 (-0.81 to 0.24)	VL	-0.28 (-0.81 to 0.24)	VL	ROB, intransitivity, imprecision	-0.28 (-0.83, 0.25)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	TPN-ER	NA	NA	NA	NA	-0.18 (-1.04 to 0.68)	M	-0.18 (-1.04 to 0.68)	L	ROB, imprecision	-0.18 (-1.09, 0.72)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-ER	TPN-NR	NA	NA	NA	NA	0.29 (-0.85 to 1.43)	L	0.29 (-0.85 to 1.43)	VL	ROB, intransitivity, imprecision	0.28 (-0.91, 1.49)	VL	Major concerns	Major concerns	No concerns	Yes

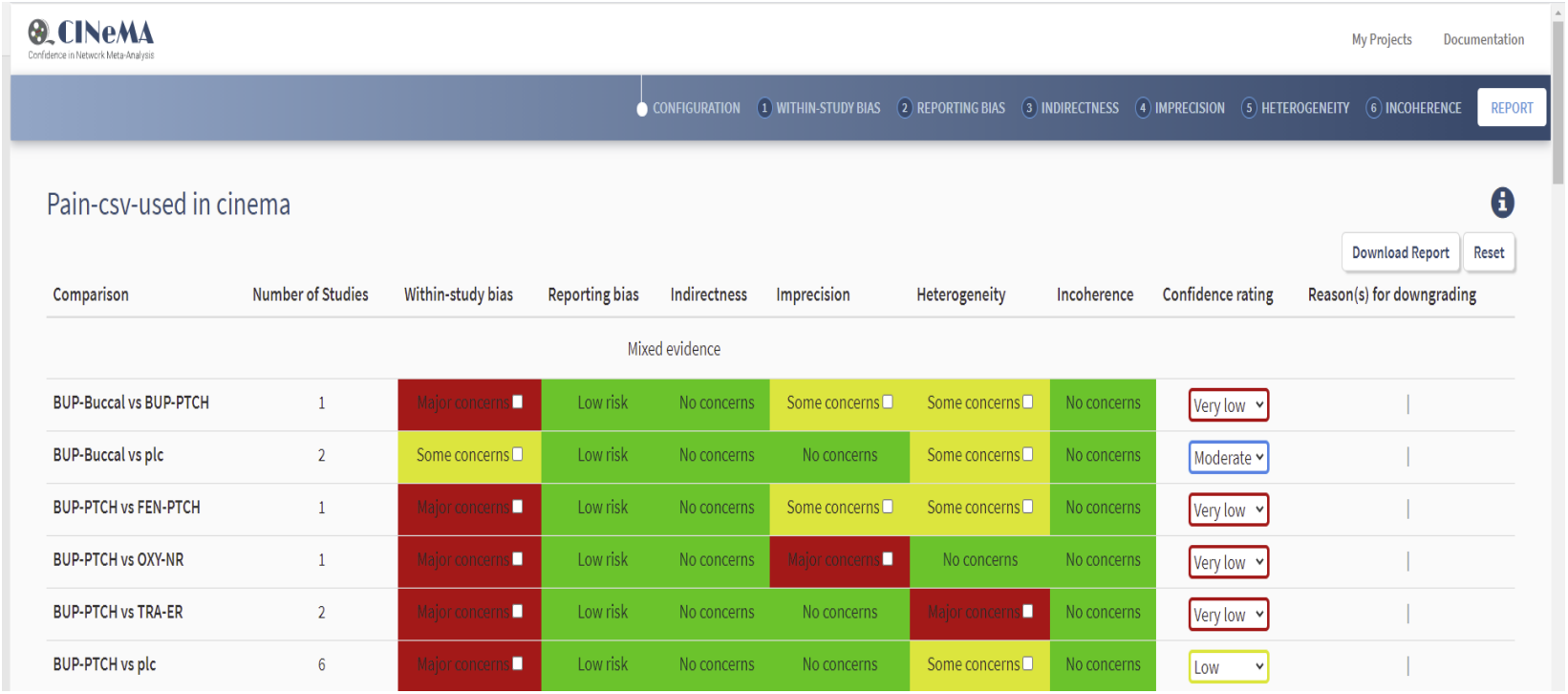
TRA-NR	TPN-NR	NA	NA	NA	NA	0 (-1.21 to 1.21)	L	0 (-1.21 to 1.21)	VL	ROB, intransitivity, imprecision	-0.001 (-1.27, 1.27)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-NR	TPN-NR	0.1 (-0.29 to 0.49)	1	0	M	NA	NA	0.1 (-0.68 to 0.88)	L	ROB, imprecision	0.1 (-0.72, 0.92)	VL	Major concerns	Major concerns	No concerns	Yes
TRA-NR	TRA-ER	-0.17 (-0.91 to 0.57)	1	0	M	-0.32 (-0.9 to 0.25)	L	-0.29 (-0.78 to 0.19)	L	ROB, imprecision	-0.28 (-0.791, 0.213)	VL	Major concerns	Some concerns	Some concerns	No
OXY-NR	TRA-ER	NA	NA	NA	NA	-0.19 (-1.03 to 0.65)	L	-0.19 (-1.03 to 0.65)	VL	ROB, intransitivity, imprecision	-0.18 (-1.07, 0.69)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-NR	TRA-NR	NA	NA	NA	NA	0.1 (-0.82 to 1.03)	L	0.1 (-0.82 to 1.03)	VL	ROB, intransitivity, imprecision	0.10 (-0.87, 1.07)	VL	Major concerns	Major concerns	No concerns	Yes

Footnote: Results are mean difference (95% CIs). Direct estimations are from DerSimonian and Laird random-effects meta-analysis.
Direct estimations rated down if there were risk of bias (ROB), indirectness, publication bias, or heterogeneity.
Indirect estimations rated down if there was intransitivity.
Network estimates rated down if there were incoherence or imprecision (either due to inclusion of the half MID in either side of 95%CI, or because the evidence is provided by a small number of participants- a total number of observations less than the optimal information size [≤300]).
Small-study effects were assessed when there were at least 10 studies using Egger test.
H: high certainty of evidence; M: moderate; L: low; VL: very low. MPH: morphine; FEN: fentanyl; BUP: buprenorphine; OXY: oxycodone; TPN: tapentadol; TRA: tramadol; HMOR: hydromorphone; OMOR: oxymorphone; COD: codein; HYD: hydrocodone. ER: Extended-released; NR: Normal-released.
[¥]Rated down twice for ROB
*The best estimate is direct evidence because of inflated 95%CI around the network.



Appendix 4. 2: Bar graph summarizing the percentage of information for each comparison in CINeMA framework.

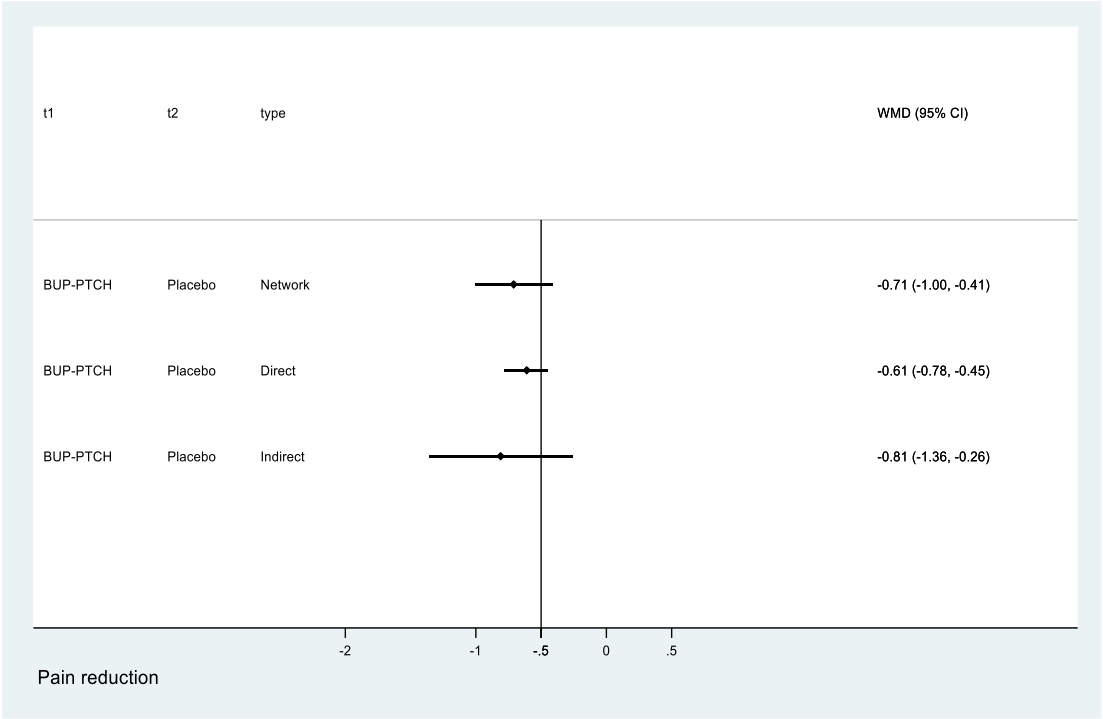
The green implies no concern (low risk of bias), yellow implies some concern (moderate Risk of bias), and red implies major concern (high risk of bias). Rules that can be used to summarize the ROB for each comparison of network to automatically produce the judgment includes “Majority ROB,” “Average ROB,” and “Highest ROB.” For example, average ROB uses a weighted average score for each comparison based on percentage contribution of studies at each level of bias.



Appendix 4. 3: A part of final output generated by CINeMA framework.

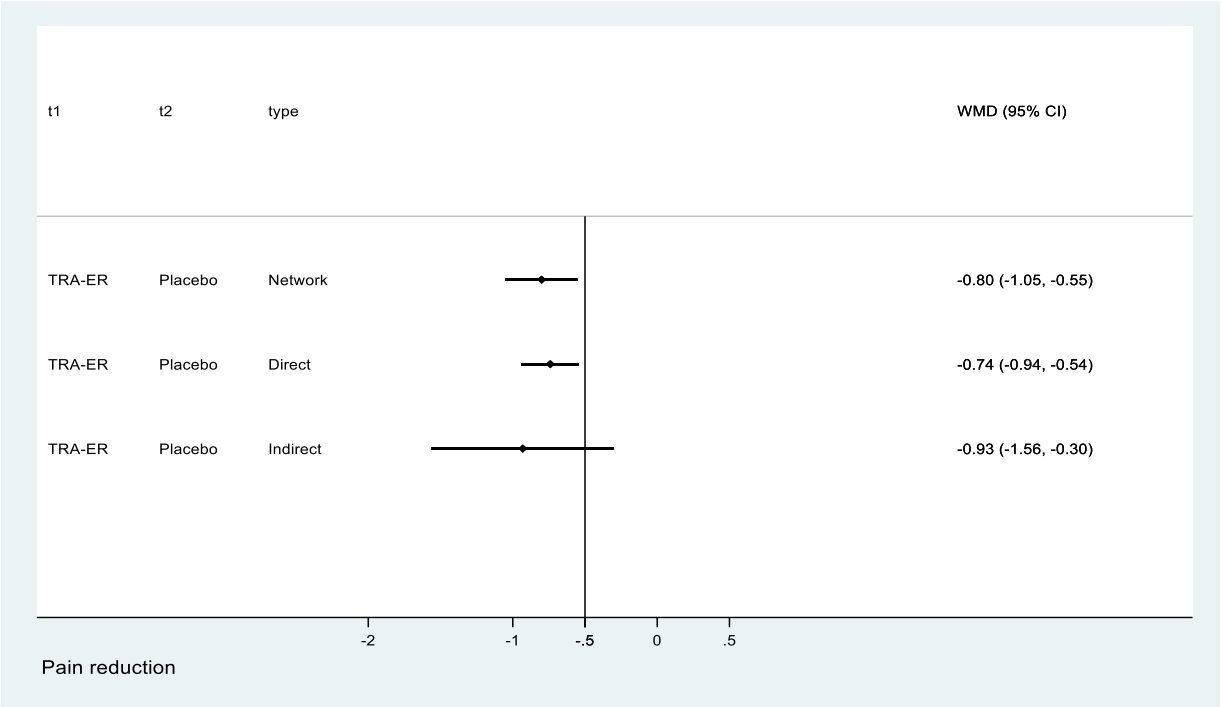
The table illustrating the level of concern for each domain for each network comparison. The default confidence rating is “High” confidence which can be downgrading by one, two, or three levels that will result in a confidence rating of “moderate”, “low”, or “very low” respectively.

Appendix 4. 4: direct, indirect, and network estimates for buprenorphine patches vs placebo



Direct evidence: 6 studies- contributed 87.5% and rated down one time for risk of bias (*moderate certainty*).
There are three first-order loops available includes buprenorphine patches-ER tramadol-placebo (~5% the lower certainty of the two direct constituted the indirect was *low certainty*), buprenorphine patches- buprenorphine buccal- placebo (~2.5%- the lower certainty of the two direct constituted the indirect was moderate but rated down one time because of intransitivity-*low certainty*), and buprenorphine patches- fentanyl patches- placebo (~2%- the lower certainty of the two direct constituted the indirect was moderate but rated down one time because of intransitivity-*low certainty).*
Finally, the confidence interval of network estimate was inflated a bit, so the best estimate would be direct evidence with narrower confidence interval, but still rated down for imprecision since 95%CI included half MID (*Low CoE*).

Appendix 4. 5: direct, indirect, and network estimates for ER tramadol vs placebo

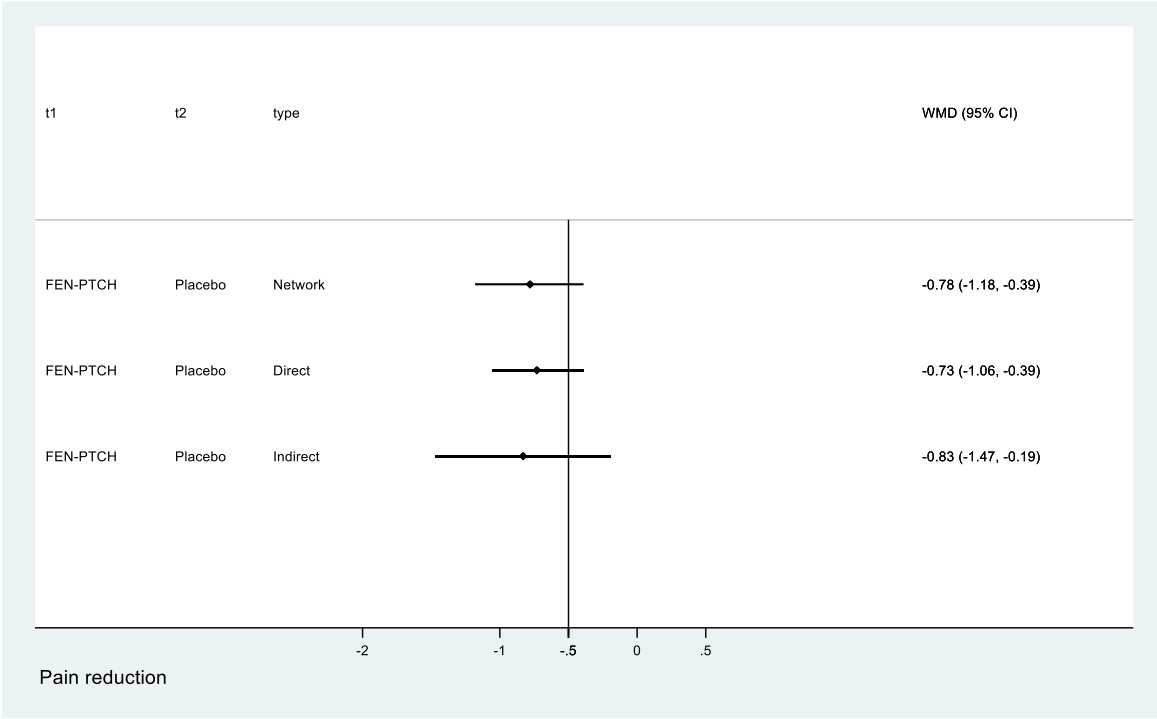


Direct evidence contributed approximately 87% and rated down one time for risk of bias (*moderate certainty*).

There are two first-order loops available includes ER tramadol- NR tramadol- placebo (~4%-*low CoE*) and ER tramadol- buprenorphine patches- placebo (~8.5%- *low CoE*).

Finally, network estimate rated as moderate CoE since no imprecision and no incoherence concern existed.

Appendix 4. 6: direct, indirect, and network estimates for fentanyl patches vs placebo

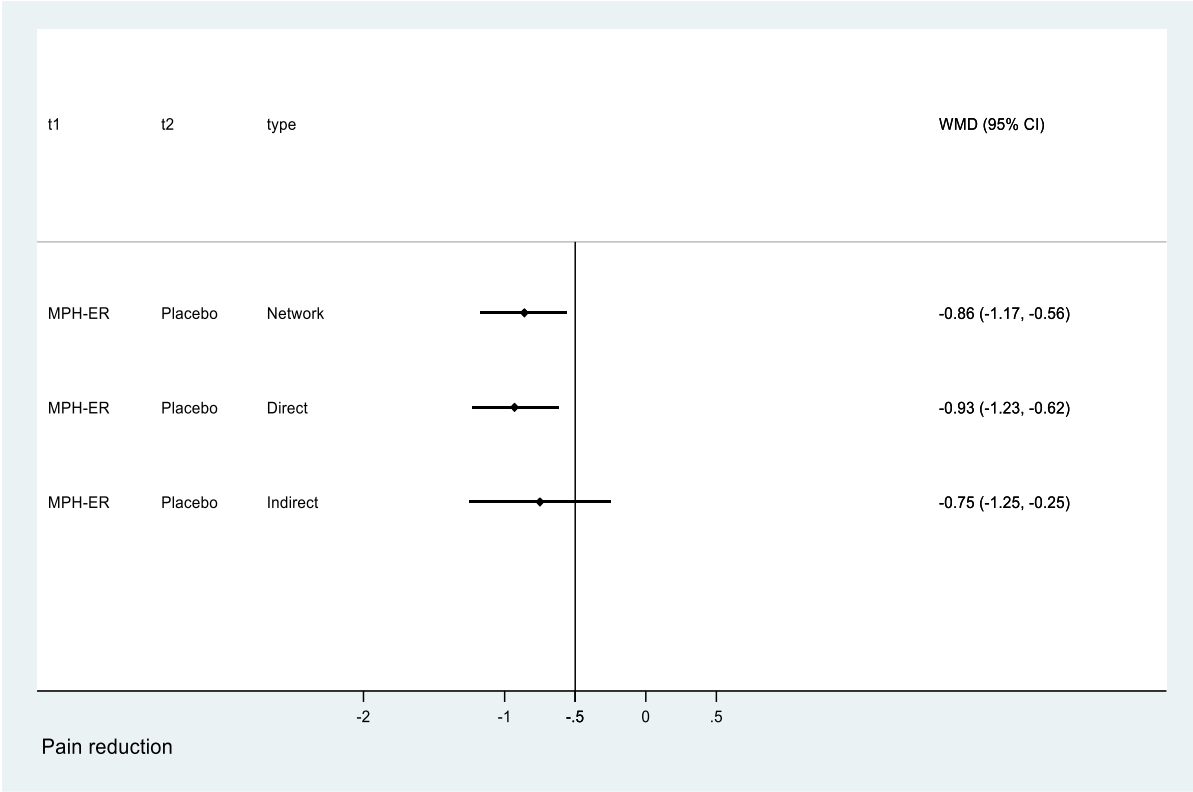


The direct evidence contributed ~33% and rated down one time for risk of bias (*moderate certainty*).

There are two first-order loops available includes fentanyl patches- buprenorphine patches- placebo (~6%) and fentanyl patches- ER morphine- placebo (~46.7%). So, the most dominant first-order loop is the second one with moderate certainty which rated down one more time because of the intransitivity and ended with *low certainty*.

Finally, certainty of evidence rated as low for the network estimate because of imprecision.

Appendix 4. 7: direct, indirect, and network estimates for ER morphine vs placebo

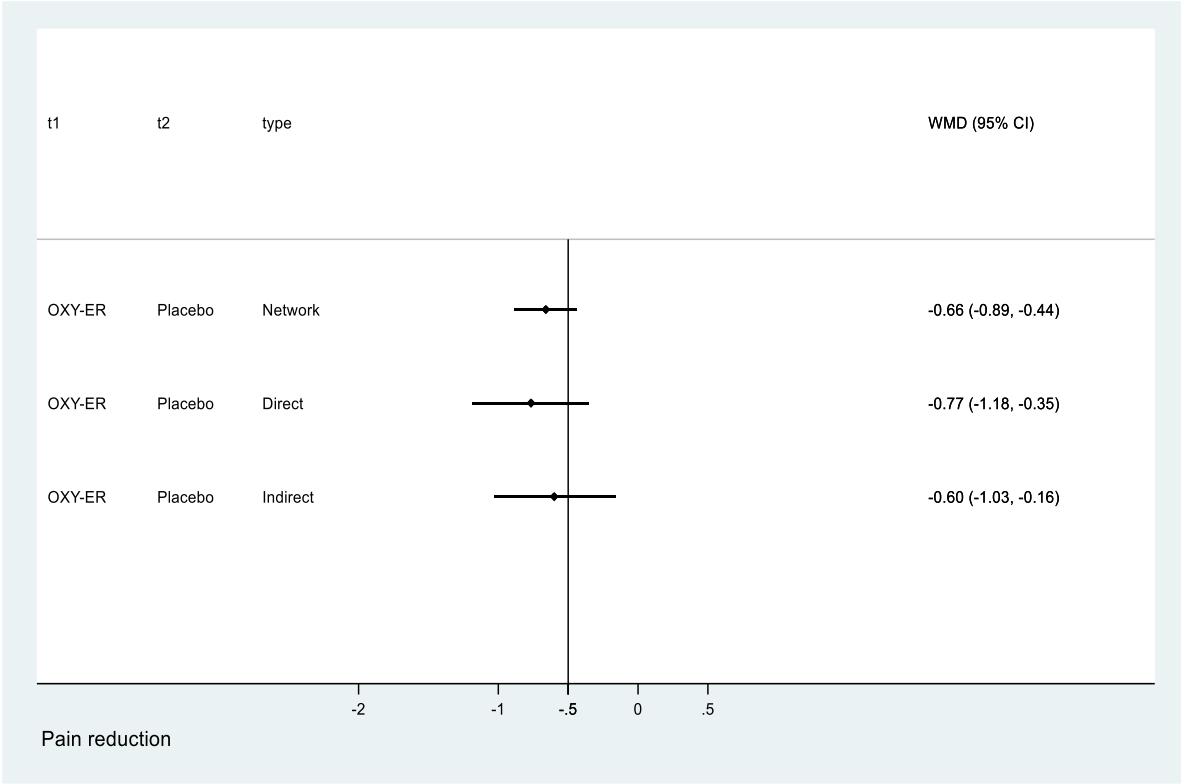


Direct evidence contributed ~41.5% and rated down one time for risk of bias (moderate certainty).

There are two first-order loops available includes 1) ER morphine- fentanyl patches- placebo (~25.5%) and 2) ER morphine- ER oxycodone- placebo (~11%). The first one is the dominant with moderate certainty.

Finally, network estimate rated as moderate CoE since no imprecision and incoherence concern existed.

Appendix 4. 8: direct, indirect, and network estimates for ER oxycodone vs placebo



Direct evidence contributed ~28% and rated down twice because of risk of bias and heterogeneity (low certainty).

There are 3 first-order loop available includes 1) ER oxycodone- ER tapentadol- placebo (~35%), 2) ER oxycodone- ER hydromorphone- placebo (8.6%), and 3) ER oxycodone –ER morphine- placebo (~19%). The most dominant loop is the first one with moderate certainty.

Finally, network rated down one more time due to imprecision and ended with low certainty.

Appendix 4. 9: Direct, indirect, and network estimates based on GRADE Working Group (GWG) system and CINeMA framework for physical function (on a 0-100-point Sf-36 physical component score)

GWG system											CINeMA framework					
Comparison		Direct Estimates MD (95%CI)	#of Studies	I^{2} %	Direct GRADE	Indirect Estimates MD (95%CI)	Indirect GRADE	NMA estimate MD (95%CI)	NMA GRADE	Reasons	NMA MD (95%CI)	NMA CoE	Reasons			
													ROB	Imprecision	Heterogeneity	Intransitivity
BUP-Buccal	Placebo	3.73 (0.7 to 6.76)	2	0	M	NA	NA	3.67 (-0.02 to 7.37)	L	ROB, imprecision	3.67 (0.01 to 7.34)	L	Some concerns	No concerns	Some concerns	Yes
BUP-PTCH	Placebo	2.03 (-0.27 to 4.34)	4	0	M	2.33 (-7.56 to 12.23)	M	2.16 (-0.6 to 4.92)	L	ROB, imprecision	2.15 (-0.58 to 4.9)	L	Major concerns	Some concerns	No concerns	No
COD-ER	Placebo	17.76 (7.78 to 27.74)	1	0	M	NA	NA	17.76 (7.35 to 28.17)	L	ROB, imprecision [£]	17.76 (7.37 to 28.14)	L	Major concerns	No concern	No concerns	Yes
FEN-PTCH	Placebo	1 (-0.27 to 2.29)	3	0	M	2.56 (-1.25 to 6.37)	M	1.53 (-0.6 to 3.65)	L	ROB, imprecision	1.52 (-0.57 to 3.61)	L	Major concerns	Some concern	No concerns	No
HMOR-ER	Placebo	2.95 (0.53 to 5.36)	3	37	M	4.77 (0.76 to 8.78)	L	3.45 (1.28 to 5.61)	L	ROB, imprecision	3.45 (1.31 to 5.58)	L	Major concerns	No concern	Some concerns	No
HYD-ER	Placebo	-1.13 (-5.28 to 3.02)	1	0	M	NA	NA	-1.13 (-6.23 to 3.97)	L	ROB, imprecision	-1.13 (-6.18 to 3.92)	VL	Some concerns	Major concerns	No concerns	Yes
MPH-ER	Placebo	5.37 (1.76 to 8.98)	4	0	M	0.45 (-2.19 to 3.08)	M	1.98 (-0.3 to 4.26)	L	ROB, imprecision, incoherence [1]	1.96 (-0.26 to 4.18)	L	Major concerns	Some concerns	No concerns	No
OMOR-ER	Placebo	2.15 (0.3 to 4)	1	0	M	NA	NA	1.67 (-1.4 to 4.75)	L	ROB, imprecision	1.67 (-1.35 to 4.70)	VL	Major concerns	Some concerns	Some concerns	No
OXY-ER	Placebo	1.03 (-0.2 to 2.28)	8	82	L	1.93 (-0.94 to 4.8)	L	1.21 (0.01 to 2.4)	L	ROB, heterogeneity	1.19 (0.03 to 2.35)	L	Major concerns	No concerns	Some concerns	No
TPN-ER	Placebo	1.93 (0.36 to 3.5)	5	88.5	L	4.18 (-0.69 to 9.05)	L	2.13 (0.67 to 3.59)	L	ROB, heterogeneity,	2.12 (0.70 to 3.54)	L	Major concerns	No concerns	Some concerns	No

										imprecision [2]						
TRA-ER	Placebo	2.09 (-0.3 to 4.49)	4	74.5	L	NA	NA	1.81 (-0.32 to 3.95)	L	ROB, heterogeneity, imprecision [2]	1.78 (-0.23 to 3.80)	VL	Major concerns	Some concerns	No concerns	Yes
BUP-PTCH	BUP-Buccal	NA	NA	NA	NA	-1.51 (-6.12 to 3.09)	L	-1.51 (-6.12 to 3.09)	VL	ROB, intransitivity imprecision	-1.51 (-6.09 to 3.05)	VL	Major concerns	Major concerns	No concerns	Yes
COD-ER	BUP-Buccal	NA	NA	NA	NA	14.09 (3.04 to 25.13)	L	14.09 (3.04 to 25.13)	L	ROB, intransitivity	14.08 (3.07 to 25.09)	L	Major concerns	No concerns	No concerns	Yes
FEN-PTCH	BUP-Buccal	NA	NA	NA	NA	-2.15 (-6.41 to 2.11)	L	-2.15 (-6.41 to 2.11)	VL	ROB, intransitivity imprecision	-2.15 (-6.37 to 2.067)	VL	Major concerns	Some concerns	Some concerns	Yes
HMOR-ER	BUP-Buccal	NA	NA	NA	NA	-0.23 (-4.51 to 4.05)	L	-0.23 (-4.51 to 4.05)	VL	ROB, intransitivity imprecision	-0.22 (-4.46 to 4.01)	VL	Major concerns	Major concerns	No concerns	Yes
HYD-ER	BUP-Buccal	NA	NA	NA	NA	-4.8 (-11.1 to 1.49)	M	-4.8 (-11.1 to 1.49)	L	ROB, imprecision	-4.80 (-11.05 to 1.43)	L	Some concerns	Some concerns	No concerns	Yes
MPH-ER	BUP-Buccal	NA	NA	NA	NA	-1.7 (-6.04 to 2.65)	L	-1.7 (-6.04 to 2.65)	VL	ROB, intransitivity imprecision	-1.71 (-6.0 to 2.57)	VL	Major concerns	Major concerns	No concerns	Yes
OMOR-ER	BUP-Buccal	NA	NA	NA	NA	-2 (-6.81 to 2.81)	L	-2 (-6.81 to 2.81)	VL	ROB, intransitivity imprecision	-2.0 (-6.75 to 2.74)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	BUP-Buccal	NA	NA	NA	NA	-2.47 (-6.35 to 1.42)	VL	-2.47 (-6.35 to 1.42)	VL	ROB, intransitivity imprecision	-2.48 (-6.32 to 1.36)	VL	Major concerns	Some concerns	Some concerns	Yes
TPN-ER	BUP-Buccal	NA	NA	NA	NA	-1.54 (-5.51 to 2.43)	VL	-1.54 (-5.51 to 2.43)	VL	ROB, intransitivity imprecision	-1.55 (-5.48 to 2.37)	VL	Major concerns	Some concerns	Some concerns	Yes
TRA-ER	BUP-Buccal	NA	NA	NA	NA	-1.86 (-6.13 to 2.41)	VL	-1.86 (-6.13 to 2.41)	VL	ROB, intransitivity imprecision	-1.90 (-6.07 to 2.28)	VL	Major concerns	Some concerns	Some concerns	Yes

COD-ER	BUP-PTCH	NA	NA	NA	NA	15.6 (4.83 to 26.37)	VL	15.6 (4.83 to 26.37)	L	ROB, intransitivity	15.60 (4.86 to 26.34)	L	Major concerns	No concerns	No concerns	Yes
FEN-PTCH	BUP-PTCH	-0.8 (-9.69 to 8.09)	1	0	M	-0.61 (-4.23 to 3.01)	M	-0.63 (-4.01 to 2.74)	L	ROB, imprecision	-0.63 (-3.97 to 2.70)	VL	Major concerns	Major concerns	No concerns	No
HMOR-ER	BUP-PTCH	NA	NA	NA	NA	1.29 (-2.22 to 4.79)	M	1.29 (-2.22 to 4.79)	L	ROB, imprecision	1.29 (-2.17 to 4.76)	VL	Major concerns	Some concerns	Some concerns	No
HYD-ER	BUP-PTCH	NA	NA	NA	NA	-3.29 (-9.09 to 2.51)	L	-3.29 (-9.09 to 2.51)	VL	ROB, intransitivity imprecision	-3.28 (-9.03 to 2.46)	VL	Major concerns	Some concerns	Some concerns	Yes
MPH-ER	BUP-PTCH	NA	NA	NA	NA	-0.18 (-3.71 to 3.34)	M	-0.18 (-3.71 to 3.34)	L	ROB, imprecision	-0.19 (-3.68 to 3.28)	VL	Major concerns	Major concerns	No concerns	No
OMOR-ER	BUP-PTCH	NA	NA	NA	NA	-0.48 (-4.61 to 3.65)	M	-0.48 (-4.61 to 3.65)	L	ROB, imprecision	-0.48 (-4.56 to 3.59)	VL	Major concerns	Major concerns	No concerns	No
OXY-ER	BUP-PTCH	NA	NA	NA	NA	-0.95 (-3.95 to 2.05)	L	-0.95 (-3.95 to 2.05)	VL	ROB, imprecision	-0.96 (-3.93 to 2.005)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	BUP-PTCH	NA	NA	NA	NA	-0.03 (-3.14 to 3.09)	L	-0.03 (-3.14 to 3.09)	VL	ROB, imprecision	-0.034 (-3.11 to 3.05)	VL	Major concerns	Major concerns	No concerns	No
TRA-ER	BUP-PTCH	NA	NA	NA	NA	-0.35 (-3.83 to 3.14)	VL	-0.35 (-3.83 to 3.14)	VL	ROB, imprecision	-0.37 (-3.77 to 3.02)	VL	Major concerns	Major concerns	No concerns	Yes
FEN-PTCH	COD-ER	NA	NA	NA	NA	-16.23 (-26.86 to -5.61)	L	-16.23 (-26.86 to -5.61)	L	ROB, intransitivity	-16.23 (-26.83 to -5.64)	L	Major concerns	No concerns	No concerns	Yes
HMOR-ER	COD-ER	NA	NA	NA	NA	-14.31 (-24.94 to -3.68)	L	-14.31 (-24.94 to -3.68)	L	ROB, intransitivity	-14.30 (-24.93 to -3.70)	L	Major concerns	No concerns	No concerns	Yes
HYD-ER	COD-ER	NA	NA	NA	NA	-18.89 (-30.48 to -7.3)	L	-18.89 (-30.48 to -7.3)	L	ROB, intransitivity	-18.89 (-30.44 to -7.33)	L	Major concerns	No concerns	No concerns	Yes
MPH-ER	COD-ER	NA	NA	NA	NA	-15.78 (-26.44 to -5.13)	L	-15.78 (-26.44 to -5.13)	L	ROB, intransitivity	-15.80 (-26.42 to -5.17)	L	Major concerns	No concerns	No concerns	Yes
OMOR-ER	COD-ER	NA	NA	NA	NA	-16.09 (-26.94 to -5.23)	L	-16.09 (-26.94 to -5.23)	L	ROB, intransitivity	-16.08 (-26.90 to -5.27)	L	Major concerns	No concerns	No concerns	Yes
OXY-ER	COD-ER	NA	NA	NA	NA	-16.55 (-27.03 to -6.08)	VL	-16.55 (-27.03 to -6.08)	VL	ROB, intransitivit	-16.56 (-27.01 to -6.11)	L	Major concerns	No concerns	No concerns	Yes

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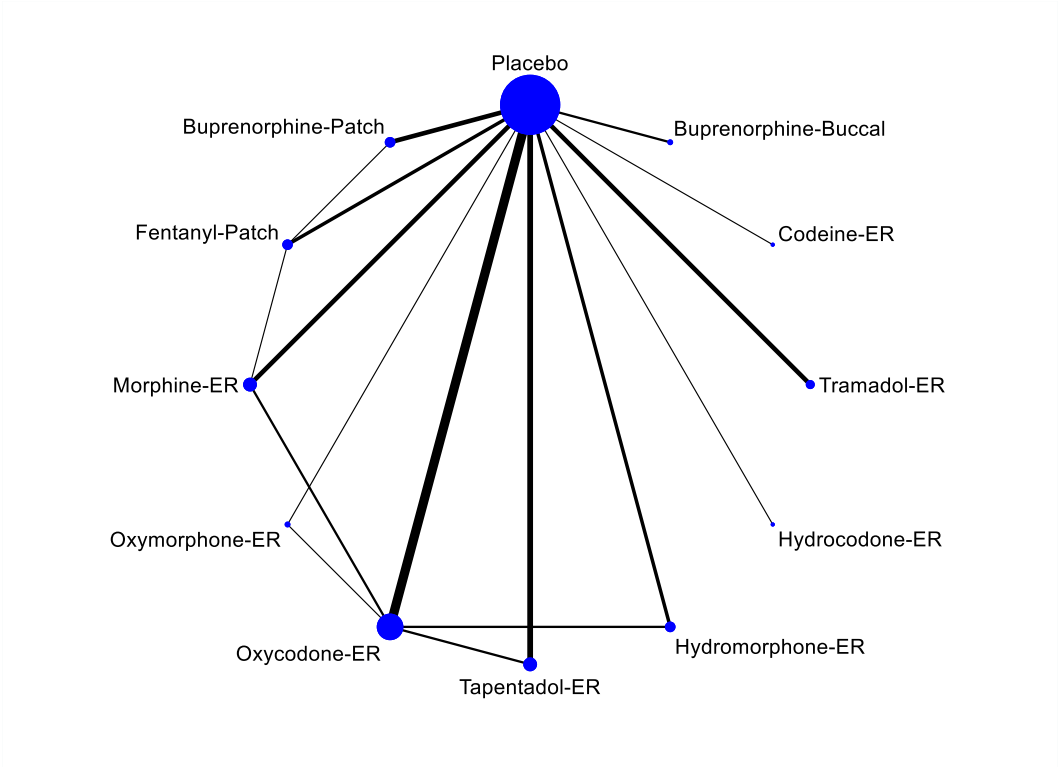
TPN-ER	COD-ER	NA	NA	NA	NA	-15.63 (-26.14 to -5.12)	VL	-15.63 (-26.14 to -5.12)	VL	ROB, intransitivity	-15.63 (-26.11 to -5.15)	ML	Major concerns	No concerns	No concerns	Yes
TRA-ER	COD-ER	NA	NA	NA	NA	-15.95 (-26.57 to -5.33)	VL	-15.95 (-26.57 to -5.33)	VL	ROB, intransitivity	-15.97 (-26.55 to -5.39)	ML	Major concerns	No concerns	No concerns	Yes
HMOR-ER	FEN-PTCH	NA	NA	NA	NA	1.92 (-1.09 to 4.93)	M	1.92 (-1.09 to 4.93)	L	ROB, imprecision	1.92 (-1.04 to 4.90)	L	Major concerns	Some concerns	No concerns	No
HYD-ER	FEN-PTCH	NA	NA	NA	NA	-2.66 (-8.18 to 2.87)	M	-2.66 (-8.18 to 2.87)	L	ROB, intransitivity imprecision	-2.65 (-8.12 to 2.82)	VL	Major concerns	Major concerns	No concerns	Yes
MPH-ER	FEN-PTCH	-0.2 (-0.28 to -0.11)	1	0	M	1.5 (-2.28 to 5.28)	M	0.45 (-1.88 to 2.79)	L	ROB, imprecision	0.43 (-1.83 to 2.70)	VL	Major concerns	Some concerns	Some concerns	No
OMOR-ER	FEN-PTCH	NA	NA	NA	NA	0.15 (-3.56 to 3.86)	M	0.15 (-3.56 to 3.86)	L	ROB, imprecision	0.14 (-3.50 to 3.80)	VL	Major concerns	Major concerns	No concerns	No
OXY-ER	FEN-PTCH	NA	NA	NA	NA	-0.32 (-2.67 to 2.03)	L	-0.32 (-2.67 to 2.03)	VL	ROB, imprecision	-0.32 (-2.63 to 1.97)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	FEN-PTCH	NA	NA	NA	NA	0.61 (-1.95 to 3.16)	L	0.61 (-1.95 to 3.16)	VL	ROB, imprecision	0.60 (-1.90 to 3.11)	VL	Major concerns	Some concerns	Some concerns	No
TRA-ER	FEN-PTCH	NA	NA	NA	NA	0.29 (-2.72 to 3.29)	VL	0.29 (-2.72 to 3.29)	VL	ROB, intransitivity imprecision	0.26 (-2.64 to 3.16)	VL	Major concerns	Major concerns	No concerns	Yes
HYD-ER	HMOR-ER	NA	NA	NA	NA	-4.58 (-10.11 to 0.96)	L	-4.58 (-10.11 to 0.96)	VL	ROB, intransitivity, imprecision	-4.58 (-10.07 to 0.90)	VL	Major concerns	Some concerns	No concerns	Yes
MPH-ER	HMOR-ER	NA	NA	NA	NA	-1.47 (-4.57 to 1.63)	M	-1.47 (-4.57 to 1.63)	L	ROB, imprecision	-1.49 (-4.52 to 1.54)	VL	Major concerns	Some concerns	Some concerns	No
OMOR-ER	HMOR-ER	NA	NA	NA	NA	-1.77 (-5.48 to 1.94)	M	-1.77 (-5.48 to 1.94)	L	ROB, imprecision	-1.78 (-5.42 to 1.86)	VL	Major concerns	Some concerns	Some concerns	No
OXY-ER	HMOR-ER	-3.66 (-6.51 to -0.81)	1	0	M	-1.54 (-4.46 to 1.39)	L	-2.24 (-4.54 to 0.06)	L	ROB, imprecision	-2.25 (-4.50 to -0.008)	L	Major concerns	No concerns	Some concerns	No

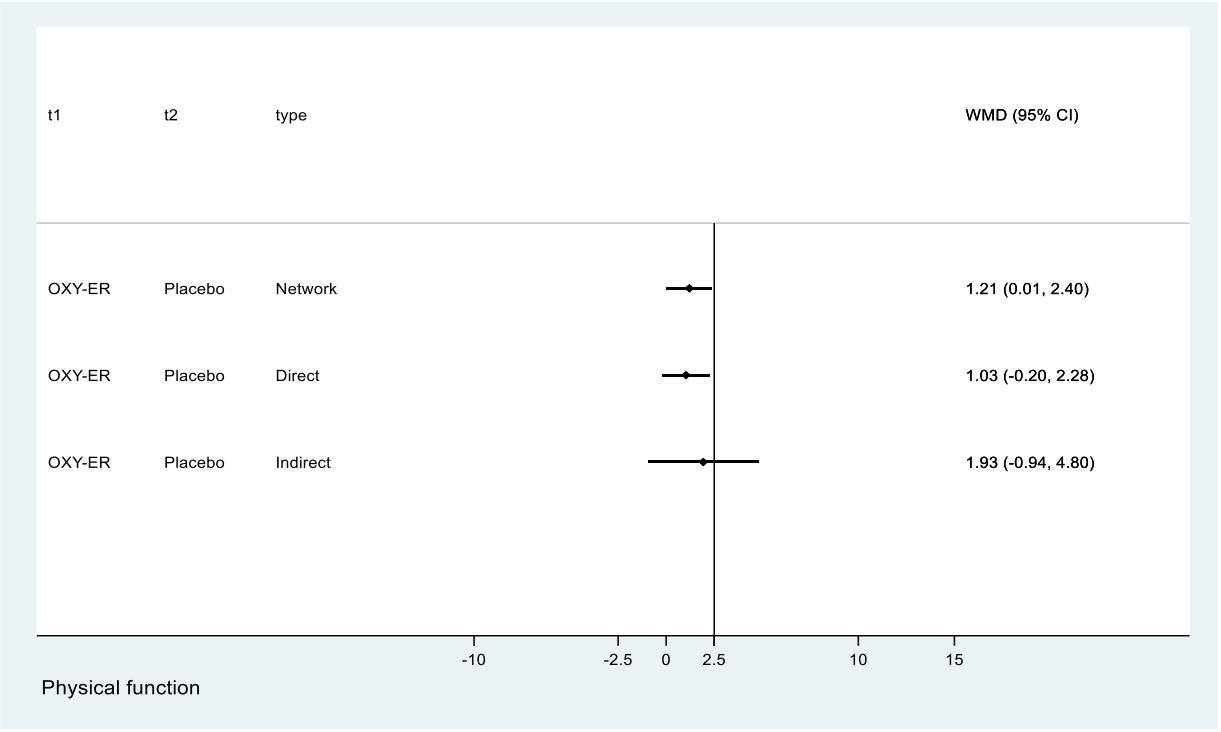
TPN-ER	HMOR-ER	NA	NA	NA	NA	-1.31 (-3.88 to 1.26)	L	-1.31 (-3.88 to 1.26)	VL	ROB, imprecision	-1.32 (-3.84 to 1.19)	VL	Major concerns	Some concerns	Some concerns	No
TRA-ER	HMOR-ER	NA	NA	NA	NA	-1.64 (-4.7 to 1.42)	VL	-1.64 (-4.7 to 1.42)	VL	ROB, intransitivity imprecision	-1.67 (-4.60 to 1.26)	VL	Major concerns	Some concerns	Some concerns	Yes
MPH-ER	HYD-ER	NA	NA	NA	NA	3.11 (-2.48 to 8.69)	L	3.11 (-2.48 to 8.69)	VL	ROB, intransitivity imprecision	3.08 (-2.43 to 8.61)	VL	Major concerns	Some concerns	Some concerns	Yes
OMOR-ER	HYD-ER	NA	NA	NA	NA	2.8 (-3.15 to 8.76)	L	2.8 (-3.15 to 8.76)	VL	ROB, intransitivity imprecision	2.80 (-3.09 to 8.69)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	HYD-ER	NA	NA	NA	NA	2.34 (-2.9 to 7.57)	VL	2.34 (-2.9 to 7.57)	VL	ROB, intransitivity imprecision	2.32 (-2.86 to 7.51)	VL	Major concerns	Major concerns	No concerns	Yes
TPN-ER	HYD-ER	NA	NA	NA	NA	3.26 (-2.04 to 8.57)	VL	3.26 (-2.04 to 8.57)	VL	ROB, intransitivity imprecision	3.25 (-1.99 to 8.50)	VL	Major concerns	Some concerns	Some concerns	Yes
TRA-ER	HYD-ER	NA	NA	NA	NA	2.94 (-2.59 to 8.47)	VL	2.94 (-2.59 to 8.47)	VL	ROB, intransitivity imprecision	2.91 (-2.53 to 8.35)	VL	Major concerns	Major concerns	No concerns	Yes
OMOR-ER	MPH-ER	NA	NA	NA	NA	-0.3 (-4.06 to 3.46)	M	-0.3 (-4.06 to 3.46)	L	ROB, imprecision	-0.28 (-3.97 to 3.40)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	MPH-ER	0.8 (-2.12 to 3.72)	2	21.5	M	-2.03 (-5.18 to 1.11)	VL	-0.77 (-3.11 to 1.56)	L	ROB, imprecision	-0.76 (-3.06 to 1.54)	VL	Major concerns	Some concerns	Some concerns	No
TPN-ER	MPH-ER	NA	NA	NA	NA	0.16 (-2.47 to 2.79)	L	0.16 (-2.47 to 2.79)	VL	ROB, imprecision	0.16 (-2.42 to 2.75)	VL	Major concerns	Some concerns	Some concerns	No
TRA-ER	MPH-ER	NA	NA	NA	NA	-0.17 (-3.22 to 2.89)	VL	-0.17 (-3.22 to 2.89)	VL	ROB, intransitivity imprecision	-0.17 (-3.18 to 2.82)	VL	Major concerns	Major concerns	No concerns	Yes
OXY-ER	OMOR-ER	0.05 (-1.95 to 2.05)	1	0	M	-2.16 (-8.9 to 4.58)	L	-0.47 (-3.56 to 2.62)	L	ROB, imprecision	-0.47 (-3.50 to 2.55)	VL	Major concerns	Major concerns	No concerns	No

TPN-ER	OMOR-ER	NA	NA	NA	NA	0.46 (-2.89 to 3.81)	L	0.46 (-2.89 to 3.81)	VL	ROB, imprecision	0.45 (-2.83 to 3.74)	VL	Major concerns	Major concerns	No concerns	No
TRA-ER	OMOR-ER	NA	NA	NA	NA	0.14 (-3.6 to 3.87)	L	0.14 (-3.6 to 3.87)	VL	ROB, intransitivity imprecision	0.11 (-3.52 to 3.74)	VL	Major concerns	Major concerns	No concerns	Yes
TPN-ER	OXY-ER	1.18 (-1.26 to 3.62)	2	93.8	L	0.6 (-2.03 to 3.22)	L	0.93 (-0.72 to 2.57)	L	ROB, heterogeneity[2]	0.92 (-0.68 to 2.54)	VL	Major concerns	Some concerns	Some concerns	No
TRA-ER	OXY-ER	NA	NA	NA	NA	0.61 (-1.79 to 3)	VL	0.61 (-1.79 to 3)	VL	ROB, intransitivity imprecision	0.58 (-1.73 to 2.91)	VL	Major concerns	Some concerns	Some concerns	Yes
TRA-ER	TPN-ER	NA	NA	NA	NA	-0.32 (-2.87 to 2.23)	VL	-0.32 (-2.87 to 2.23)	VL	ROB, intransitivity imprecision	-0.34 (-2.80 to 2.12)	VL	Major concerns	Some concerns	Some concerns	Yes



Appendix 4. 10: network map for physical function

39 studies totally included with 12 nodes and 17 direct comparisons. The size of the circle corresponds to the number of particpants randomized to that node. The drugs directly compared are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison.



Appendix 4. 11: Comparison of the direct, indirect, and network estimates of effect of ER oxycodone vs placebo

The contribution of direct evidence was almost 60% and rated down twice for risk of bias and heterogeneity (Low certainty). There are four first-order loops available for this comparison, including ER oxycodone- ER oxymorphone- Placebo (14%-the lower certainty of the two direct constituted the indirect was moderate but rated down one time because of intransitivity-low certainty), ER oxycodone – ER tapentadol- Placebo (12.5%-the lower certainty of the two direct constituted the indirect was low), ER oxycodone- ER hydromorphone- Placebo (6%), and ER oxycodone- ER morphine- Placebo (3%).

Chapter 5: Opioid-Sparing effects of medical cannabis or cannabinoids for chronic pain: A systematic review and meta-analysis of randomized and observational studies

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Author contribution:

A. Noori was the primary investigators. J.W. Busse, A.Noori, G.H. Guyatt conceived and designed the study. R. Couban performed the literature search. A. Noori, A. Miroshnychenko, Y. Shergill, V. Ashoorion and Y. Rehman selected the studies, extracted the relevant information, and assessed the risk of bias of selected studies. A. Noori synthesised the data. A. Noori wrote the first draft of the paper. A. Noori, J.W. Busse, G.H. Guyatt and T. Agoritsas critically revised the manuscript for important intellectual content. Noori, J.W. Busse, L. Thabane, G.H. Guyatt, M. Bhandari and N. Buckley interpreted the findings. J.W. Busse, L. Thabane and G.H. Guyatt provided methodological support. All authors reviewed the paper and approved the final version.

Opioid-Sparing effects of medical cannabis or cannabinoids for chronic pain: A systematic review and meta-analysis of randomized and observational studies

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ABSTRACT

Objective: To assess the efficacy and harms of adding medical cannabis to prescription opioids among people living with chronic pain.

Design: Systematic review.

Data sources: CENTRAL, EMBASE, and MEDLINE.

Main outcomes and measures: Opioid dose relief, pain relief, sleep disturbance, physical and emotional functioning, and adverse events.

Study selection criteria and methods: We included studies that enrolled patients with chronic pain receiving prescription opioids and explored the impact of adding medical cannabis. We used GRADE to assess the certainty of evidence for each outcome.

Results: Eligible studies included five randomized trials (all enrolling chronic cancer-pain patients) and 12 observational studies. All randomized trials instructed participants to maintain their opioid dose, which resulted in a very low certainty evidence that adding cannabis has little or no impact on opioid use (weighted mean difference [WMD] -3.4 milligram morphine equivalent [MME]; 95% confidence interval [CI] -12.7 to 5.8). Randomized trials provided high certainty evidence that cannabis addition had little or no effect on pain relief (WMD -0.18cm; 95%CI -0.38 to 0.02; on a 10 cm VAS for pain) or sleep disturbance (WMD -0.22 cm; 95%CI -0.4 to -0.06; on a 10 cm VAS for sleep disturbance; minimally important difference [MID] is 1 cm) among chronic cancer-pain patients. Addition of cannabis likely increases nausea (relative risk [RR] 1.43; 95%CI

1.04 to 1.96; risk difference [RD] 4%, 95%CI 0% to 7%) and vomiting (RR 1.5; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%) (both moderate certainty) and may have no effect on constipation (RR 0.85; 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%) (low certainty). Eight observational studies provided very-low certainty evidence that adding cannabis reduced opioid use (WMD -22.5 MME; 95%CI -43.06 to -1.97).

Conclusion: Opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to very-low certainty evidence.

Systematic review registration PROSPERO CRD42018091098

Funding Source: This review received no external funding or other support

Keywords: chronic pain; opioids; cannabis; cannabinoids; drug substitution; sparing effect; tapering

Strengths and limitations of this study

- This is the first meta-analysis to pool the results of randomized controlled trials (RCTs) and observational studies exploring the opioid-sparing effects of medical cannabis among people living with chronic pain.
- We conducted a comprehensive search for eligible studies, appraised the risk of bias of included studies, and evaluated the certainty of evidence using the GRADE approach.

- Most observational studies incorporated inadequate adjustment for confounding, and all randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use.

Introduction

Chronic pain affects approximately one in five adults and is a common reason for seeking medical care.[1, 2] Opioids are commonly prescribed for this condition, particularly in North America;[3] however, they only provide benefit to a minority of patients. A 2018 systematic review of 96 trials found high certainty evidence that, versus placebo, opioids provide important pain relief (≥1cm improvement on a 10-cm visual analog scale for pain) to 12% of patients for whom they are prescribed.[4] Moreover, opioids are associated with harms such as overdose and death,[5, 6] which are dose-dependent.[7-10] As a result, there is considerable interest in therapies that may allow patients with chronic pain using opioid therapy to reduce their opioid intake.

One promising approach is adding cannabis therapy, which low certainty evidence suggests may be similarly effective to opioids for reducing pain and improving physical functioning among people living with chronic pain.[4] Experimental studies have shown that opioids and cannabis have similar signal transduction systems,[11] and observational studies in the US demonstrated that the rates of opioid-related mortality reduced after cannabis was legalized.[12-14] Between 64% and 77% of patients with chronic pain responding to cross-sectional surveys reported a reduction in long-term opioid use after adding medical cannabis to their treatment.[15, 16] A 2017 systematic review concluded that pre-clinical studies provided robust evidence for the opioid-sparing effects of cannabis.[17]

To clarify the issue, we undertook a systematic review of randomized controlled trials and observational studies to explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes, and related harms in patients with chronic pain using prescribed opioid therapy.

This systematic review is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicevidnece.org) and BMJ. This systematic review informed a parallel guideline published on BMJ.com[18] and MAGICapp (https://app.magicapp.org/#/guideline/jMMYPj).

METHODS

We followed standards for meta-analysis of observational studies in epidemiology (MOOSE)[19] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[20] and registered our review (PROSPERO Identifier: CRD42018091098).

Eligibility criteria

We included randomized controlled trials (RCTs) and observational studies, including cohort studies and case-control studies, in any language, that explored the impact of adding medical cannabis (i.e. phytocannabinoids, endocannabinoids, or synthetic cannabinoids) on the use of prescription opioids among people living with chronic pain. We defined pain as chronic if patients reported that symptoms had persisted for ≥3 months.[21] We excluded editorials, letters to the editor, pre-clinical studies, conference

abstracts, case reports, case series, cross-sectional studies, and studies with less than 2-weeks follow-up. We also excluded studies of recreational cannabis use as these products typically contain much higher amounts of the psychotropic cannabinoid tetrahydrocannabinol (THC) than would be administered for therapeutic purposes.[22, 23] We classified observational study designs according to recommendations by the Cochrane Observational Studies Methods Group.[24]

Literature search and study selection

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and MEDLINE from inception to March 2020 with no restriction on language of publication. An experienced medical librarian (RC) developed our database-specific search strategies (Appendix 5-1). We also searched the ClinicalTrials.gov registry to identify ongoing trials, and reference lists of all eligible studies and related systematic reviews for additional eligible studies. Two teams of paired reviewers independently screened titles, abstracts and full-text studies for eligibility using online systematic review software (Rayyan QCRI, Qatar Computing Research Institute). Reviewers resolved disagreements through discussion.

Data collection

Using standardized forms and a detailed instruction manual, pairs of reviewers independently abstracted data from each eligible study, including study and patient characteristics, and details of treatment (e.g. dose, formulation, and duration of cannabis add-on therapy). Our primary outcome was opioid dose. We also captured all patient-

important outcomes, as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,[25] including pain relief, sleep disturbance, physical and emotional functioning. Regarding adverse events, we focused on vomiting, nausea, and constipation as a systematic review of values and preferences[26] demonstrated that patients living with chronic pain experience gastrointestinal complaints as the most important opioid-induced adverse events. We contacted authors to obtain unpublished data.

Risk of bias assessment

Following training and calibration exercises two independent reviewers used a modified Cochrane risk of bias tool[27, 28] to assess the risk of bias among eligible RCTs for each outcome according to the following domains: allocation concealment, blinding of participants, study personnel, outcome assessors and data analyst, and loss to follow-up (≥20% missing data was assigned high risk of bias). Response options for each item were 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias). (Appendix 5.2) We used criteria suggested by the CLARITY group [29] to assess the risk of bias of observational studies including selection bias, confidence that all patients had the condition of interest, control for confounding variables, validity of outcome assessment(s), and infrequent missing data (<20%) (details available at www.evidencepartners.com/resources/methodological-resources/). (Appendix 5.4).

Data analysis

We calculated inter-rater agreement regarding the eligibility of full-text studies using an adjusted kappa (κ) statistic.[30] We conducted separate analyses for randomized controlled trials and observational studies. All continuous measures for pain intensity and sleep disturbance were converted to a 10 cm visual analogue scale (VAS); the minimally important difference (MID) for both was 1 cm.[31, 32] All continuous outcomes that were reported by more than one study were pooled to derive the weighted mean difference (WMD) and associated 95% confidence interval (95% CI). We pooled binary outcomes (adverse events) as relative risks (RRs) and risk differences (RDs) and their associated 95% CIs. We conducted all meta-analyses with random-effects models and the DerSimonian-Laird method.[33]

When studies reported effects on continuous outcomes as the median and interquartile range, we derived the mean and SD using the method presented by Wan *et al.* [34] We also converted medians to means using the approach recommended by the Cochrane Handbook as a sensitivity analysis. When authors failed to report a measure of precision associated with mean differences, we imputed the SD from eligible studies that reported these measures (Technical appendix).[35] We included each comparison reported by multi-arm studies and calculated a correction factor to account for the unit of analysis error (i.e. when information from a treatment arm is used more than once in the same meta-analysis).[36] We explored the consistency of association between our pooled results and studies reporting the same outcome domains that were not possible to pool. We used Stata (StataCorp, Release 15.1, College Station, Texas) for all analyses. Comparisons were 2-tailed using a threshold of $p \leq 0.05$.

Subgroup analyses and meta-regression

We examined heterogeneity among pooled RCTs using the I^2 statistic, and through visual inspection of forest plots for pooled observational data, because statistical tests of heterogeneity can be misleading when sample sizes are large and associated confidence intervals are therefore narrow.[37] When we had at least two studies in each subgroup, we explored sources of heterogeneity with five pre-specified subgroup hypotheses, assuming greater benefits with: (1) shorter vs. longer duration of follow-up; (2) higher vs. lower risk of bias; (3) enriched vs non-enriched study design; (4) chronic non-cancer vs. chronic cancer-related pain; and (5) higher vs lower tetrahydrocannabinol [THC] content. We assumed similar directions of subgroup effects for harms, except for study design and THC content in which we expected greater harms with non-enriched trials and higher THC content. However, apart from item two (risk of bias), studies did not report sufficient data to undertake subgroup analyses.

The certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence on an outcome-by-outcome basis as high, moderate, low or very low.[38] With GRADE, RCTs begin as high-certainty evidence, but can be rated down because of risk of bias, imprecision, inconsistency, indirectness, or publication bias. We rated down for imprecision if the 95% CI associated with a pooled continuous outcome included ½ the MID, or if the estimate of precision associated with the RR for binary outcomes included no effect. We considered an I^2 value

between 75% and 100% to represent considerable inconsistency.[39] We rated down the certainty of evidence for indirectness if there were important differences between our research question and the patients enrolled, intervention tested, or outcomes reported among studies contributing to our meta-analyses.[40]

Using GRADE, observational studies begin as low certainty evidence, and while they can be rated down further for the same reasons as RCTs, they can also be rated up in the presence of a large magnitude of the effect, a dose-response gradient, or consideration of plausible confounders or other biases that increase confidence in the estimated effect.[41] We only reported the pooling results of observational studies when they resulted in the same or higher certainty of evidence than evidence from RCTs. When there were at least 10 studies for meta-analysis, we explored for small-study effects by visual assessment of funnel plot asymmetry and Egger's statistical test.[42]

Patients and public involvement

Patients and public were not involved in this research.

RESULTS

Of 5133 records identified, we reviewed 133 articles in full text, and 18 studies reported in 17 publications proved eligible (Figure 5.1); five RCTs in four publications[43-46] and 13 observational studies.[47-59] One study enrolled a mixed group of opioid and non-opioid users;[50] however, our attempts to contact the authors to acquire pain intensity data for the

sub-group of patients prescribed opioids proved unsuccessful. All five RCTs[43-46] and three observational studies[51, 54, 55] enrolled patients with chronic cancer-related pain; the remaining 10 observational studies explored adding cannabis to opioids for patients with chronic non-cancer pain (e.g. chronic low back pain, fibromyalgia, painful chronic pancreatitis),[47, 52, 53, 57-59] or a mix of cancer and non-cancer pain (Table 5.1).[48-50, 56]

Among the 18 included studies, the percentage of female participants was 48% (median of individual trials 48%, interquartile range [IQR] 43% to 58%), and the median of the mean age was 56.3 (IQR 51.2 to 59.9). Follow-up ranged from 2 to 5 weeks among RCTs, and from 4 weeks to 6.4 years for observational studies. Only 1 RCT[43] used an enrichment design (following the open-label phase, patients with at least 15% improvement in pain were randomized to the intervention and control groups) and all RCTs advised patients to maintain stable doses of all other prescribed pain medications, including opioids, during the study period (Table 5.1). All included RCTs, and three of the observational studies[48, 51, 52] administered synthetic cannabis products (i.e. nabilone, dronabinol, and nabiximole), five observational studies[49, 50, 56, 58, 59] reported different combinations of THC: CBD products, and 6 other observational studies[47, 53-55, 57] did not provide details on the type of cannabis or cannabinoids provided (Table 5.1, Appendix 5.5). Ten studies reported receiving industry funding,[43-46, 49, 51, 52, 57, 58] five studies[50, 53-56] reported no-industry funding, and three studies[47, 48, 59] did not report funding information (Table 5.1).

Risk of bias of included studies

All included RCTs reported adequate allocation concealment and blinding of patients and health-care providers; however, three trials[43, 45, 46] were at risk of bias due to high loss to follow up (Appendix 5.6). Each RCT specified that they employed an intention-to-treat analysis. All observational studies were at high risk of bias, typically due to lack of confidence in the assessment of exposure, non-representative samples, and insufficient control for confounding (Appendix 5.7-8).

Outcomes for medical cannabis add-on therapy

Opioid dose reduction

The primary limitation of RCTs was that all investigators instructed patients to not alter their dose of opioids. This represents a very serious indirectness of the findings regarding the research question, warranting rating down two levels, and was the primary reason for very low certainty evidence from the 1176 patients.[43-45] Their results raised the possibility that adding medical cannabis may not be associated with a reduction in opioid use among patients living with chronic cancer pain (WMD -3.4 MME; 95%CI -12.7 to 5.9; Table 5.2; Appendix 5.13). There were no differences in effect based on the loss to follow-up (Appendix 5.14; test of interaction *P*=0.758).

Very-low certainty evidence from 8 observational studies (7 of which enrolled people with chronic non-cancer pain)[47, 48, 50, 51, 53-55, 58] raised the possibility that adding medical cannabis may reduce the use of opioids among patients with predominantly chronic non-cancer pain (WMD -22.5 MME; 95%CI -43.06 to -1.97; Table 5.2; Appendix 5.15). Three observational studies that could not be pooled, as they only reported opioid

reduction as a percentage, also found that providing medical cannabis allowed patients to decrease their opioid dose. The first study assessed the impact of providing medical cannabis to 61 patients with chronic low back pain who were prescribed opioid therapy (median opioid dose was 21 mg MME/day) and reported that 52% of patients (32 of 61) stopped all use of opioids at a median follow-up of 6.4 years.[57] The second study [49] reported that of 94 patients with chronic pain (both cancer and non-cancer pain) who began using CBD hemp extract, 53% were able to decrease their use of prescription opioids at 8 weeks. A third study[56] included 600 patients with chronic pain who indicated willingness to taper their opioid dose and were administered 0.5g daily of medicinal cannabis for each 10% reduction in opioid dose. After 6 months' follow-up, 55% of patients reported a 30% reduction in opioid dose on average and 26% of them discontinued opioid use.

Pain relief

High-certainty evidence from 5 RCTs[43-46] demonstrated that adding medical cannabis to opioid therapy resulted in trivial or no difference in cancer related pain (WMD -0.18 cm; 95%CI -0.38 to 0.02 on the 10 cm VAS for pain; MID 1cm; Table 5.2; Appendix 5.16). Results did not differ depending on loss to follow-up (Appendix 5.17, a test of interaction *P*=0.623). Very low certainty evidence from observational studies suggested a large decrease in pain when medical cannabis was added to opioids (Appendix 5.18).

Sleep disturbance

Five RCTs[43-46] provided high certainty evidence that adding medical cannabis to prescription opioids results in a trivial improvement in sleep disturbance in people living with cancer-related chronic pain (WMD -0.22 cm; 95%CI -0.4 to -0.06 on the 10 cm VAS for sleep disturbance; MID 1cm; Table 5.2; Appendix 5.19). Results did not differ between trials reporting the low and high loss to follow-up (Appendix 5.20, a test of interaction *P* =0.93). Very low certainty evidence from observational studies suggested an improvement in sleep disturbance when medical cannabis was added to opioids (Appendix 5.9).

Other reported outcomes

A single RCT[44] reported moderate certainty evidence that adding cannabis likely has little or no effect on emotional and physical functioning (Appendix 5.10-11).

Adverse events

Nausea, vomiting, or constipation

4 RCTs[43-46] provided moderate certainty evidence that adding medical cannabis to opioid therapy likely increases the incidence of nausea (RR 1.43, 95%CI 1.04 to 1.96; RD 4%, 95%CI 0% to 7%; Appendix 5.21-22) and vomiting (RR 1.50; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%; Appendix 5.23-24) in patients with cancer-related chronic pain prescribed opioid therapy. Three RCTs[43, 45, 46] provided low certainty evidence that adding medical cannabis to opioid therapy may not increase constipation (RR 0.85, 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%; Appendix 5.25-26). Appendix 5.12 summarizes adverse events reported in observational studies.

DISCUSSION

Very-low certainty evidence from randomized trials and observational studies was conflicting and leaves uncertain whether the addition of medical cannabis affects the use of prescribed opioids among people living with chronic pain. Compared with long-term opioid therapy for chronic cancer pain without medical cannabis, high certainty evidence showed that adding medical cannabis had little to no effect on pain or sleep disturbance. Results provided moderate certainty evidence that adding cannabis therapy to opioids likely increases both nausea (RR 1.43, 95%CI 1.04 to 1.96) and vomiting (RR 1.50; 95%CI 1.01 to 2.24), and low certainty evidence suggested no effect on constipation (RR 0.85, 95%CI 0.54 to 1.35).

Strengths of our review include a comprehensive search for eligible randomized and observational studies, appraisal of the risk of bias among individual studies, and use of the GRADE approach to rate the certainty of evidence. Our review has limitations, primarily due to features of primary studies eligible for review, which failed to report all recommended outcomes that have been established as important for people living with chronic pain. Most observational studies incorporated inadequate adjustment for confounding. All randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use. All eligible RCTs enrolled patients with chronic cancer-related pain, and the generalizability to non-cancer chronic pain is uncertain. Specifically, substitution effects of medical cannabis for prescription opioids may also differ between chronic cancer and non-cancer pain; however, lack of variability among studies eligible for our review precluded exploration of this subgroup effect.

Studies included in our review administered different formulations of cannabis and cannabinoid products; however, pooled effects of outcomes reported in RCTs showed no important heterogeneity.

A meta-analysis of pre-clinical studies,[17] a narrative systematic review,[60] and several cross-sectional and case studies have reported an apparent reduction in opioid use with addition of cannabis therapy.[9, 10, 61-65] In a national US population-based survey[66] of 2,774 cannabis users (both medical and non-medical use) 36% of respondents reported substituting cannabis for prescription opioids (discontinued opioid use). In this survey, the 60% of participants who identified as medical cannabis users were much more likely to substitute cannabis for prescription drugs than recreational users (OR 4.59; 95%CI 3.87 to 5.43). Another US survey[67] that included 841 patients prescribed long-term opioid therapy for chronic pain reported that 61% used medical cannabis, and 97% of this subgroup reported coincident reduction of their opioid use. Consistent with these findings, very low certainty evidence from observational studies in our review also suggests that adding medical cannabis allows patients predominantly with chronic non-cancer pain to reduce their use of opioids. Although RCT results do not support reduction in opioid dose by adding medical cannabis for opioids, the evidence is also very low certainty, primarily because investigators instructed patients to maintain their current opioid dose. This is a critical limitation, despite the 2019 NICE guideline having concluded that providing medical cannabis for chronic pain does not reduce opioid use on the basis of these trials.[68] Future trials should randomize chronic pain patients who voluntarily agree to engage in a trial of opioid tapering to receive medical cannabis or

placebo and report all patient-important outcomes.[69] Forced opioid tapering is ineffective[70] and may cause harm.[71]

Conclusion

The opioid-sparing effects of medical cannabis for chronic pain remain uncertain. Based on moderate-to-high certainty evidence, adding medical cannabis to opioid therapy among chronic cancer pain patients had little or no effect on neither pain relief nor sleep disturbance and likely increases the risk of nausea and vomiting. The accompanying BMJ Rapid Recommendation[18] provides contextualized guidance based on this evidence, as well as three other systematic reviews on benefits,[72] harms[73] and patients' values and preferences[74].

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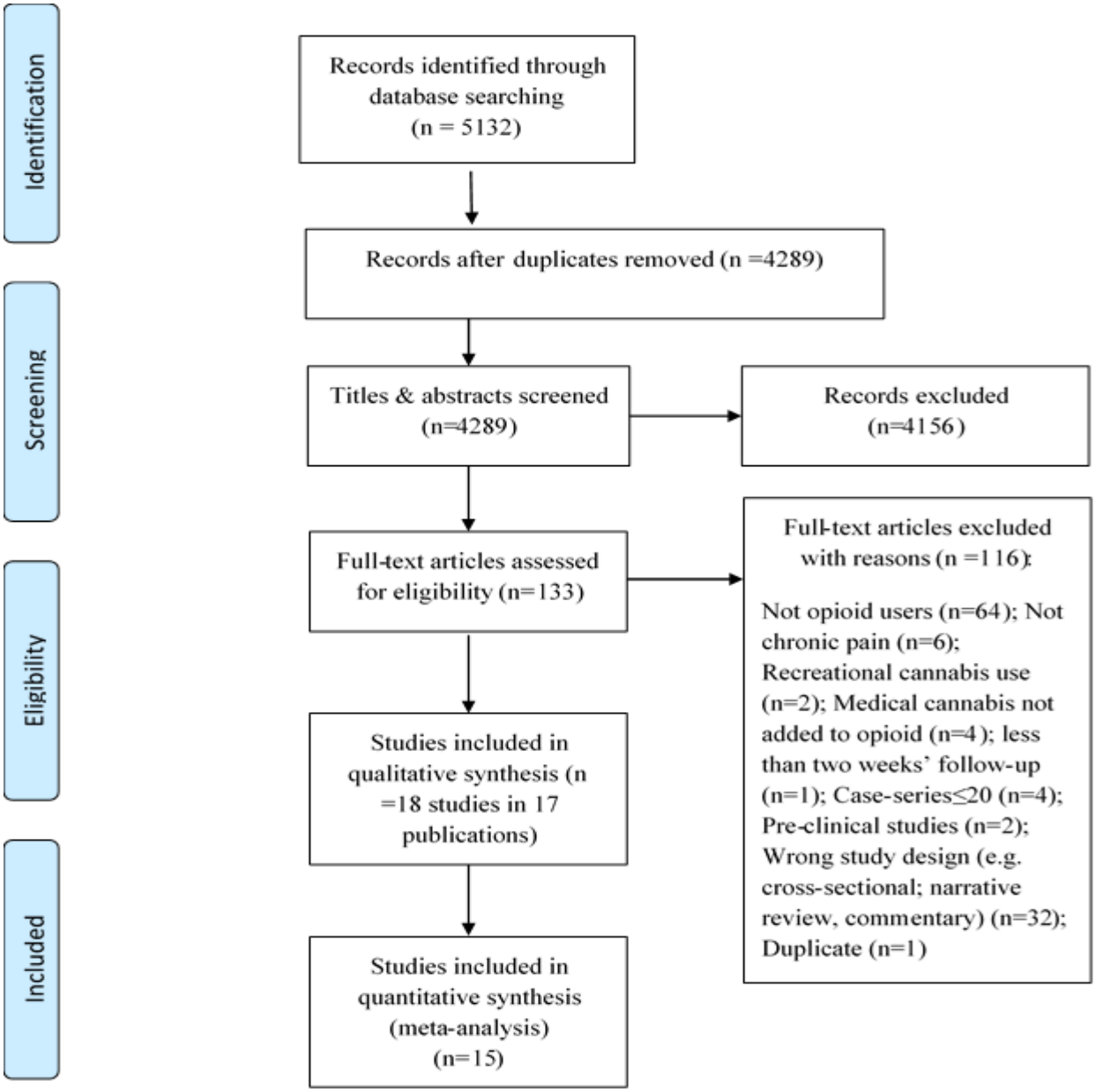

Figure 5. 1: Study selection process in review of opioid-sparing effects of cannabis in chronic pain

Table 5. 1: Characteristics of included studies (n=18)

Author-year (country)	Study design	No. of participants (% prescribed opioids)	Type of chronic pain (specific condition)	Age mean (SD)	% Female	Baseline opioid dose	Follow-up duration	Medical cannabis dose	Analgesic Co-intervention	Funding source
Fallon et al., 2017 study I (multicenter trial£)[1]	Parallel arm RCT	n=399; nabiximols [n=20], placebo [n=199] (100%)	100% chronic cancer pain	59.8 (10.9)	43%	Receiving opioid therapy of <500 MME/day (Nabiximols group: 199MME/day± 131; placebo group: 207MME/day± 135)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Fallon et al., 2017 study II (multicenter trial£)[1]	Parallel arm RCT	n=206; nabiximols [n=103], placebo=103 (100%)	100% chronic cancer pain	61.5 (11.3)	49%	Receiving opioid therapy of <500 MME/day (Nabiximols: 212MME/day± 136; placebo: 209MME/day± 121)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Johnson et al., 2010 (multicenter trial£)[2]	Parallel arm RCT	n=177; THC: CBD extract [n= 60], THC extract [n=58],	100% chronic cancer pain	60.2 (12.3)	46%	Receiving opioid therapy for at least one-week before enrollment	2 weeks	One spray: 2.7mg THC/2.5mg CBD. The maximum permitted dose:	Patients were excluded if they planned to undergo clinical interventions that would affect pain	GW Pharmaceuticals

		placebo [n=59] (100%)				(THC:CBD: 258MME/day± 789; THC: 188MME±234 ; placebo: 367±886)		8 actuations over 3-hours and 48 actuations over 24-hours		
Lichtman et al., 2018 (multicenter£)[3]	Parallel arm RCT	n=398; nabiximol [n=199], placebo [n=198] (100%)	100% chronic cancer pain	60 (11.5)	46%	Receiving opioid therapy of <500 MME/day (nabiximols: 193MME/day± 130; placebo: 186MME/day± 131)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Portenoy et al., 2012 (multicenter£)[4]	Parallel arm RCT	n=360; nabiximols low dose (1-4 sprays/day) [n=91], medium dose (6-10 sprays/day) [n=88], high dose (11-16 sprays/day) [n=90], placebo [n=91] (100%)	100% chronic cancer pain	58 (12.2)	48%	Receiving opioid therapy of <500 MME/day (median was 120MME/day; range 3 to 16,660)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Patients were allowed to use breakthrough opioid analgesic as required	GW Pharmaceuticals; Otsuka Pharmaceutical Co., Ltd.
Barlow et al., 2019 (US)[5]	Retrospective chart-review	Enrolled in MCP [n=34], not enrolled in MCP	100% CNCP (chronic painful	49.9 (10.5)	45%	Not enrolled in MCP 183MME/day± 284; enrolled	Range 4 to 297 weeks	NR	NR	NR

		[n=19] (100%)	pancreatitis)			in MCP 190MME/day± 273				
Bellnier et al., 2018 (US)[6]	One-arm observational study	n= 29 (100%)	90% CNCP; 10% cancer pain	61 (10)	65%	Patients were receiving a median opioid dose of 79.94MME/day	13 weeks	10mg capsules of THC/ CBD in a 1:1 ratio 3-times daily	NR	NR
Capano et al., 2020 (US)[7]	One-arm observational study	n= 131 (100%)	100% chronic pain (cancer and non-cancer)	56.1 (range: 39 to 70)	68%	Receiving at least 50MME/day	8 weeks	30mg CBD/1mg THC	NR	Ananda Professional.
Haroutounian et al., 2016 (Israel)[8]	One-arm observational study	n=73 (35%)	93.2% CNCP; 6.8% chronic cancer pain	51.2 (15.4)[¥]	38%[¥]	Receiving a median opioid dose of 60MME/day (range 45 - 90)	26 weeks	Cigarettes: 6% to 14% THC, 0.2% to 3.8% CBD; Oral: 11% to 19% THC, 0.5% to 5.5% CBD	All participants were encouraged to attempt gradual dose reduction and possible discontinuation of other analgesics	No-external funding
Maida et al., 2008 (Canada)[9]	Prospective cohort	Enrolled in MCP [n=47], not enrolled in MCP [n=65] (100%)	100% chronic cancer pain	69.7 (10.1)	42%	nabilone treated:60MME/day±64; nabilone untreated: 67MME/day±101	4 weeks	On average 1.79 mg twice daily nabilone	Patients were permitted to use concomitant analgesics	Valeant Pharma-ceuticals Canada Ltd
Narang et al., 2008 (US)[10]	One-arm observational study	n=30 (100%)	100% CNCP	Median=43.5	53%	Receiving an average opioid dose of	4 weeks	Flexible dose schedule, dronabinol	NR	Solvay Pharmaceuticals,

				(range=21-67)		68MME/day±57		5mg to 20mg 3 times daily		Inc.
O'Connell et al., 2019 (US)[11]	One-arm observational study	n=77 (100%)	100% CNCP	54.1 (range=26-76)	58%	Receiving a mean opioid dose of 140MME/day±184	26 weeks	NR	NR	No industry funding
Pritchard et al.,2020 (US)[12]	Retrospective cohort	cannabis and opioids co-use [n=22], opioids only [n=61] (100%)	100% chronic cancer pain	53.1 (11.7)	23%	MCP enrolled: 144MME/day±129; MCP not enrolled: 119MME/day ±100	26 weeks	NR	NR	No industry funding
Pawasarat et al., 2020 (US)[13]	Retrospective chart review	Enrolled in MCP [n=137], not enrolled in MCP [n=95] (100%)	100% chronic cancer pain	58 (IQR:14.7)	56%	MCP enrolled: median 45MME/day, IQR=135; MCP not enrolled: median 97.5MME/day, IQR=150	Between 39 and 52 weeks for MCP enrolled; <26 weeks for not enrolled	NR	NR	No industry funding
Rod et al., 2019 (Canada)[14]	One-arm observational study	n=600	100% chronic pain (cancer and non-cancer)	NR	NR	Receiving a mean opioid dose of 120 MME/day (range 90 to 240MME/day)	26 weeks	CBD and THC ranged between 4% to 6%. Doses related directly to the opioid taper.	All participants indicated ready to reduce opioid dose and also received psychological supports (e.g. CBT, mindfulness, relaxation)	No external funding

Takakuwa et al., 2020 (US)[15]	One-arm observational study	n=61 (100%)	100% CNCP (back pain)	50 (11.4)	38%	Receiving a median opioid dose of 21MME/day	Median of 6.4 years among patients who ceased opioids completely	NR	NR	The Society of Cannabis Clinicians
Vigil et al., 2017 (US)[16]	Retrospective chart review	Enrolled in MCP [n=37], not enrolled [n=29] (100%)	100% CNCP (90% back pain)	56.3 (11.8)	36%	Maximum daily dosage of < 200MME/day (enrolled in MCP: mean 24MME/day±23; not enrolled in MCP: mean 16MME/day±14)	52 weeks	NR	NR	University of New Mexico Medical Cannabis Research Fund
Yassin et al., 2019 (Israel)[17]	One-arm observational study	n=31 (100%)	100% CNCP (fibromyalgia)	33.4 (12.3)	90%	Receiving duloxetine 30 mg once daily and Targin (Oxycodone) 5 mg three times/day	26 weeks	THC to CBD ratio was 1:4; 20 g/month for 3 months, increased up to 30 g/month at the end of 6 months	During the study treatment, all other opiates and atypical analgesics were stopped.	NR

*CNCP: Chronic non-cancer pain; MCP: Medical Cannabis Program; MME: milligram morphine equivalent; FU: follow-up; NR: not reported

¥ Based on the whole population including opioid users and non-users
£In Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States

Table 5. 2: GRADE Evidence Profile of medical cannabis or cannabinoids for patients with chronic pain prescribed long-term opioid therapy

# of studies	# of Patients	FU Duration (Weeks)	Risk of bias[a]	Inconsistency (I^2, P-value)[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)	Overall certainty of evidence
Opioid dose: morphine milligram equivalents (MME) per day									
4 RCTs[1-3]	1,176	2 to 5	No serious risk of bias [e]	No serious inconsistency [40%, *P*=0.15]	Very serious indirectness [f]	Serious imprecision [g]	Not detected	WMD -3.4MME (-12.7 to 5.8)	Very Low
8 Observational studies[5, 6, 8, 9, 11-13, 16]	453	4 to 297	Serious risk of bias [h]	Serious inconsistency [visual inspection]	No serious indirectness	No serious imprecision	Not detected	WMD -22.5MME (-43.06 to -1.97)	Very low
Pain: 10 cm VAS for pain; lower is better; the MID = 1 cm									
5 RCTs[1-4]	1,536	2 to 5	No serious risk of bias	No serious inconsistency [28%, *P*=0.20]	No serious indirectness	No serious imprecision	Not detected	WMD -0.18 (-0.38 to 0.02)	High
Sleep disturbance: 10 cm VAS for sleep disturbance; lower is better; the MID= 1 cm									
5 RCTs[1-4]	1,536	2 to 5	No serious risk of bias	No serious inconsistency [0%, *P*=0.45]	No serious indirectness	No serious imprecision	Not detected	WMD -0.22 (-0.39 to -0.06)	High
Nausea									

4 RCTs[1-4]	1330	2 to 5	Serious risk of bias	No serious inconsistency [0%, *P*=0.88]	No serious indirectness	No serious imprecision	Not detected	RR 1.43 (1.04 to 1.96)	Moderate
Vomiting									
4 RCTs[1-4]	1330	2 to 5	Serious risk of bias	No serious inconsistency [0%, *P*=0.50]	No serious indirectness	No serious imprecision	Not detected	RR 1.5 (1.01 to 2.24)	Moderate
Constipation									
3 RCTs[1, 3, 4]	1153	5	Serious risk of bias [i]	No serious inconsistency [0%, *P*=0.92]	No serious indirectness	Serious imprecision [g]	Not detected	RR 0.85 (0.54 to 1.35)	Low

WMD: weighted mean difference; RR: relative risk; 95% CI: 95% confidence interval; VAS: visual analogue scale; MID: minimally important difference; FU: follow-up.

[a] We assessed risk of bias using a modified Cochrane risk of bias instrument.

[b] Inconsistency refers to unexplained heterogeneity of results. For RCTs an I^2 of 75-100% indicates that heterogeneity may be considerable. We assessed heterogeneity of pooled observational studies through visual inspection of forest plots.

[c] Indirectness results if the intervention, control, patients or outcomes are different from the research question under investigation.

[d] Serious imprecision refers to situations in which the confidence interval includes both benefit and harm (the 95%CI includes 1 MID).

[e] Some of the included RCTs were at high risk of bias, due to loss to follow-up (>20%); however, we did not rate down for risk of bias as subgroup analysis showed no difference in treatment effect between trials at high and low risk of bias for missing outcome data (test of interaction p= 0.758 and p=0.623 for opioid dose reduction and pain respectively).

[f] Downgraded twice due to indirectness since all trials instructed participants to maintain their opioid dose during the study period.
[g] The 95%CI around the WMD includes no effect.
[h] Studies are based on non-representative samples.
[i] Most RCTs were at high risk of bias due to loss to follow-up (>20%).

Appendix 5. 1: Literature Search Strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.

The search terminology included all types of chronic pain AND any kinds of cannabinoids:

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 exp Analgesics, Opioid/ (111496)

2 opioid*.mp. (112576)

3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol
supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (150565)

4 or/1-3 (207118)

5 exp Narcotics/ (119511)

6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or

isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine
or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum
or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10373)

7 or/1-6 (213683)

Annotation: opioid block

8 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (52087)

9 Cannabis/ (8573)

10 exp CANNABINOIDS/ (13258)

11 8 or 9 or 10 (52087)

Annotation: cannabis block

12 7 and 11 (6089)

Annotation: opioid and cannabis

13 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading

word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (65717)

14 Chronic Pain/ (12620)

15 exp Osteoarthritis/ (59676)

16 osteoarthrit*.mp. (84419)

17 osteo-arthritis.mp. (375)

18 exp Arthritis, Rheumatoid/ (109607)

19 exp Neuralgia/ (19415)

20 Diabetic Neuropathies/ (14247)

21 (neuropath* adj5 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23043)

22 neuralg*.mp. (26154)

23 zoster.mp. (20386)

24 Irritable Bowel Syndrome/ (6748)

25 IBS.mp. (8435)

26 Migraine Disorders/ (24388)

27 migraine.mp. (37040)

28 Fibromyalgia/ (8088)

29 fibromyalg*.mp. (11178)

30 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5426)

31 Pain, Intractable/ (6126)

32 Phantom Limb/ (1816)

33 Hyperalgesia/ (11136)

34 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (37369)

35 radiculopathy.mp. (8722)

36 musculoskeletal pain/ or headache/ (29687)

37 exp Headache Disorders/ (33178)

38 headache*.mp. (89612)

39 exp Temporomandibular Joint Disorders/ (16711)

40 whiplash.mp. or exp whiplash injury/ (3896)

41 exp Cumulative Trauma Disorders/ (13326)

42 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (14079)

43 Pain Measurement/de [Drug Effects] (6594)

44 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (43072)

45 ((noncancer* or non-cancer* or back or discogen* or chronic* or recurrent or persist* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or non-malign* or shoulder* or knee* or hip or hips) adj3 pain).mp. (206944)

46 exp Pain/ (379991)

47 pain*.mp. (745044)

48 or/13-47 (1122771)

49 12 and 48 (1034)

Database: Embase <1974 to 2019 September 04>

Search Strategy:

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1 exp narcotic analgesic agent/ (317763)

2 (opioid* or opiate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (188237)

3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or

dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (278150)

4 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine
or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum
or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (50642)

5 or/1-4 (403926)

6 exp cannabis/ (32390)

7 cannabinoid/ or cannabidiol/ or cannabinoid derivative/ or cannabinol/ or cannabinol derivative/ or cannabis derivative/ or delta8 tetrahydrocannabinol/ or delta8 tetrahydrocannabinol derivative/ or "delta9(11) tetrahydrocannabinol"/ or dronabinol/ or medical cannabis/ or nabiximols/ or tetrahydrocannabinol/ or tetrahydrocannabinol derivative/ or tetrahydrocannabinolic acid/ (26180)

8 (Cannabis or cannabinol or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or

tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (69860)

9 6 or 7 or 8 (75281)

10 5 and 9 (16412)

11 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (109897)

12 chronic pain/ (57642)

13 exp osteoarthritis/ (122475)

14 osteoarthrit*.mp. (136019)

15 osteo-arthritis.mp. (424)

16 degenerative arthrit*.mp. (1563)

17 exp rheumatoid arthritis/ (194747)

18 exp neuralgia/ (99958)

19 diabetic neuropathy/ (22699)

20 (neuropath* adj5 (pain* or diabet*)).mp. (71799)

21 neuralg*.mp. (29200)

22 zoster.mp. (36684)

23 irritable colon/ (24792)

24 (Irritable Bowel Syndrome or IBS).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (24025)

25 exp migraine/ (60235)

26 migraine.mp. (66593)

27 fibromyalgia/ (19402)

28 fibromyalg*.mp. (20958)

29 reflex sympathetic dystrophy.mp. (2356)

30 (complex regional pain syndromes or causalgia).mp. (1275)

31 intractable pain/ (4701)

32 phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (7388)

33 hyperalgesia/ (18711)

34 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (27031)

35 exp backache/ (104042)

36 radiculopathy.mp. or exp radiculopathy/ (37176)

37 musculoskeletal pain/ (10292)

38 exp arthralgia/ (58208)

39 headache/ (204055)

40 headache*.mp. (264831)

41 temporomandibular joint disorder/ (13308)

42 ((TMJ or TMJD) and pain*).mp. (3648)

43 whiplash.mp. or whiplash injury/ (4815)

44 exp cumulative trauma disorder/ (20089)

45 exp pain/ (1249315)

46 pain*.mp. (1280762)

47 or/11-46 (1963522)

48 10 and 47 (3115)

Search Name: cannabis pain

Date Run: 05/09/2019 16:12:03

Comment:

ID	Search Hits	
#1	MeSH descriptor: [Cannabis] explode all trees	293
#2	MeSH descriptor: [Cannabinoids] explode all trees	743

#3 MeSH descriptor: [Endocannabinoids] explode all trees 46

#4 MeSH descriptor: [Endocannabinoids] explode all trees 46

#5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 4215

#6 #1 or #2 or #3 or #4 or #5 4215

#7 MeSH descriptor: [Pain] explode all trees 45094

#8 (pain*):ti,ab,kw (Word variations have been searched) 164064

#9 #7 or #8 169846

#10 #6 and #9 578

#11 [mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"] or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex regional pain syndromes"] or [mh causalgia] or [mh ^"reflex sympathetic dystrophy"] or [mh ^"pain Intractable"] or [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain Measurement"/DE] 28499

#12 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyni* or ischialgi* or crps or rachialgi*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*) 104465

#13 (irrita* or inflam*) near/4 (bowel or colon) 7249

#14 #11 or #12 or #13 113256

#15 #6 and #14 in Trials 353

Characteristics of eligible studies and Risk of Bias Assessment

Appendix 5. 2: Detailed guidance for risk of bias assessment RCTs

Domain	*Judgment*
Random allocation concealment	**Definitely yes (low risk):** used central allocations (e.g. computer, telephone) **Probably yes (low risk):** sequentially numbered, opaque, sealed envelopes; studies did not provide enough information about concealment approach; however, it was placebo-control trial with double blinded design. **Probably no (high risk):** not enough information was provided and study was not blinded. **Definitely no (high risk):** used any unconcealed approach of allocation (e.g. case record number, day of week, health-care decision).
Blinding of patients	**Definitely yes (low risk):** explicitly mentioned that patients were blinded **Probably yes (low risk):** a placebo-controlled double-blinded trial. **Probably no (high risk):** no explicit statement about blinding status and not double-blinded placebo-controlled trial. **Definitely no (high risk):** explicitly mentioned that patients were not blinded.
Blinding of health care providers	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of data collector	**Definitely yes (low risk):** explicitly mentioned that this group was blinded.

	Probably yes (low risk): mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of outcome assessor	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Blinding data analyst	**Definitely yes (low risk):** explicitly mentioned that this group were blinded **Probably yes (low risk):** **Probably no (high risk):** no explicit statement about blinding and only mentioned double-blinded. **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Loss to follow-up	**Definitely yes:** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome, or missing outcome data were balanced across groups. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. **Definitely no (high risk):** the retention rate was less than 80%.
Sample size	We also considered the sample size lower than 300 for continuous as high risk of bias and rated down on the basis of imprecision in GRADE assessment.

Appendix 5. 3: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with control group

Domain	***Judgment***
Did the study match participants for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? *(This item queries how confident we are that the reported association or lack thereof is not due to confounding).*	**Definitely yes (low risk):** studies that adjusted based on all important covariates including age, sex, baseline pain, baseline opioid dose, and other disabilities. **Probably yes (low risk):** studies that adjusted at a minimum for baseline pain and baseline opioid dose. **Probably no (high risk):** studies that did not provide any details about analysis method. **Definitely no (high risk):** Studies that did not adjust based on baseline opioid dose or baseline pain.
Was selection of exposed and non-exposed cohorts drawn from the same population? *(this item queries whether participants who co-used cannabis and opioids or used opioids alone were drawn from the same population)*	**Definitely yes (low risk):** Studies in which selection for participation is not dependent on exposure status (cannabis and opioid co-use). **Probably yes (low risk):** studies that did not provide enough information about recruitment to judge whether recruitment into the study was dependent on exposure status or not. **Probably no (high risk): NA** **Definitely no (high risk):** studies that compared cannabis and opioid co-users and non-users from different cohort.
Can we be confident in the assessment of exposure? *(this item queries how confident we are about the quantification of cannabis and opioids co-use).*	**Definitely yes (low risk):** if study reported some ascertainment methods for cannabis use (e.g. urine analysis), or study prescribed the specific dose of medical cannabis to the participants. **Probably yes (low risk):** self-report of cannabis use.

	Probably no (high risk): when study did not provide any details about assessing exposure status. **Definitely no (high risk):** participants self-reported cannabis usage only at baseline, or exposure status not assessed during the 4-weeks follow-up at least one time, or level of cannabis usage was not similar among participants. For example, some studies allowed patients to select the type or dose of cannabis themselves.
Can we be confident in the assessment of the presence or absence of prognostic factors?	**Definitely yes (low risk):** when patients self-reported the prognostic factors. **Probably yes (low risk):** when the method of assessment was not reported, it was considered as probably yes. *Note that for this item, we are only concerned with the measurement of the prognostic factors that mentioned in item number 1 as minimum adjusted variables (baseline pain intensity and opioid dose).
Were co-interventions similar between groups? *(this item queries how similar are the use of other pain killers (e.g. NSAIDs) between cannabis users and non-users.*	**Definitely yes (low risk):** study reported that co-intervention other than study intervention were limited during the study period. **Probably yes (low risk):** when co-intervention usage was approximately balanced between both intervention and control groups. **Probably no (high risk):** when study did not provide enough information about other drugs that participants may use. **Definitely no (high risk):** when participants were allowed to use all other co-interventions that

	could affect the outcome of the study.
Was the follow up of cohorts adequate? *(This item queries the risk of bias associated with loss to follow-up and missing outcome data).*	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance, if patients were required to come to clinic for outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.
Can we be confident in the assessment of outcome? *(This item queries our confidence in the accuracy of the measurement of the outcome).*	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** study used non-validated/reliable instrument.

Appendix 5. 4: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with no control group

Domain	*Judgment*
Is the source population (sampling frame) representative of the general population?	**Definitely yes (low risk):** participants were selected from a representative sample (e.g. national population registry) **Probably yes (low risk):** single community center, however the center was the only referral center that provided cannabis legally to participants. **Probably no (high risk):** based on the provided information source population could not be defined. **Definitely no (high risk):** sampling from one center or clinic or hospital or patients selected through using convenience sampling.
Is the assessment of the outcome accurate both at baseline and at follow-up?	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** used of different instruments at different follow-up intervals with concern of accuracy of responses, or used invalidated/reliable instruments.
Is there little missing data?	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance,

	if patients were required to come to clinic for outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.

Appendix 5. 5: Characteristics of Eligible studies

Barlowe et al-2019

Study design	*Retrospective chart review.*
Participants	34 chronic painful pancreatitis patients with chronic use of opioids enrolled in a state therapeutic cannabis program were compared to 19 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	Cohort of patients who enrolled into the program had received cannabis therapy with a range from 34 to 297 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Bellnier et al-2018

Study design	One-arm observational study (before/after).
Participants	29 patients with chronic pain who used opioids enrolled in a state therapeutic cannabis program.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	13 weeks
Funding source	Not reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain Quality Assessment Scale (PQAS) paroxysmal domain

Capano et al-2020

Study design	One-arm observational study (before/after).

Participants	131 patients with chronic pain who used opioids enrolled in a pain clinic cannabis therapy.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	8 weeks
Funding source	Industry fund reported.
Outcome	- Reduction of opioid use (reported as percentage of patients who reduced their opioid use after 8 weeks). - Pain disability index - Pittsburgh Sleep Quality Index - Pain intensity and interference index (PEG)

Haroutounian et al-2016

Study design	*One-arm observational study (before/after).*
Participants	Chronic non-cancer pain (14 individuals had pain due to cancer) with a duration of 3 months or longer, and a lack of satisfactory analgesic response or intolerable adverse effects with at least 2 analgesics from 2 different drug classes at full dose (Opioid user: N=73; 35%).
Intervention (comparison)	The initial recommended medical cannabis dose was 20 g/mo added to opioids, which could be obtained as smoked cannabis, baked cookies or oil taking from cannabis dispensary centers. Cannabis could be titrated up to 3 times a day until satisfactory pain relief was gained (before using cannabis).
Follow-up	26 weeks.
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily intravenous [IV] morphine equivalence dosages among opioid users).

Maida et al-2008

Study design	*Prospective cohort study.*
Participants	47 patients with chronic cancer pain who were opioid user and treated with nabilone were compared to 65 non-treated patients.
Intervention (comparison)	nabilone added to opioids (no nabilone).
Follow-up	4 weeks.
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily morphine equivalence dosages); -Pain reduction (Edmonton Symptom Assessment System 0: no pain-10: most severe pain);

	-anxiety, nausea, depression.

Narange et al-2008

Study design	*Phase II: One-arm observational study (before/after).*
Participants	30 patients with chronic non-cancer pain who were taking opioids for a long time.
Intervention (comparison)	The starting dose was 5mg of dronabinol twice daily and titrated up to 20 mg 3 times a day added to opioids (before using dronabinol).
Follow-up	4 weeks
Funding source	Industry funding reported.
Outcome	-Pain reduction (VAS 0: no pain-10: most severe pain); -pain interfere with sleep (Brief pain inventory) -sleep disturbance -adverse events including anxiety, dizziness, and inability to concentrate.

O'Connell et al-2019

Study design	*One-arm observational study (before/after).*
Participants	77 mixed type of chronic non-cancer pain patients who used opioids (96%) or benzodiazepines.
Intervention (comparison)	Medical cannabis including THC, CBD products added to opioid (before using cannabis)
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages among opioid users). -pain reduction (VAS 0: no pain-10: most severe pain).

Pritchard-2019

Study design	*Retrospective chart review.*
Participants	22 patients who had chronic cancer-related pain and used opioids with the presence of THC in their urine drug screening were compared to 61 patients with opioid use only.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	26 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Pawasarat-2020

Study design	*Retrospective chart review.*
Participants	137 chronic cancer-related pain patients with chronic use of opioids enrolled in a State of New Jersey Medicinal Marijuana Program Registry were compared to 95 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).

Follow-up	Between 36 and 52 weeks for enrolled patients and 24 weeks for non-enrolled patients.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain).

Rod-2019

Study design	*One-arm observational study (before/after).*
Participants	600 of chronic pain patients who used opioids and indicated they were prepared to reduce their opioid dose.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	- Reduction or cease of opioid use (reported as percentage of patients who ceased or reduced their opioid use after 6 months).

Takakuwa et al-2020

Study design	*One-arm observational study (before/after).*
Participants	61 of chronic non-cancer pain patients (low-back pain) who used opioids.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	Median of 6.4 years among patients who ceased opioids completely
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily morphine equivalence dosages among chronic and intermittent opioid users).

Vigil et al-2017

Study design	*Retrospective chart review.*
Participants	37 habitual opioid using, severe CNCP patients enrolled in the Medical Cannabis Program were compared to 29 non-enrolled patients.
Intervention (comparison)	Medical cannabis added to opioids (no cannabis).
Follow-up	52 weeks
Funding source	No industry funding reported.
Outcome	-Cessation of opioid (defined as the absence of opioid prescriptions activity during the last three months of observation) -Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages); -Pain reduction only among cannabis users (VAS 0: no pain-10: most severe pain); -Quality of life (no effect; good benefit; great benefit; negative effect; and extremely negative effect of co-prescription of cannabis on quality of life).

Yassin et al-2019

Study design	*One-arm observational study (before/after).*
Participants	31 patients with fibromyalgia were treated for at least 12 months with 5 mg of oxycodone hydrochloride equivalent to 4.5 mg oxycodone and 2.5 mg naloxone hydrochloride twice a day and duloxetine 30 mg once a day.
Intervention (comparison)	20 grams of smoked medical cannabis added to opioids (before cannabis inhalation).
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	-Pain reduction (VAS 0: no pain-10: most severe pain) -Change in pain medication use in 5 categories: 1) increased doses, 2) stable dose through medical cannabis therapy duration, 3) less than half reduction in medication consumption, 4) more than half reduction in analgesic consumption, 5) deceased analgesic consumption. - Owestry Disability Index reduction (scale 0: no disability, 100: total disability)

Johnson et al-2010

Study design	*Parallel, multi-center randomized double-blinded, placebo-controlled trial.*
Participants	177 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	tetrahydrocannabinol: cannabidiol (THC:CBD) extract added to opioids (placebo)
Follow-up	2 weeks
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Physical, emotional, role, and social functioning (QLQ-C30) -Nausea, vomiting, constipation.

Portenoy et al-2012

Study design	*Parallel, randomized double-blinded, placebo-controlled trial.*
Participants	360 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Nabiximols at a low dose (1–4 sprays/day), medium dose (6–10 sprays/day), or high dose (11–16 sprays/day) added to opioids-(placebo)
Follow-up	5 weeks

Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) - Nausea, vomiting, constipation.

Fallon et al-2017-Study 1

Study design	*Parallel, multi-center randomized double-blinded, placebo-controlled trial.*
Participants	399 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL) added to opioids (placebo)
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) - Nausea, vomiting, constipation.

Fallon et al-2017-Study 2

Study design	*Parallel, multi-center randomized double-blinded, placebo-controlled trial.*
Participants	206 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL)) added to opioids (placebo)-patients who tolerated titrated dose of cannabis and showed an improvement of at least 15% on pain NRS score randomized into this study (randomized withdrawal design).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance)

Lichtman et al-2017

Study design	*Parallel, multi-center randomized double-blinded, placebo-controlled trial.*
Participants	397 patients with chronic cancer pain who were under treatment by opioid regimen.

Intervention (comparison)	Nabiximols was added to opioids and was titrated the maximum allowed daily dosage of 10 sprays per day (placebo).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (NRS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance)

Appendix 5. 6: Risk of bias assessment for RCTs

Study (author-year)	Allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of Data analyst	Loss to follow-up (≤20%)
Johnson et al-2010	PYes	PYes	PYes	PYes	PYes	PNo	Plow-risk[€]
Portenoy et al-2012	DYes	DYes	PYes	PYes	PYes	PNo	Dhigh-risk[£]
Fallon et al-2017 Study 1	PYes	PYes	PYes	PYes	PYes	PNo	Dhigh-risk[¥]
Fallon et al-2017 Study 2	PYes	PYes	PYes	PYes	PYes	PNo	Plow-risk[€]
Lichtman et al-2017	PYes	PYes	PYes	PYes	PYes	PNo	Dhigh-risk[¥]

***** DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.
[£] The rate of loss to follow-up was more than 27%.
[¥]The rate of loss to follow-up was approximately 26%.
[€]The rate of loss to follow-up was approximately less than 20%

All RCTs used intention-to-treat (ITT) analysis, which included all randomized patients who had at least one post-randomization efficacy endpoint into the analysis.

Appendix 5. 7: Risk of bias assessments for chart reviews with control group

Study	Were the exposed and unexposed drawn from same population?	Are we confident in the assessment of exposure?	Can we be confident in the assessment of the presence or absence of prognostic factors?	Can we be confident in the outcome assessment?	Was there adequate follow-up?	Were the co-interventions similar?	Did the authors adjust for different confounders?	Overall risk of bias
Vigil 2017	DYes	DNo	PYes	PNo	PYes	PNo	PYes	High
Maida 2008	DYes	DYes	PYes	DYes	PNo	PNo	PYes	High
Barlowe 2019	DYes	DNo	PYes	DYes	PNo	PNo	PNo	High
Pritchard-2020	DYes	DYes	PYes	DYes	DNo	PNo	PNo	High
Pawasarat-2020	DYes	DNo	PYes	DYes	DYes	PNo	PNo	High

***** DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.

Appendix 5. 8: Risk of bias assessments for one-arm studies with no control group

Study	Is the source population (sampling frame) representative of the general population?	Is the assessment of the outcome accurate both at baseline and at follow-up?	Is there little missing data?	Overall risk of bias
Haroutounian et al-2016	DNo	DYes	PNo	High
Narang et al-2008	DNo	DYes	PYes	High
Yassin et al-2019	DNo	DYes	PYes	High
O'Connell et al-2019	DNo	DYes	PYes	High
Takakuwa et al-2020	DNo	DYes	PYes	High
Vigil et al-2017	DNo	PNo	PYes	High
Bellnier-2018	DNo	DYes	DYes	High
Capano et al-2020	DNo	DYes	PNo	High
Rod-2019	DNo	PNo	PNo	High

***** DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.

Appendix 5. 9: Other reported outcomes in observational studies

Sleep disturbance results from two observational studies

Capano et[1] al assessed the effect of adding CBD among patients with chronic pain who were opioid users for at least 1 year.	The mean of Pittsburgh Sleep Quality Index* decreased from 12.09±4.1 at baseline to 10.3±4.3 at the end of week 8.	Very-low certainty evidence; p value=0.03
Narang et al[2] also evaluated the impact of adding dronabinol among 30 patients taking opioids for chronic pain.	The sleep disturbance decreased significantly at the end of week 4.	Very low certainty evidence; p-value <0.01

*Ranges between 0 to 21 with the higher total score (referred to as global score) indicating worse **sleep quality**.

Other reported outcomes in one observational study

Capano et[1] al reported that pain disability index[1] did not show a significant reduction, from 38.02±15.2 at baseline to 34.1±12.4 at week 4 (P-value=0.09)
Pain intensity and inference index[2] reduced from 6.5±1.9 to 5.7±2 after 8 weeks' follow up (P-value=0.006)

[1]Ranges from 0 to 70 (The higher the index the greater the person's disability due to pain).

[2]PEG ranges from 0 to 10 (The higher the worse pain and interference).

Appendix 5. 10: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for physical function among patients with chronic pain from 1 RCT (Johnson et al-2010)

Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Physical functioning	Cannabis=118, placebo=59 (1 RCT)	Two weeks	THC: CBD vs. placebo: -4.23 (P=0.108) THC vs. placebo: -1.25 (P=0.631)	Moderate [b]	Adding cannabis to opioids probably does not improve physical functioning.

[a] In favor of placebo; [b] Due to imprecision.

Appendix 5. 11: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for emotional function among patients with chronic pain from 1 RCT (Johnson et al-2010)

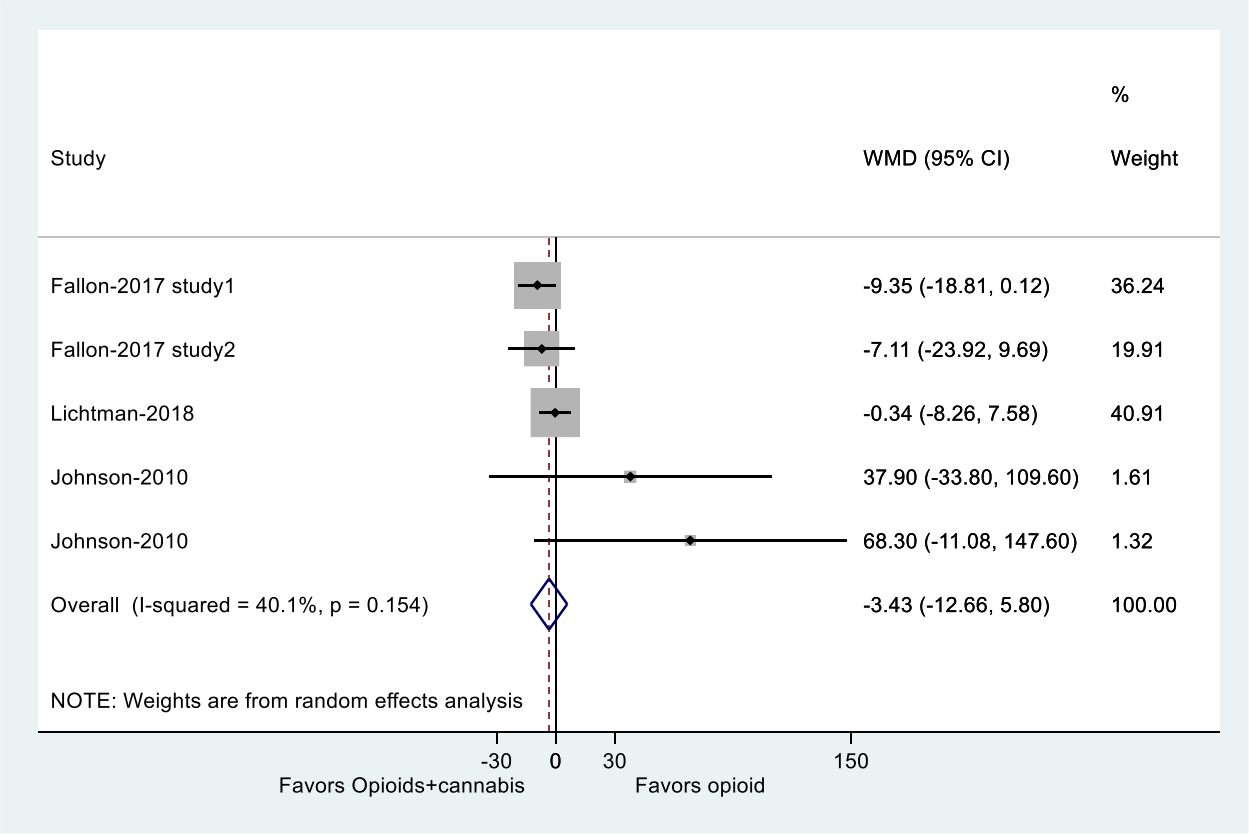
Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Emotional functioning	Cannabis=118, placebo=59 (1 RCT)	Two weeks	THC: CBD vs. placebo: 6.73 (P=0.084) THC vs. placebo: 5.22 (P=0.174)	Moderate[b]	Adding cannabis to opioids probably does not improve emotional functioning.

[a] In favor of cannabis; [b] Due to imprecision.

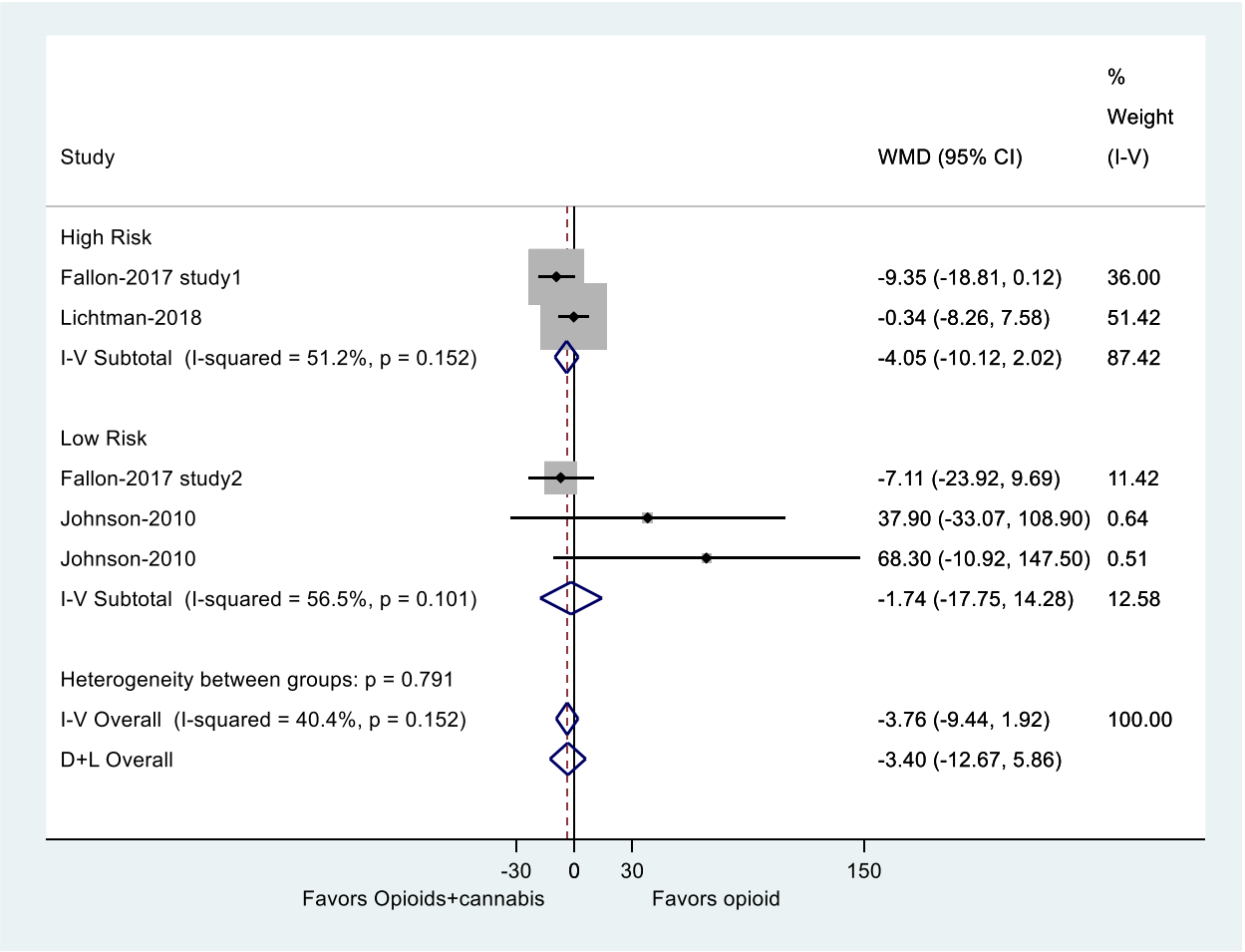
Appendix 5. 12: Summary of adverse events among included observational studies*

Study	Method of assessment	Adverse events reported
Haroutounian et al	Self-reported.	Two participants discontinued treatment due to serious side effects.
Maida et al	Self-reported	Anxiety (P=0.028), nausea (P<0.001), and distress (P=0.021) were decreased significantly among patients who used nabilone in comparison to patients who did not use it.
Narang et al	Self-reported (29-item symptom Side Effect Checklist).	Phase II: Dry mouth, tiredness (both P<0.0001), abnormal thinking, anxiety, facial flushing, eye irritation, headache, and ringing in the ears, and drowsiness (P< 0.05) showed a significantly higher occurrence at the 20 mg dronabinol dose compared with placebo. -Dry mouth, difficulty speaking, forgetfulness, confusion, dizziness, and euphoria were more occurred in both treatment group versus placebo (P= 0.01)
Vigil et al	Self-reported.	No respondents reported any serious side effects from cannabis use (only 9% of patients reported cannabis affected negatively their concentration).
Yassin et al	Self-reported	Mostly mild adverse events were reported (e.g. red eye, sore throat, increase appetite); only 6 patients out of withdrew due to the side effects in non-cannabis group.

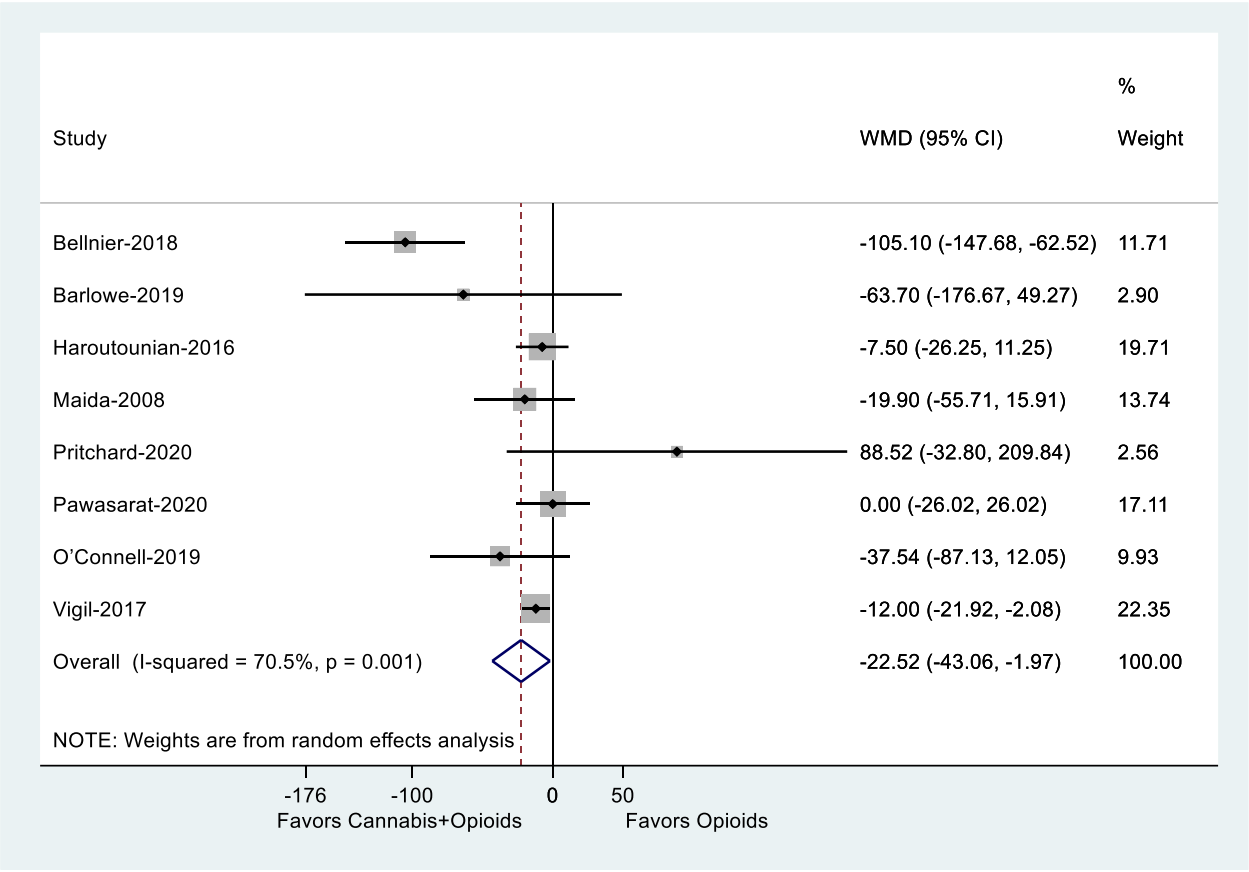
*O'Connell et al, Barlowe et al, Rod 2019, and Takakuwa et al did not report adverse events.



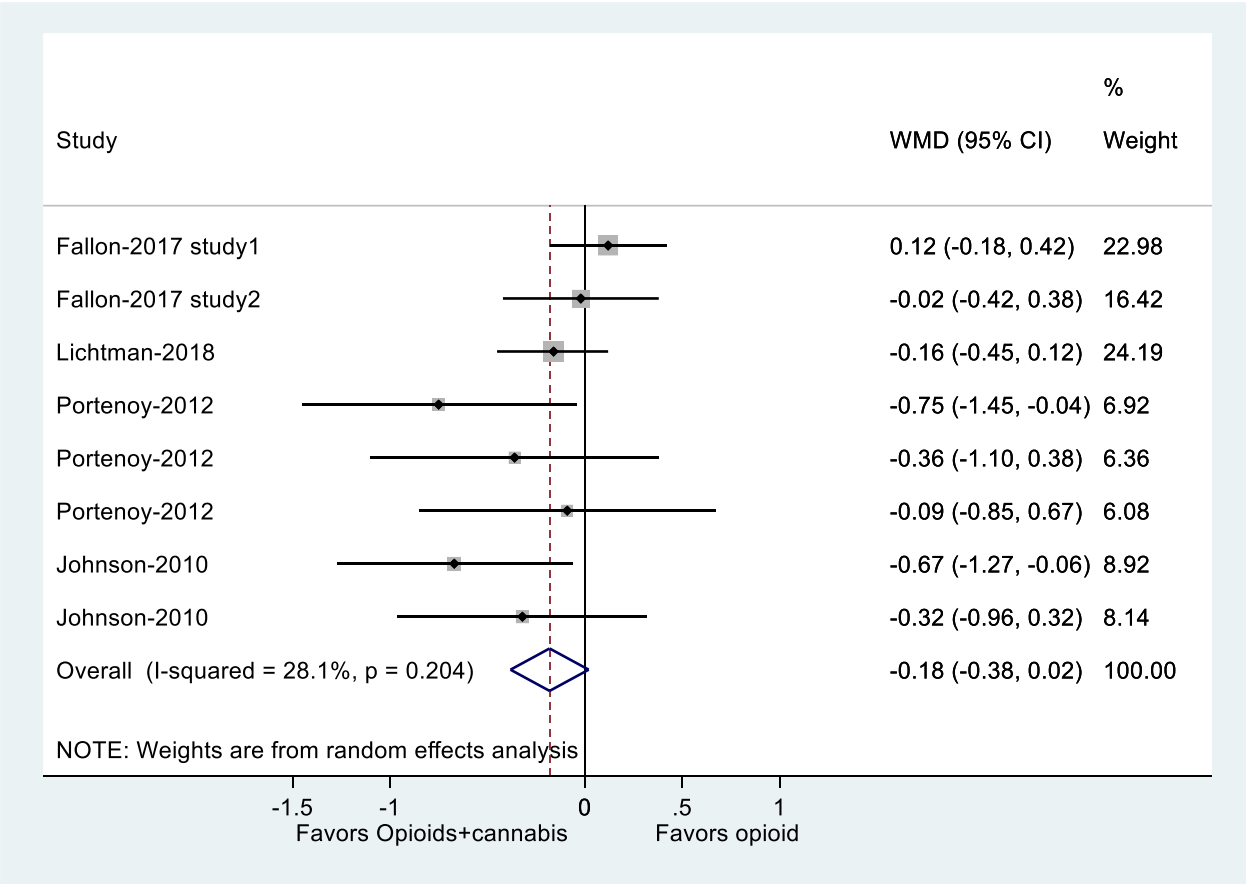
Appendix 5. 13: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



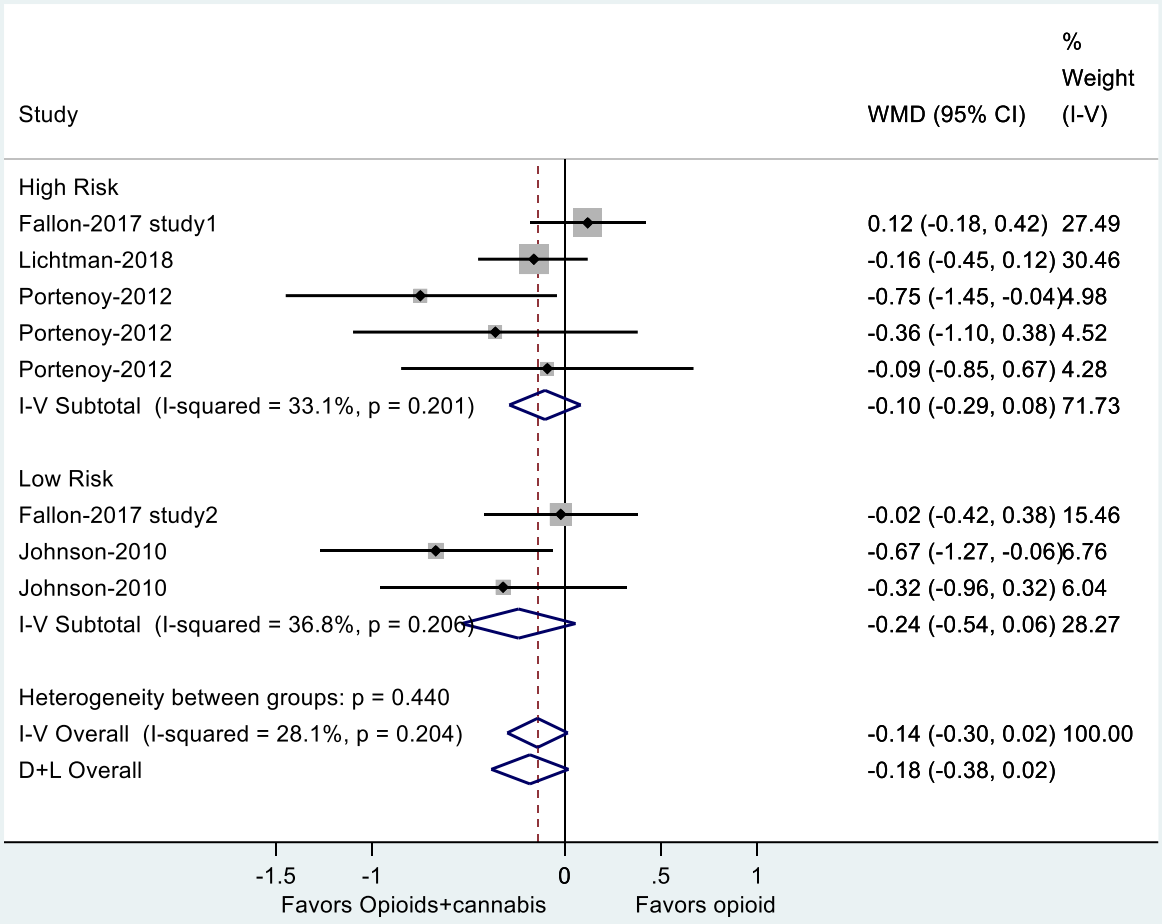
Appendix 5. 14: Subgroup analysis for opioid dose reduction and risk of bias (high risk vs. low risk) from 4 RCTs of Cannabis+opioids vs. placebo



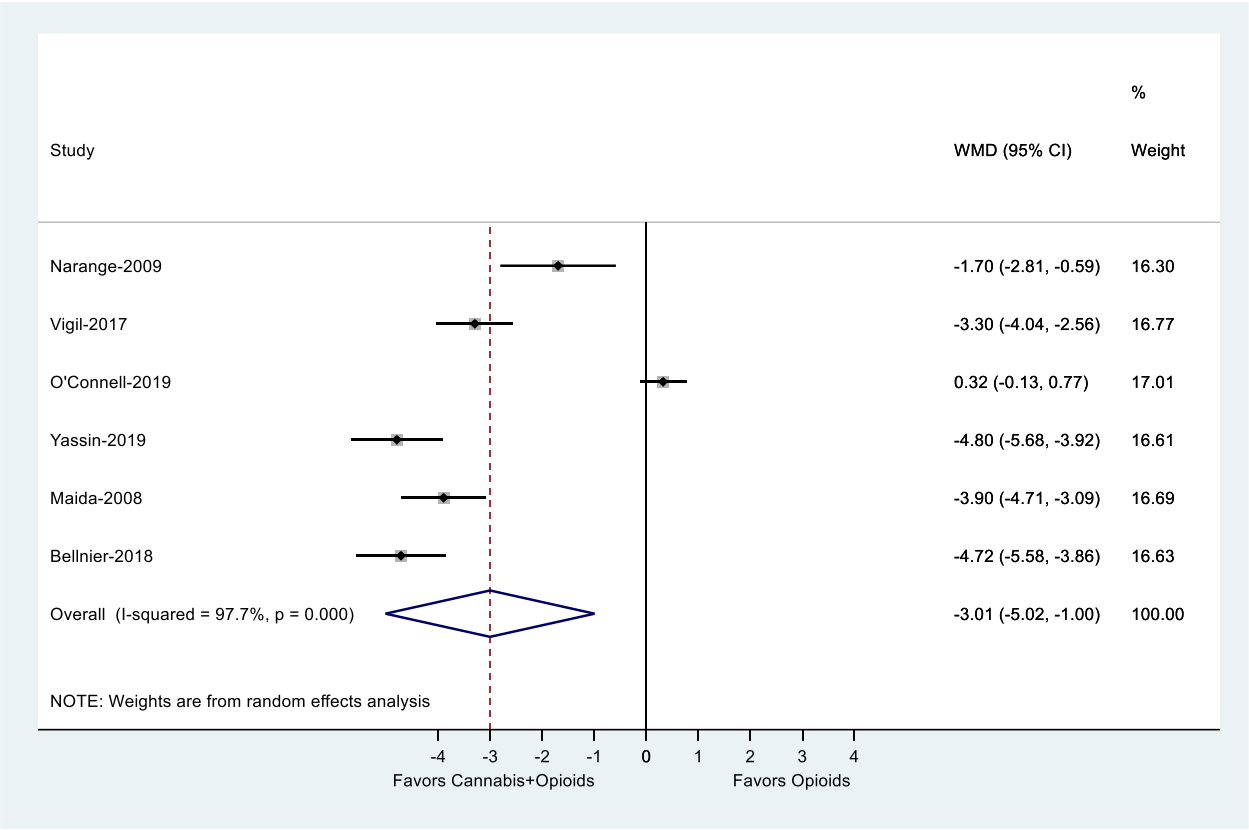
Appendix 5. 15: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies



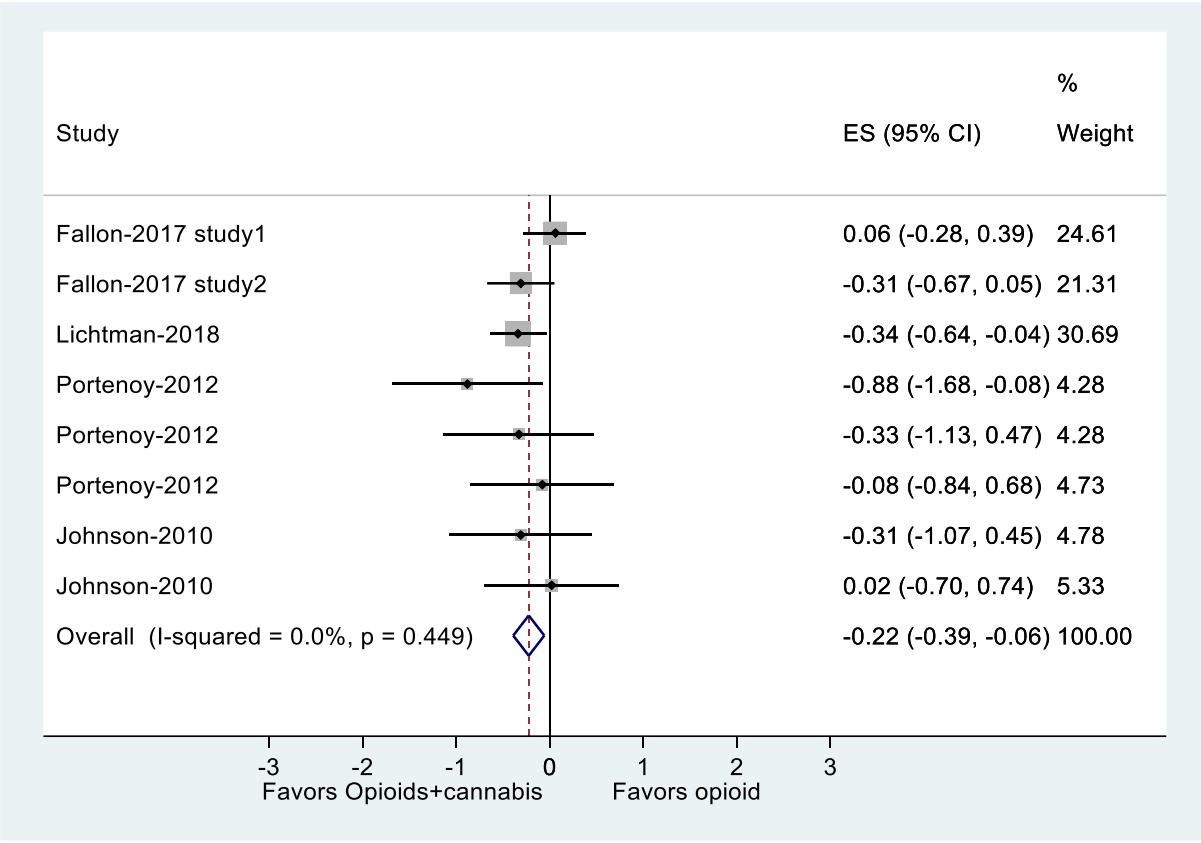
Appendix 5. 16: forest plot for pain relief on a 10-cm Visual Analog Scale (VAS) among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



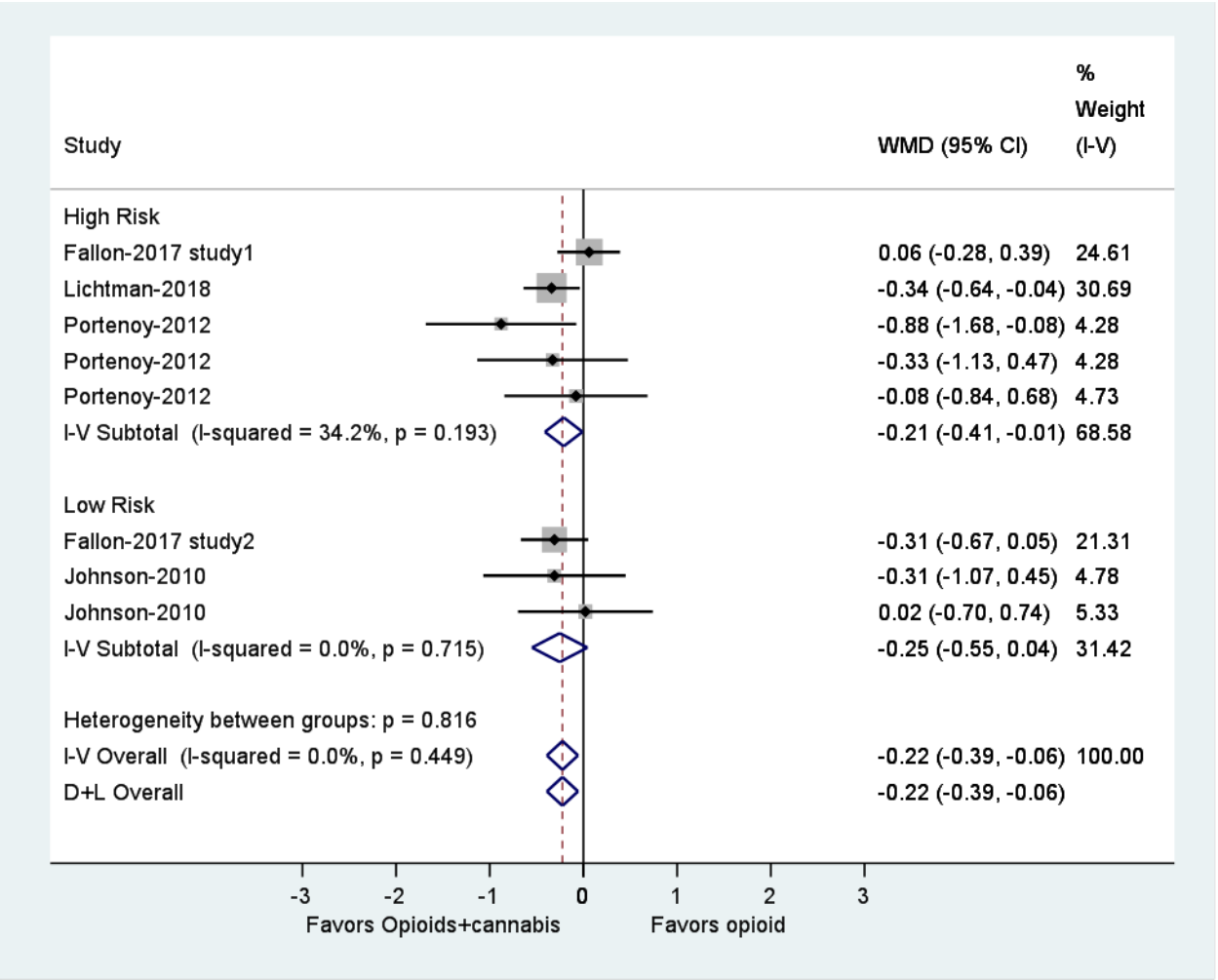
Appendix 5. 17: Subgroup analysis for pain relief on a 10-cm VAS and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



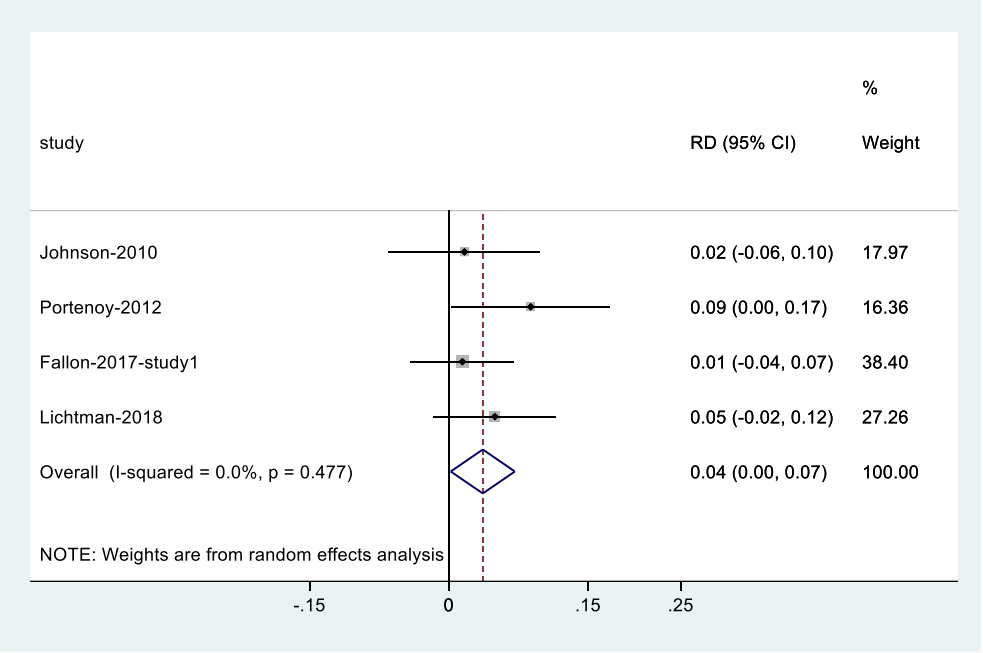
Appendix 5. 18: forest plot for pain relief on a 10-cm VAS among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies with no control group



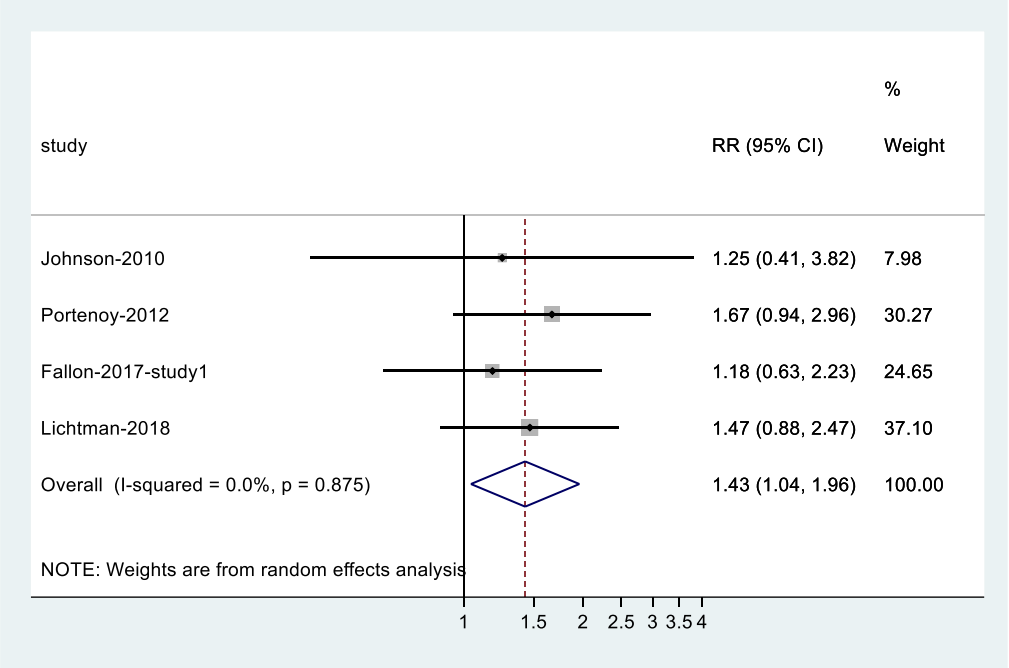
Appendix 5. 19: forest plot for sleep disturbance on a 10 cm VAS for sleep disturbance among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



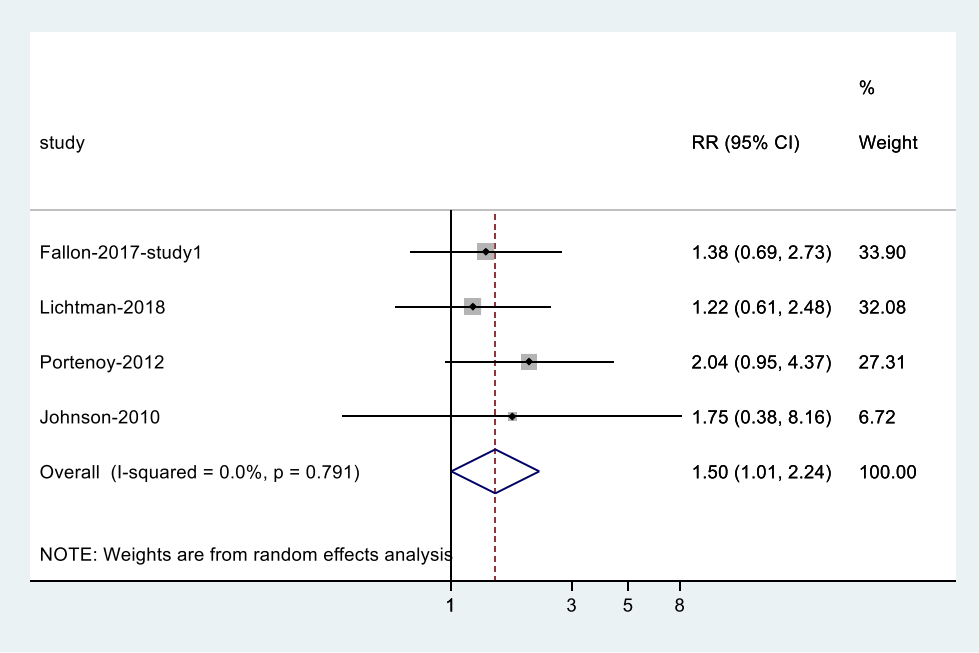
Appendix 5. 20: Subgroup analysis for sleep disturbance a 10-cm VAS for sleep disturbance and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



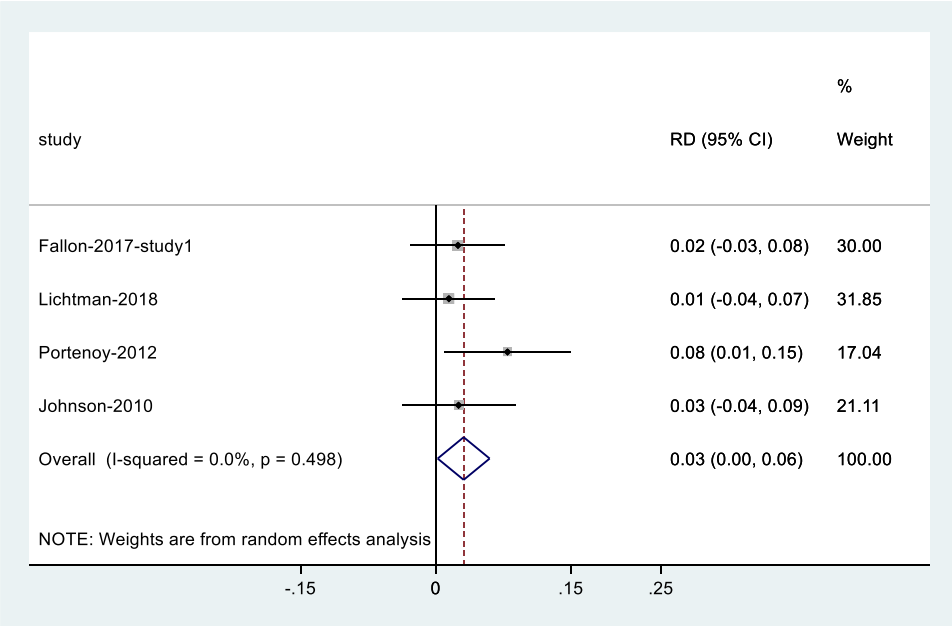
Appendix 5. 21: Risk difference of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



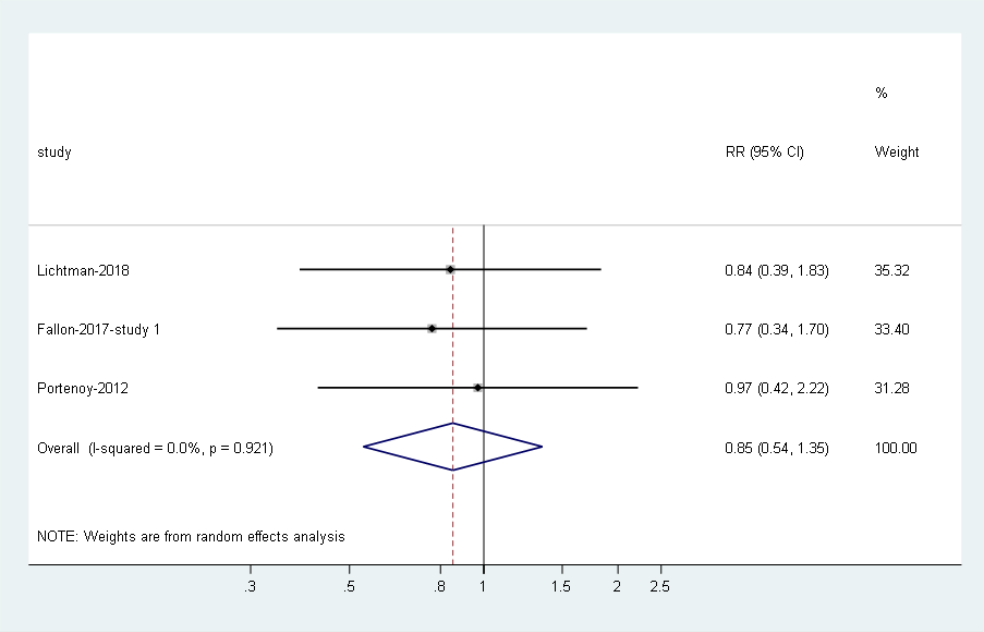
Appendix 5. 22: Relative Risk of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



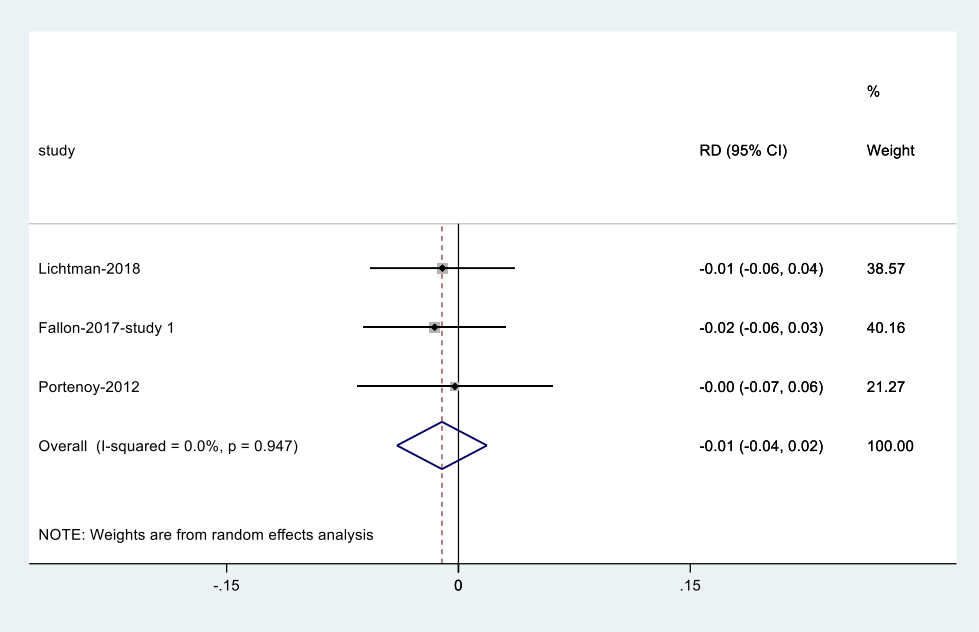
Appendix 5. 23: Relative Risk of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Appendix 5. 24: Risk Difference of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Appendix 5. 25: Relative Risk of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Appendix 5. 26: Risk difference of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs

Technical Appendix

This appendix provides additional details on two different methods of estimation, including 1) estimating the mean and standard deviation (SD) from sample size, median, and interquartile range (IQR); 2) estimating missing SD (for two non-randomized studies [5,7]) using the available SD from other included studies.

Estimating the mean and standard deviation (SD) from sample size, median, and IQR:

1) Pawasarat et al 2020 original reported data: median total morphine equivalent=45, n=137, and IQR=135.

-Using Wan et al method[1] produced: mean=60, SD=101

-Method recommended by Cochrane as *sensitivity analysis*:

$$S \approx \frac{q_3 - q_1}{1.35}.$$

q3-q1=IQR. This method produced SD=100.

2) Bellnier et al 2018 original reported data: median total morphine equivalent (before adding cannabis) =79.94, range=0 to 450, median (after adding cannabis) =19.65; range =0 to 150, n=29.

-Using Wan et al method produced: mean (before)=152.4, SD=111; mean (after)=47.3, SD=37.0

-Using Cochrane approach (Hozo et al[3]): Mean (before)= 152.4, SD= 112.5; mean (after)= 47.3, SD= 37.5

We finally included estimation by Wan et al method. The excel sheet including all formula was provided by Wan et al in supplementary file of their article[1].

Estimating missing SD using the available SD from other included studies:

Maida et al 2008 did not report SD around the mean at the end of follow-up for pain intensity. Original reported data: mean (SD) before adding cannabis= 7.1(2.4); after adding cannabis mean=3 (missing)

Connell et al 2019 original reported data: mean (SD) before adding cannabis=6.25 (missing); mean after adding cannabis=6.57 (missing)

We imputed missing SDs for these two studies from the given SDs related to other five included studies using prognostic method that presented by Ma et al[2]:

$$SEM_j^* = \frac{\sum_{i=1}^{k} SEM_i\sqrt{n_i}}{k\sqrt{n_j^*}}.$$

Assume there are k + l trials altogether where k trials are with full given information

SEM: value for trial *j (missing)* with sample size:

n_j: sample size for study with missing information.

SD (imputed) for first study= 1.51

SDs (imputed) for second study=1.76, 1.20

[1] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;**14**(1):135.

[2] Ma J, Liu W, Hunter A, et al. Performing meta-analysis with incomplete statistical information in clinical trials. BMC medical research methodology 2008;8(1):56.

[3] Hozo, S.P., Djulbegovic, B. & Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5, 13 (2005). https://doi.org/10.1186/1471-2288-5-13

Chapter 6: Discussion and future directions

This section provides an overview of the main findings from the chapters included in my thesis. Also, the implications of study findings, important limitations, and directions for future research are presented. By applying the findings from my thesis, investigators can improve the credibility of future research in chronic pain.

In the first part of this thesis, we evaluated the comparative effectiveness and harms of individual opioids for chronic noncancer pain by performing a network meta-analysis of randomized controlled trials. When restricted to moderate certainty evidence, opioids were similarly effective for pain relief and no opioid showed superiority for pain relief or improvement of physical functioning. All opioids increased the risk of gastrointestinal adverse events compared to placebo while no opioids were more harmful than others. Therefore, as clinical effects and harms are similar, appropriate opioids selection probably should be based on the patients' value and preference. Also, no individual policy for specific types of opioid is required. The main limitation of this NMA was the sparse network with few head-to-head trials comparing individual opioids. Our findings support the pooling of effect estimates across different types of opioids to inform the effect on chronic noncancer pain.

We also adopted the minimally contextualize approach on the results of the NMA and categorized opioids based on their certainty of the evidence, relative effect estimates, and finally checking the SUCRA-based ranking. Our findings will guide clinicians to be cautious when interpreting the SUCRA-based ranking as results showed that apparent differences in effects between opioids, when ranked according to SUCRA, ignored the certainty of evidence. The minimally contextualize approach for interpreting results from

NMA that we used highlights its advantages relative to relying on SUCRA values for establishing the relative effectiveness of competing interventions.

In the next chapter, we evaluated the agreement between the GRADE Working Group (GWG) system and the CINeMA approach regarding the generated certainty of evidence. This study was the first to explore concordance between these systems and showed that judgment across the domains yielded discrepant certainty of evidence ratings for network estimates for 29% to 40% of comparisons. A limitation we encountered was that the most included studies in this review were at high risk of bias (89%) and consequently, there was limited variability to detect differences between CINeMA and GWG systems. Future studies should aim to apply these competing approaches to other network meta-analyses to replicate or refute our findings.

Finally, we conducted a systematic review and meta-analysis of opioid-sparing effects of cannabinoids in chronic pain and found conflicting results; very low certainty evidence from randomized trials that cannabis is not a substitute for opioids, and very low certainty evidence from observational studies that providing medical cannabis does facilitate opioid reduction. Moderate-to-high certainty evidence suggested adding medical cannabis to opioid therapy among chronic cancer pain patients had little or no effect on pain relief or sleep disturbance and likely increases the risk of nausea and vomiting. Future trials should randomize chronic pain patients who voluntarily agree to engage in a trial of opioid tapering to receive medical cannabis or placebo and report all patient-important outcomes.