



BMJ Open Cannabis for medical use versus opioids for chronic non-cancer pain: a systematic review and network meta-analysis of randomised clinical trials

Haron M. Jeddi ¹, Jason W. Busse ^{1,2,3}, Behnam Sadeghirad ^{1,2,3}, Mitchell Levine^{1,4,5,6,7}, Michael J. Zoratti¹, Li Wang^{2,3}, Atefeh Noori^{1,8}, Rachel J. Couban², Jean-Eric Tarride^{1,6,7}

To cite: Jeddi HM, Busse JW, Sadeghirad B, *et al.* Cannabis for medical use versus opioids for chronic non-cancer pain: a systematic review and network meta-analysis of randomised clinical trials. *BMJ Open* 2024;**14**:e068182. doi:10.1136/bmjopen-2022-068182

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-068182>).

Received 14 September 2022
Accepted 27 November 2023



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Haron M. Jeddi;
markjeddi@me.com

ABSTRACT

Objective The objective of this study is to evaluate the comparative benefits and harms of opioids and cannabis for medical use for chronic non-cancer pain.

Design Systematic review and network meta-analysis.

Data sources EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021.

Study selection Randomised trials comparing any type of cannabis for medical use or opioids, against each other or placebo, with patient follow-up ≥ 4 weeks.

Data extraction and synthesis Paired reviewers independently extracted data. We used Bayesian random-effects network meta-analyses to summarise the evidence and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to evaluate the certainty of evidence and communicate our findings.

Results Ninety trials involving 22 028 patients were eligible for review, among which the length of follow-up ranged from 28 to 180 days. Moderate certainty evidence showed that opioids provide small improvements in pain, physical functioning and sleep quality versus placebo; low to moderate certainty evidence supported similar effects for cannabis versus placebo. Neither was more effective than placebo for role, social or emotional functioning (all high to moderate certainty evidence). Moderate certainty evidence showed there is probably little to no difference between cannabis for medical use and opioids for physical functioning (weighted mean difference (WMD) 0.47 on the 100-point 36-item Short Form Survey physical component summary score, 95% credible interval (CrI) -1.97 to 2.99), and cannabis resulted in fewer discontinuations due to adverse events versus opioids (OR 0.55, 95% CrI 0.36 to 0.83). Low certainty evidence suggested little to no difference between cannabis and opioids for pain relief (WMD 0.23 cm on a 10 cm Visual Analogue Scale (VAS), 95% CrI -0.06 to 0.53) or sleep quality (WMD 0.49 mm on a 100 mm VAS, 95% CrI -4.72 to 5.59).

Conclusions Cannabis for medical use may be similarly effective and result in fewer discontinuations than opioids for chronic non-cancer pain.

PROSPERO registration number CRD42020185184.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A Bayesian random-effects network meta-analysis was used to evaluate the comparative effectiveness of cannabis for medical use and opioids for management of chronic non-cancer pain.
- ⇒ We conducted a comprehensive search for eligible trials and used the GRADE approach to appraise the certainty of evidence for treatment effects and focused our analysis on patient-important outcomes.
- ⇒ Twenty-four randomised controlled trials evaluating cannabis for medical use were included in our review; however, none of these trials administered inhaled forms of cannabis and the generalisability of our findings to smoked or vaporised cannabis is uncertain.
- ⇒ For the comparison of cannabis for medical use and opioids, the majority of our outcomes were informed by indirect evidence since we found only one trial directly comparing both interventions for chronic pain.

INTRODUCTION

Chronic non-cancer pain impacts 20% of the global population and is associated with reduced quality of life, disability and considerable socioeconomic burden.¹⁻⁴ Opioids are commonly prescribed for chronic non-cancer pain and may provide improvement in pain relief, physical functioning and quality of sleep compared with placebo⁵; however, they are also associated with harms including addiction, overdose and death.⁶⁻⁷ There is a growing interest in cannabis as an alternative to long-term opioid use,⁸ and countries increasingly permit therapeutic use of cannabis.⁹ Two-thirds of cannabis for medical use users endorse management of chronic pain as their indication for use.¹⁰ Despite the increasing availability of cannabis for medical use, its use for chronic pain remains controversial due, in part, to conflicting recommendations. A 2019 guideline from the National

Institute for Health and Care Excellence made strong recommendations against the use of cannabis for chronic pain, and in 2021 the International Association for the Study of Pain (IASP) released a position statement against the use of cannabinoids for pain.^{11 12} Alternately, a 2021 BMJ Rapid Recommendation made a conditional recommendation to offer a trial of non-inhaled cannabis for medical use for people living with chronic pain if standard care was insufficient.¹³ The European Pain Federation also issued a position paper stating that cannabis-based medicines can be used by experienced physicians when guideline recommended first-line and second-line therapies for chronic pain do not provide sufficient benefit.¹⁴ We undertook a systematic review and network meta-analysis (NMA) of randomised controlled trials (RCTs) to explore the comparative benefits and harms of cannabis for medical use and opioids for chronic non-cancer pain.

METHODS

We adhered to the Preferred Reporting items for Systematic Reviews and Meta-Analyses extension statement for NMA (PRISMA-NMA),¹⁵ registered our review on PROSPERO (CRD42020185184)¹⁶ and followed Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidance for communicating our findings.¹⁷

Data sources and searches

We searched EMBASE, MEDLINE, CINAHL, AMED, PsycINFO, PubMed, Web of Science, Cannabis-Med, Epistemonikos and the Cochrane Library (CENTRAL) from inception to March 2021, without language restrictions, including grey literature from ClinicalTrials.gov. An experienced medical librarian developed database-specific search strategies (online supplemental eAppendix 1). We reviewed reference lists of eligible studies, and relevant reviews and guidelines, to identify additional studies. We included RCTs that enrolled ≥ 20 patients with chronic non-cancer pain (pain lasting ≥ 3 months), randomised them to any type of cannabis for therapeutic use, an opioid or placebo and followed them for ≥ 4 weeks to allow for sufficient time for functional outcomes to manifest among treatment responders.¹³ Trials including patients with chronic cancer and non-cancer pain were included if outcome data were reported separately. We excluded conference abstracts and trials of combination products (eg, opioids with non-steroidal anti-inflammatory drugs or antidepressants).

Pairs of reviewers independently screened titles and abstracts, and full-text reports, and extracted data using standardised, pilot-tested forms using online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; <http://systematic-review.net/>). For all eligible trials, we (LW, AN, RC and HMJ) collected information regarding study characteristics, intervention details, patient characteristics and all patient-important outcomes as guided by the Initiative on Methods, Measurement

and Pain Assessment in Clinical Trials.^{18 19} Discrepancies were resolved by discussion or, when necessary, by an adjudicator.

Risk of bias assessment

Risk of bias was assessed for eligible studies, independently and in duplicate, by pairs of reviewers using a modified Cochrane risk of bias instrument (RoB 1.0) according to the following domains: random sequence generation, allocation concealment, blinding of participants, caregivers, outcome assessors, and data analysts, and loss to follow-up ($\geq 20\%$ missing data were considered as high risk of bias).^{20 21}

Data analysis

Instruments used in the RCTs mostly consisted of the Visual Analogue Scale (VAS) and the Numerical Rating Scale for measuring pain intensity and sleep quality, and the Short Form-36 (SF-36) for other important patient outcomes (eg, physical functioning, emotional functioning, role functioning and social functioning). These instruments are reliable and valid in chronic pain populations.^{22–24}

Online supplemental eTable 1 lists additional instruments that were used to capture patient-important outcomes and references supporting their psychometric properties. We converted continuous measures to common scales on a domain-by-domain basis when different instruments were used to measure the same construct by rescaling the mean and SD of the other instruments: (1) pain relief to a 10 cm VAS; (2) physical functioning to the 100-point SF-36 physical component summary (PCS) score; (3) emotional functioning to the 100-point SF-36 mental component summary (MCS) score; (4) role functioning to the 100-point SF-36 subscale for role limitations due to physical problems; (5) social functioning to the 100-point SF-36 subscale for social functioning and (6) sleep quality to a 100 mm VAS.²⁵

We calculated direct estimates for any comparison reported by two or more studies as the weighted mean difference (WMD) and associated 95% credible interval (95% CrI) using change score from baseline to the end of follow-up to address interpatient variability. When SDs for continuous outcomes were not reported by study authors, they were estimated using confidence intervals or exact p values.²⁶ To optimise interpretability of our findings for statistically significant continuous outcomes, we used the network estimate of treatment effects to model the risk difference (RD) for achieving the minimally important difference (MID) or higher. We used an MID of 1 cm for the 10 cm VAS for pain,²⁷ 10 mm for sleep quality, 10 points for SF-36 subscales (role and social functioning) and 5 points for SF-36 PCS and MCS scores.^{28 29}

For discontinuations due to adverse events, we used a binomial likelihood distribution and logit link to generate the pooled OR with corresponding 95% CrI. We constructed separate models for enriched and non-enriched trials, as enriched trials typically exclude patients who report problematic adverse events during

an open-label run-in period prior to randomisation.³⁰ For estimating the number of patients expected to discontinue due to adverse events, we calculated the absolute effects for network estimates by multiplying the OR and its 95% CrI with the estimated baseline risk for discontinuations due to adverse events. We used median risk in the placebo group of included randomised trials as the baseline risk.

For studies that reported outcomes at several time points, we used data from the longest follow-up. We performed all conventional pairwise meta-analyses using DerSimonian and Laird random-effects models. Heterogeneity between RCTs for each direct comparison was assessed with visual inspection of forest plots and the I^2 statistic.³¹ For all direct comparisons, we assessed small study effects using funnel plots and Egger's test when 10 or more trials were available.³²

The feasibility of conducting a random-effects Bayesian NMA was assessed for all outcomes—this included assessing homogeneity of included studies, patients, and intervention characteristics, and network connectivity. We used edge-splitting (side-splitting) to evaluate the consistency of relative treatment effects between direct (eg, pairwise meta-analysis) and indirect evidence, and leverage plots to visually inspect model fit.³³ Models were programmed with three chains, and the convergence was assessed using the Gelman-Rubin statistic.³⁴ All analyses began with a burn-in phase (1000 iterations), followed by 100 000 iterations with 1000 adaptations. We used non-informative priors with mean 0 and SD 15u, where u is the largest maximum likelihood estimator of treatment differences on the linear scale in single trials.³⁵ Statistical superiority was asserted when the 95% CrI excluded the null effect (ie, 0.0 for WMDs and 1.0 for ORs). All analyses were programmed in R V.3.5.3 (<https://www.R-project.org>) using BUGSnet.³⁵

We tested the following a priori subgroup hypotheses that treatment effects were associated with: (1) neuropathic versus non-neuropathic pain; (2) shorter versus longer (≤ 2 months vs > 2 months) follow-up; (3) trials at risk of bias (on a criterion-by-criterion basis); (4) enriched enrolment trials versus not enriched and (5) higher opioid doses versus lower opioid doses by evaluating the following morphine milligram equivalent (MME) per day thresholds: (1) high=MME > 100 mg; (2) intermediate=MME 50–99 mg and (3) low=MME < 50 mg. We assessed the credibility of significant subgroup effects (ie, test of interaction $p \leq 0.05$) with the ICEMAN tool.³⁶ We used network meta-regression to explore the association between treatment effects and length of follow-up and sample size. The deviance information criterion (DIC) was used to assess model fit.

Quality of evidence

We used the GRADE approach to assess the certainty of the evidence for all outcomes and effect estimates from NMA.³⁷ Ratings of the certainty of evidence for direct and indirect estimates included assessment of risk of bias,

inconsistency, indirectness, publication bias and intransitivity (only for indirect estimates). We judged network estimates as imprecise if the 95% CrI included half the MID for continuous outcomes (eg, 0.5 cm for pain) or the null effect (OR of 1) for discontinuation due to adverse events.

Role of the funding source

The funders had no role in study design, data collection, analysis, interpretation or writing of the manuscript, or the decision to submit.

Patient and public involvement

Patients and the public were not involved in this research.

RESULTS

Of 20 012 citations identified, 90 studies from 89 publications proved eligible for review (figure 1, online supplemental eAppendix 2–3). No trials of inhaled cannabis were eligible for our review due to inadequate duration of follow-up (< 4 weeks). Sixty-six trials compared opioids to placebo,^{38–102} 23 trials compared cannabis for medical use to placebo^{103–125} and 1 trial¹²⁶ randomised patients to nabilone or dihydrocodeine. The evidence network for all our outcomes is presented in figure 2. Among the included studies, the median of the mean age of participants was 56 years (IQR 50–62), 58% were female, the median of the mean duration of pain was 8.1 years (IQR 5.0–12.7) and the median of the mean pain score at enrolment was 6.05 (IQR 4.65–6.90). Twenty-nine trials enrolled patients with neuropathic pain, 60 with non-neuropathic pain and 1 trial enrolled patients with mixed pain. (Table 1 and online supplemental eTable 2 for details on the pain conditions and other baseline characteristics).

Most trials (75 of 90; 83%) were judged to be at high risk of bias for at least one domain. Adequate generation of a randomisation sequence was reported by 53 (59%) trials, 64 (71%) reported concealment of allocation, and almost all trials reported blinding of patients (99%) and healthcare providers and data collectors (98%) (online supplemental eTable 3). Sixty-five (72%) trials reported $\geq 20\%$ missing outcome data (online supplemental eTable 3). We did not find evidence of incoherence. For closed-loop networks, consistency was met based on DIC values. For open loop networks, direct and indirect estimates are reported separately (online supplemental eTable 4, 5 and online supplemental eFigure 1).

Moderate certainty evidence showed that, compared with placebo, opioids provide small improvements in pain (modelled RD for achieving the MID 15%, 95% CrI 13% to 17%), physical functioning (modelled RD for achieving the MID 5%, 95% CrI 3% to 8%) and sleep quality (modelled RD for achieving the MID 8%, 95% CrI 4% to 13%). Low to moderate certainty evidence supported similar effects for cannabis for medical use versus placebo. Neither was more effective than placebo for role, social or emotional functioning (all high to

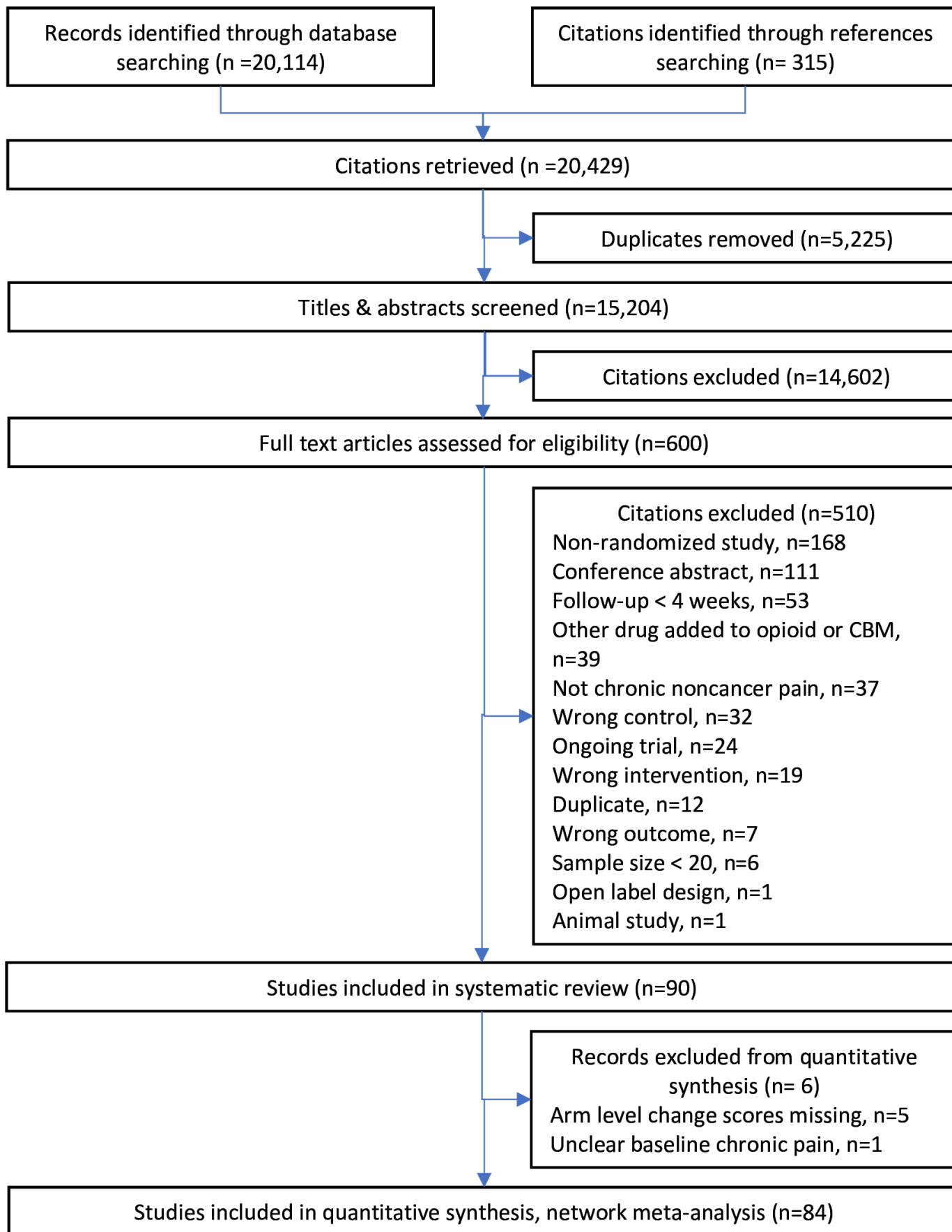


Figure 1 Study selection process for the systematic review and network meta-analysis.

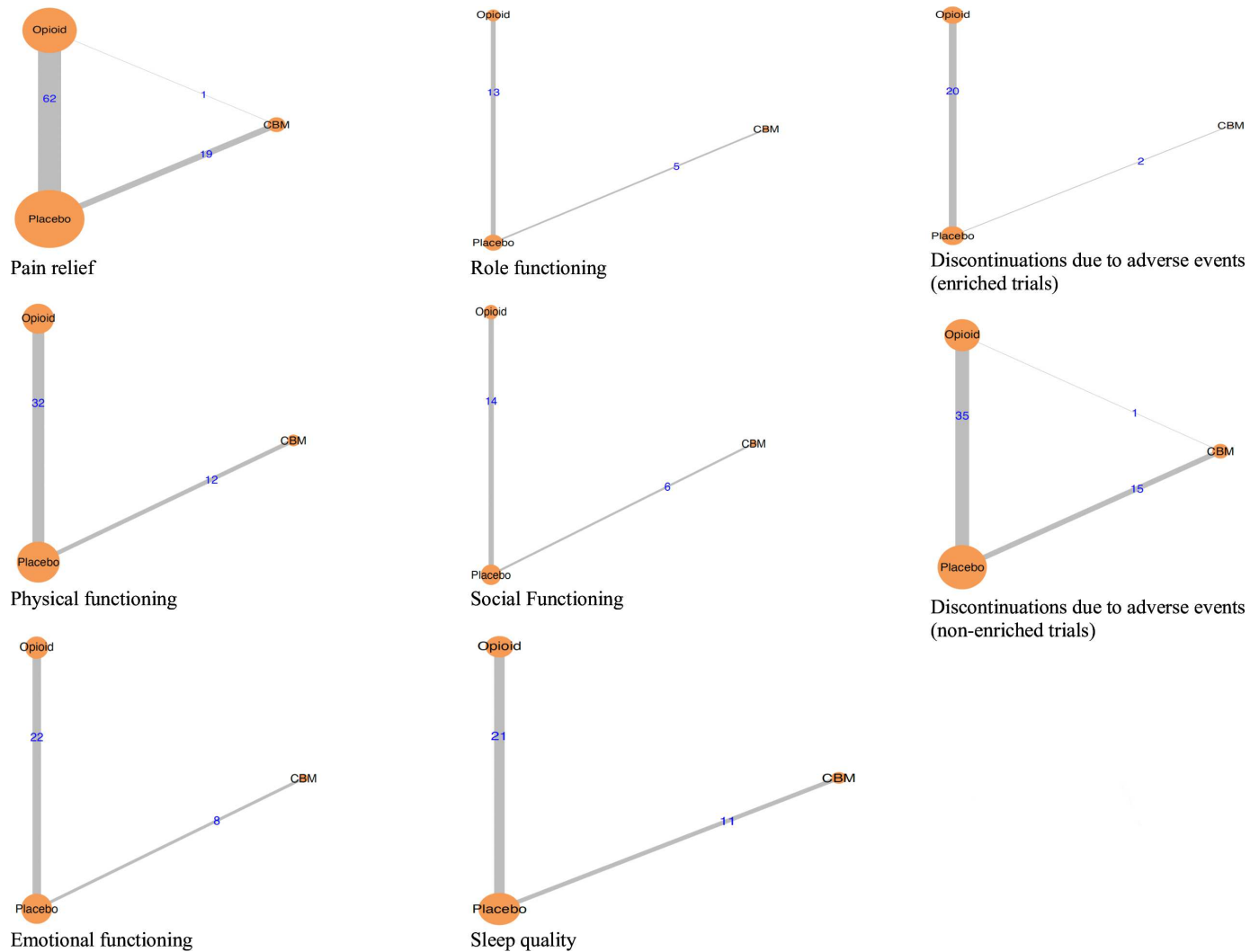


Figure 2 Evidence network for network meta-analysis outcomes.

moderate certainty evidence) (table 2, online supplemental eTable 4 and online supplemental eFigure 2–13).

Low certainty evidence from 82 RCTs involving 19 693 patients suggested that there may be little to no difference in pain relief between cannabis for medical use and opioids (WMD 0.23 cm on a 10 cm VAS, 95% CrI –0.06 to 0.53) (table 2, online supplemental eFigure 1 and online supplemental eTable 4). Moderate certainty evidence from 44 RCTs involving 12 727 patients shows there is probably little to no difference in physical functioning with cannabis for medical use compared with opioids (WMD 0.47 points on the 100-point SF-36 PSC score, 95% CrI –1.97 to 2.99) (table 2, online supplemental eTable 4). Low certainty evidence from 32 RCTs involving 8201 patients suggests that there may be little to no difference in sleep quality between cannabis for medical use and opioids (WMD 0.49 mm on a 100 mm VAS, 95% CrI –4.72 to 5.59) (table 2, online supplemental eTable 4). There were insufficient data to construct networks for health-related quality of life (online supplemental eAppendix 4).

Discontinuations due to adverse events were reported in 22 enrichment trials (6 831 patients) and in 51 non-enrichment trials (13 012 patients). Among enrichment trials, low certainty evidence suggests that there may be little to no difference in discontinuations due to adverse events between cannabis for medical use and opioids (OR 0.77, 95% CrI 0.07 to 8.83). Moderate certainty evidence shows that in non-enriched studies, discontinuations due to adverse events are probably less for cannabis for medical use versus opioids (OR 0.55, 95% CrI 0.36 to 0.83) (table 2). Moderate and high certainty evidence showed that, compared with placebo, opioids and cannabis for medical use, respectively, probably result in higher discontinuations compared with placebo (modelled RD for achieving the MID for opioids vs placebo, 10%, 95% CrI 8% to 12%; cannabis for medical use vs placebo, 4%, 95% CrI 1% to 7%) (table 2, online supplemental eFigure 14–17).

We found no evidence of credible subgroup effects based on the type of pain condition (neuropathic vs non-neuropathic), length of follow-up, sample size or opioid dose (table 3, online supplemental eTable 6–12).

Table 1 Summary of study participant characteristics included in eligible randomised controlled trials

No of trials	No of patients	Age, median of mean (IQR)	% female, median of mean (IQR)	Baseline pain score, median of mean (min-max)	No of studies by pain type*	No of studies by intervention dose/format*	Follow-up, median days (min-max)	Trial type*
Opioids versus placebo								
66	18 401	58 (50–62)	56 (44.5–62)	6.01 (1.87–7.83)	Neuropathic pain, n=18 (27%) Non-neuropathic, n=47 (71%) Mixed, n=1 (2%)	MME >90 mg, n=14 (21%) MME 50–90 mg, n=19 (29%) MME <50 mg, n=21 (32%) Dose details not reported n=12 (18%)	84 (28–180)	Enriched n=20 (30%) non-enriched n=46 (70%)
Cannabis for medical use versus placebo								
23	3435	53 (50–58)	62 (40–70)	6.28 (2.15–7.80)	Neuropathic pain, n=10 (43%) non-neuropathic, n=13 (57%)	PEA, n=2 (9%) THC/CBD, n=11 (48%) THC, n=7 (30%) CBD, n=2 (9%) CBDV, n=1 (4%)	51 (28–112)	Enriched n=3 (13%) non-enriched n=20 (87%)
Cannabis for medical use versus opioids								
1	192	50	26	6.72	Neuropathic pain, n=1 (100%)	THC, n=1 (100%)	42	Non-enriched n=1 (100%)

*Values in parenthesis are percentage of trials. CBD, cannabidiol; CBDV, cannibidivarin; MME, morphine milligram equivalent; PEA, palmitoylethanolamide; THC, tetrahydrocannabinol.

Table 2 Treatment effects and certainty of evidence (GRADE) for opioids and cannabis for medical use in patients with chronic non-cancer pain

Comparison	Direct evidence		Indirect evidence		Treatment effect WMD (95% CI)	Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
	No of trials (patients)	Treatment effect WMD (95% CI)	No of trials (patients)	Treatment effect WMD (95% CI)				
Pain relief: 10 cm VAS for pain; lower is better; MID=1 cm								
Opioids versus placebo	62 (17 431)	-0.84 (-0.99 to -0.69)	62 (17 431)	-0.83 (-0.97 to -0.70)	-0.83 (-0.97 to -0.70)	-0.83 (-0.97 to -0.70)	15% (13% to 17%)	Moderate
Cannabis for medical use versus placebo	19 (2116)	-0.63 (-0.94 to -0.32)	19 (2116)	-0.59 (-0.88 to -0.32)	-0.60 (-0.87 to -0.33)	-0.60 (-0.87 to -0.33)	11% (6% to 15%)	Low
Cannabis for medical use versus opioids	1 (146)	0.13 (-0.54 to 0.80)	81 (19 547)	0.24 (-0.07 to 0.55)	0.23 (-0.06 to 0.53)	0.23 (-0.06 to 0.53)	-	Low
Physical functioning: 0–100 point SF-36 PCS score; higher is better; MID=5 points								
Opioids versus placebo	32 (10 926)	2.38 (1.05 to 3.72)	-	-	2.05 (1.01, 3.29)	2.05 (1.01, 3.29)	5% (3% to 8%)	Moderate
Cannabis for medical use versus placebo	12 (1801)	3.00 (0.08 to 5.91)	-	-	2.52 (0.37, 4.91)	2.52 (0.37, 4.91)	6% (1% to 12%)	Moderate
Cannabis for medical use versus opioids	-	-	44 (12 727)	0.47 (-1.97 to 2.99)	0.47 (-1.97 to 2.99)	0.47 (-1.97 to 2.99)	-	Moderate
Emotional functioning: 0–100 point SF-36 MCS score; higher is better; MID=5 points								
Opioids versus placebo	22 (7267)	-0.00 (-1.09 to 1.09)	-	-	-0.15 (-1.10 to 0.92)	-0.15 (-1.10 to 0.92)	-	High
Cannabis for medical use versus placebo	8 (1515)	0.72 (-1.01 to 2.45)	-	-	0.70 (-1.42 to 2.84)	0.70 (-1.42 to 2.84)	-	Moderate
Cannabis for medical use versus opioids	-	-	30 (8782)	0.85 (-1.55 to 3.18)	0.85 (-1.55 to 3.18)	0.85 (-1.55 to 3.18)	-	Low
Role functioning: 0–100 point SF-36 subscale for role limitations due to physical problems; higher is better; MID=10 points								
Opioids versus placebo	13 (3661)	0.91 (-1.17 to 2.98)	-	-	0.94 (-1.26 to 3.17)	0.94 (-1.26 to 3.17)	-	Moderate
Cannabis for medical use versus placebo	5 (528)	1.27 (-12.39 to 14.93)	-	-	0.88 (-3.78 to 6.05)	0.88 (-3.78 to 6.05)	-	Moderate
Cannabis for medical use versus opioids	-	-	18 (4189)	-0.05 (-5.16 to 5.60)	-0.05 (-5.16 to 5.60)	-0.05 (-5.16 to 5.60)	-	Moderate
Social functioning: 0–100 point SF-36 subscale for social functioning; higher is better; MID=10 points								
Opioids versus placebo	14 (4075)	0.47 (-1.47 to 2.41)	-	-	1.17 (-1.72 to 4.58)	1.17 (-1.72 to 4.58)	-	Moderate
Cannabis for medical use versus placebo	6 (795)	-1.82 (-5.79 to 2.15)	-	-	1.70 (-3.28 to 8.13)	1.70 (-3.28 to 8.13)	-	Moderate

Continued

Table 2 Continued

Comparison	Direct evidence		Indirect evidence		Treatment effect WMD (95% CI)	Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
	No of trials (patients)	Treatment effect WMD (95% CI)	No of trials (patients)	Treatment effect WMD (95% CI)				
Cannabis for medical use versus opioids		–	20 (4870)	0.55 (–5.34 to 7.41)	0.55 (–5.34 to 7.41)			Moderate
Sleep quality: 100mm VAS for sleep quality; higher is better; MID=10mm								
Opioids versus placebo	21 (6677)	5.55 (2.67 to 8.43)	–	–	5.46 (2.62 to 8.59)	8% (4% to 13%)		Moderate
Cannabis for medical use versus placebo	11 (1524)	6.04 (1.43 to 10.66)	–	–	5.95 (1.82 to 10.24)	9% (3% to 15%)		Low
Cannabis for medical use versus opioids		–	32 (8201)	0.49 (–4.72 to 5.59)	0.49 (–4.72 to 5.59)			Low
Discontinuations due to adverse events (enriched trials)								
Opioids versus placebo	20 (6699)	OR, 1.39 (1.04 to 1.86)	–	–	OR, 1.25 (0.91, 1.67)			Low
Cannabis for medical use versus placebo	2 (132)	OR, 5.00 (0.25 to 101.7)	–	–	OR, 0.96 (0.09 to 10.80)			Low
Cannabis for medical use versus opioids		–	22 (6831)	OR, 0.77 (0.07, 8.83)	OR, 0.77 (0.07 to 8.83)			Low
Discontinuations due to adverse events (non-enriched trials)								
Opioids versus placebo	35 (11 019)	OR, 3.58 (3.00 to 4.27)	35 (11 019)	OR, 3.27 (2.70 to 3.93)	OR, 3.27 (2.71 to 3.90)	10% (8% to 12%)		Moderate
Cannabis for medical use versus placebo	15 (1801)	OR, 2.47 (1.49 to 4.11)	15 (1801)	OR, 1.78 (1.15 to 2.63)	OR, 1.80 (1.19 to 2.63)	4% (1% to 7%)		High
Cannabis for medical use versus opioids	1 (192)	OR, 0.50 (0.16, 1.61)	50 (12 820)	OR, 0.54 (0.34 to 0.84)	OR, 0.55 (0.36 to 0.83)			Moderate

CrI, credible interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MCS, mental component summary; MID, minimally important difference; PCS, physical component summary; RD, risk difference; SF36, 36-Item Short Form Survey; VAS, Visual Analogue Scale; WMD, weighted mean difference.

Table 3 Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

Subgroup factors	Pain relief WMD 95% CrI	Physical functioning WMD 95% CrI	Role functioning WMD 95% CrI	Social functioning WMD 95% CrI	Discontinuations due to adverse events (non-enriched)	
					OR	95% CrI
Clinical condition	0.74 (0.30, 1.12)	-0.67 (-4.46, 3.28)	-4.66 (-21.16, 5.49)	-8.09 (-16.89, -0.69)	0.91 (0.48, 1.76)	
Length of follow-up	0.04 (-0.36, 0.45)	2.35 (-2.72, 6.56)	8.59 (-3.64, 20.37)	-0.31 (-8.27, 7.79)	*0.42* (0.15, 0.67)	
Adequate randomisation	0.14 (-0.25, 0.53)	0.36 (-2.14, 3.03)	2.92 (-9.96, 15.78)	0.07 (-4.45, 4.34)	*0.48* (0.27, 0.79)	
Adequate concealment	0.25 (-0.08, 0.58)	0.87 (-1.43, 3.37)	-0.81 (-6.88, 5.75)	-2.02 (-6.75, 1.60)	*0.51* (0.31, 0.79)	
Industry funded trials	0.23 (-0.13, 0.58)	0.72 (-2.02, 3.52)	-0.71 (-6.86, 5.72)	-0.62 (-4.94, 2.69)	*0.55* (0.33, 0.92)	
Loss to follow-up	0.32 (-0.78, 1.39)	-4.57 (-15.20, 6.66)	-4.59 (-18.01, 14.04)	-0.62 (-10.78, 10.11)	0.77 (0.09, 3.75)	
Study design	*0.53* (0.08, 0.98)	-0.39 (-5.45, 4.52)	1.40 (-3.77, 8.21)	-3.31 (-8.10, 1.48)	0.63 (0.36, 1.11)	
Non-enrichment	-0.09 (-0.64, 0.38)	0.86 (-3.74, 6.97)	-18.49 (-51.56, 8.85)	0.32 (-17.97, 13.13)	0.79 (0.13, 2.97)	
Enrichment	-0.65 (-1.65, 0.35)	NA	-22.92 (-61.99, 16.11)	-14.19 (-40.56, 12.39)	NA	
	0.25 (-0.07, 0.57)	0.37 (-2.57, 3.19)	0.55 (-5.34, 7.41)	-1.54 (-6.21, 2.32)		

All values in bold are statistically significant at the 0.05 significance level.

*Unless otherwise indicated. Results are cannabis for medical use versus opioids. Pain relief for neuropathic pain versus non-neuropathic p=0.004. Social functioning for neuropathic pain versus non-neuropathic p=0.047. P value based on test of interaction. Number of studies and p values for all comparisons are available in online supplemental eTable 7. CrI, credible interval; NA, not available; WMD, weighted mean difference.



DISCUSSION

This NMA of 90 trials that enrolled 22 028 people living with chronic non-cancer pain provides low certainty evidence that cannabis for medical use is similarly effective to opioids for pain relief and sleep quality, and moderate certainty evidence for similar effects on physical functioning. The magnitude of effects versus placebo for cannabis for medical use or opioids was modest, with the modelled RD for achieving the MID for pain, physical functioning and sleep ranging from 5% to 15%. Moderate certainty evidence also suggests that the use of cannabis for medical use versus opioids resulted in fewer discontinuations due to adverse events. Moderate to high certainty evidence showed that neither opioids nor cannabis for medical use were effective for improving emotional, social or role functioning among people living with chronic pain.

Our study, which is the first NMA exploring the comparative effectiveness of cannabis for medical use and opioids for chronic non-cancer pain, has several strengths. We conducted a comprehensive search strategy, including grey literature from ClinicalTrials.gov, used the GRADE approach to appraise the certainty of evidence for treatment effects and followed GRADE guidance for communicate our findings. We evaluated harms using discontinuations due to adverse events to facilitate pooling across trials. Further, we explored subgroup effects and assessed their credibility according to current best practices.

Clinical guidelines for chronic non-cancer pain recommend optimisation of non-opioid-based pharmacological and non-pharmacological therapies prior to initiating opioids.^{127–129} However, approximately one-third of all patients living with chronic non-cancer pain are prescribed opioids¹³⁰; and increasing concerns regarding harms of long-term opioid therapy has generated enthusiasm for alternatives, including cannabis for medical use.¹³¹ In part, because some observational studies (but not others^{132 133}) have shown an association between legalisation of cannabis for medical use and reduced prevalence of opioid use disorder and opioid overdose.^{134 135} Although prone to measured and unmeasured confounding bias, recent observational studies and studies using registry data have also shown favourable improvements in pain and health-related quality of life outcomes for cannabis for medical use when compared with opioids.^{136–139} Moreover, users of cannabis for medical use acknowledge substitution of prescription medication, particularly opioids, as a common motive.^{140 141} This issue is controversial,¹⁴² however, and recent guidelines have provided conflicting recommendations regarding the effectiveness of cannabis for medical use for chronic pain and whether the use of cannabis reduces opioid consumption.^{11–13 143} An important limitation of prior evidence syntheses is the scarcity of trials directly comparing cannabis for medical use against opioids for chronic pain. These treatment options are mostly trialled against placebo, and NMA can, therefore, establish comparative effectiveness by virtue of

this common comparator. Our findings suggest that both opioids and cannabis for medical use may provide benefits for a minority of chronic pain patients (eg, compared with placebo, 10%–15% of patients experience a 1 cm or greater relief in pain on a 10 cm scale). However, reviews of patient values and preferences show that people living with chronic pain place a high value on the possibility of achieving small but important pain relief.^{144 145} Furthermore, cannabis does not cause respiratory depression which can result from opioids consumption and lead to non-fatal or fatal overdose.¹⁴⁶

Future research should directly compare the effectiveness of opioids versus cannabis for chronic pain, and follow patients sufficiently to inform long-term benefits and harms. Trials should report all outcome measures of importance to people who live with chronic pain.^{18 19 147} Randomised trials are also needed to establish the opioid-substitution effects of cannabis for chronic pain, and observational studies to inform long-term and infrequent harms of both cannabis for medical use and opioids for chronic pain (eg, overdose and addiction).

There are some limitations associated with our study. None of the trials eligible for our review explored inhaled cannabis, and our results may not be generalisable to this method of administration. We excluded trials with combination drugs because results may be confounded by the additional drugs. As such, our results may not reflect outcomes where opioids or cannabis are used in combination with other drugs (eg, tramadol and acetaminophen). The cannabis plant contains over 500 chemical substances and the main cannabinoids included in most RCTs are tetrahydrocannabinol (THC), cannabidiol (CBD) or THC/CBD and not the full plant. We pooled different opioids and types of cannabis for medical use that may not be common forms of products used in the real world; however, subgroup analysis suggests that effects for chronic pain are similar across different opioids and cannabis for medical use products.^{148 149} Further, an NMA found no evidence to support important differences in pain relief, functional improvement or gastrointestinal adverse events between different types of opioids.¹⁴⁸ In order to facilitate pooling, we reported harms as discontinuations due to adverse events instead of reporting specific adverse events experienced by trial participants. In other meta-analyses of RCTs, cannabis for medical use was associated with greater central nervous system and gastrointestinal adverse events versus placebo.^{149 150} Both opioids and cannabis for medical use can result in use disorders^{151 152} while opioids can also result in fatal and non-fatal overdose; however, we were unable to construct a network to explore the comparative risk of these important harms as RCTs are poorly suited to detect rare harms or harms that take a while to manifest. We do not feel our analysis suffers from serious intransitivity as the distribution of potential effect modifiers were well balanced across the included studies.¹⁵³ Our results for opioids may be overestimated due to small study effects from the included RCTs for pain relief, physical

functioning and sleep and for pain relief in the cannabis RCTs.

CONCLUSIONS

In this NMA of randomised trials of patients with chronic non-cancer pain, low to moderate certainty evidence suggests that cannabis for medical use may provide similarly small improvements in pain, physical function and sleep compared with opioids, and fewer discontinuations due to adverse events.

Author affiliations

¹Department of Health Research Methods, Evidence, and Impact (HEI), Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Ontario, Canada

²Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

³Michael G. DeGroote Institute of Pain Research and Care, McMaster University, Hamilton, Ontario, Canada

⁴Department of Medicine, McMaster University, Hamilton, Ontario, Canada

⁵Division of Clinical Pharmacology and Toxicology, St. Joseph's Healthcare, Hamilton, Ontario, Canada

⁶Center for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, Ontario, Canada

⁷Programs for Assessment of Technology in Health (PATH), The Research Institute of St. Joe's Hamilton, St. Joseph's Healthcare, Hamilton, Ontario, Canada

⁸Hand Program, Division of Plastic, Reconstructive and Aesthetic Surgery, University Health Network, University of Toronto, Toronto, Ontario, Canada

Twitter Jason W. Busse @JasonWBusse

Contributors HMJ, JWB, BS, ML and JET conceived and designed the study. HMJ, LW, AN and RJC acquired the data. HMJ, JWB, BS and MJZ contributed to the statistical analyses. HMJ performed the statistical analyses. All authors interpreted the data and could access data included in the study. HMJ, JWB and JET drafted the manuscript. All authors made critical revisions to the article for important intellectual content and gave final approval for the article. HMJ guarantor of work.

Funding Parts of this study were supported by grant 119801 and FRN 147994, Co-PIs: JWB and MA Ware from the Canadian Institutes of Health Research and grant 1516-HQ-000017 from Health Canada. JWB is supported, in part, by a Canadian Institutes of Health Research Canada Research Chair in Prevention & Management of Chronic Pain.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Haron M. Jeedi <http://orcid.org/0000-0003-2018-9376>

Jason W. Busse <http://orcid.org/0000-0002-0178-8712>

Behnam Sadeghirad <http://orcid.org/0000-0001-9422-5232>

REFERENCES

- Dahlhamer J, Lucas J, Zelaya C, *et al*. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:1001-6.
- van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anaesth* 2013;111:13-8.
- Breivik H, Collett B, Ventafridda V, *et al*. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10:287-333.
- Sá KN, Moreira L, Baptista AF, *et al*. Prevalence of chronic pain in developing countries: systematic review and meta-analysis. *Pain Rep* 2019;4:e779.
- Busse JW, Wang L, Kamaleldin M, *et al*. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA* 2018;320:2448-60.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;315:1624-45.
- Humphreys K, Shover CL, Andrews CM, *et al*. Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-lancet commission. *Lancet* 2022;399:555-604.
- The lancet rheumatology. Medical cannabis: bridging the evidence gap. *Lancet Rheumatol* 2019;1:e195.
- Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - regulations in Europe and North America. *Eur J Intern Med* 2018;49:2-6.
- Boehnke KF, Gangopadhyay S, Clauw DJ, *et al*. Qualifying conditions of medical cannabis license holders in the United States. *Health Affairs* 2019;38:295-302.
- Evidence review for chronic pain: cannabis-based medicinal products: evidence review B*. National Institute for Health and Care Excellence (NICE), 2019. Available: <http://www.ncbi.nlm.nih.gov/books/NBK577083/> [accessed 5 Dec 2021].
- IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia. International association for the study of pain presidential task force on cannabis and cannabinoid analgesia position statement. *Pain* 2021;162:S1-2.
- Busse JW, Vankrunkelsven P, Zeng L, *et al*. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. *BMJ* 2021;374:2040.
- Häuser W, Finn DP, Kalso E, *et al*. European pain federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. *Eur J Pain* 2018;22:1547-64.
- Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- Jeedi M, Levine M, Busse JW, *et al*. A systematic review and network meta-analysis of cannabis versus opioids for the treatment of chronic non cancer pain [CRD42020185184]. PROSPERO; 2020. Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020185184 [Accessed 1 Dec 2020].
- Santesso N, Glenton C, Dahm P, *et al*. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol* 2020;119:126-35.
- Turk DC, Dworkin RH, Allen RR, *et al*. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337-45.
- Turk DC, Dworkin RH, Revicki D, *et al*. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain* 2008;137:276-85.
- Akl EA, Sun X, Busse JW, *et al*. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65:262-7.
- Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Patel KV, Amtmann D, Jensen MP, *et al*. Clinical outcome assessment in clinical trials of chronic pain treatments. *Pain Rep* 2021;6:e784.
- Hjermstad MJ, Fayers PM, Haugen DF, *et al*. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage* 2011;41:1073-93.

- 24 Safikhani S, Gries KS, Trudeau JJ, *et al.* Response scale selection in adult pain measures: results from a literature review. *J Patient Rep Outcomes* 2017;2:40.
- 25 Thorlund K, Walter SD, Johnston BC, *et al.* Pooling health-related quality of life outcomes in meta-analysis—a tutorial and review of methods for enhancing interpretability: enhancing interpretability in continuous meta-analysis. *Res Synth Methods* 2011;2:188–203.
- 26 Higgins JPT, Thomas J, Chandler J, eds. *Cochrane handbook for systematic reviews of interventions*. 1st ed. Wiley, 2019.
- 27 Dworkin RH, Turk DC, Wyrwich KW, *et al.* Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–21.
- 28 Zisapel N, Nir T. Determination of the minimal clinically significant difference on a patient visual analog sleep quality scale: minimal important difference in sleep quality. *J Sleep Res* 2003;12:291–8.
- 29 Ward MM, Guthrie LC, Alba MI. Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness: minimum clinically important improvements for SF-36 scales. *Arthritis Care Res (Hoboken)* 2014;66:1783–9.
- 30 Furlan A, Chaparro LE, Irvin E, *et al.* A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag* 2011;16:337–51.
- 31 Higgins JPT, Deeks JJ, Altman DG, *et al.*, eds. Chapter 10: analysing data and undertaking meta-analyses. In: *Cochrane handbook for systematic reviews of interventions version 6.3.cochrane*. 2022. Available: www.training.cochrane.org/handbook
- 32 Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–57.
- 33 Dias S, Welton NJ, Caldwell DM, *et al.* Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
- 34 Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist Sci* 1992;7.
- 35 Bêliveau A, Boyne DJ, Slater J, *et al.* BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network meta-analyses. *BMC Med Res Methodol* 2019;19:196.
- 36 Schandelmaier S, Briel M, Varadhan R, *et al.* Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:E901–6.
- 37 Guyatt GH, Juniper EF, Walter SD, *et al.* Interpreting treatment effects in randomised trials. *BMJ* 1998;316:690–3.
- 38 Afilalo M, Etropolski MS, Kuperswasser B, *et al.* Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* 2010;30:489–505.
- 39 Arai T, Kashimoto Y, Ukyo Y, *et al.* Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1 day patch in opioid-naïve patients with chronic pain. *Curr Med Res Opin* 2015;31:2207–18.
- 40 Babul N, Noveck R, Chipman H, *et al.* Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manage* 2004;28:59–71.
- 41 Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain* 2003;104:323–31.
- 42 Breivik H, Ljosaa TM, Stengaard-Pedersen K, *et al.* A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. *Scand J Pain* 2010;1:235.
- 43 Burch F, Fishman R, Messina N, *et al.* A comparison of the analgesic efficacy of tramadol contramid OAD versus placebo in patients with pain due to osteoarthritis. *J Pain Symptom Manage* 2007;34:328–38.
- 44 Buynak R, Shapiro DY, Okamoto A, *et al.* Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. *Expert Opin Pharmacother* 2010;11:1787–804.
- 45 Caldwell JR, Hale ME, Boyd RE, *et al.* Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol* 1999;26:862–9.
- 46 Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002;23:278–91.
- 47 Christoph A, Eerdeken MH, Kok M, *et al.* Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial. *Pain* 2017;158:1813–24.
- 48 Chu LF, D'Arcy N, Brady C, *et al.* Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain* 2012;153:1583–92.
- 49 DeLemos BP, Xiang J, Benson C, *et al.* Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. *Am J Ther* 2011;18:216–26.
- 50 Fishman RL, Kistler CJ, Ellerbusch MT, *et al.* Efficacy and safety of 12 weeks of osteoarthritic pain therapy with once-daily tramadol (tramadol contramid OAD). *J Opioid Manag* 2007;3:273–80.
- 51 Fleischmann RM, Caldwell JR, Roth SH, *et al.* Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Curr Ther Res* 2001;62:113–28.
- 52 Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. *J Opioid Manag* 2011;7:193–202.
- 53 Gana TJ, Pascual MLG, Fleming RRB, *et al.* Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Curr Med Res Opin* 2006;22:1391–401.
- 54 Gilron I, Bailey JM, Tu D, *et al.* Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005;352:1324–34.
- 55 Gimbel J, Spierings ELH, Katz N, *et al.* Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016;157:2517–26.
- 56 Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003;60:927–34.
- 57 Gordon A, Callaghan D, Spink D, *et al.* Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther* 2010;32:844–60.
- 58 Gordon A, Rashiq S, Moulin DE, *et al.* Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain Res Manag* 2010;15:169–78.
- 59 Hale M, Khan A, Kutch M, *et al.* Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin* 2010;26:1505–18.
- 60 Hale ME, Ahdieh H, Ma T, *et al.* Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. *J Pain* 2007;8:175–84.
- 61 Hale ME, Zimmerman TR, Eyal E, *et al.* Efficacy and safety of a hydrocodone extended-release tablet formulated with abuse-deterrence technology in patients with moderate-to-severe chronic low back pain. *J Opioid Manag* 2015;11:507–18.
- 62 Harati Y, Gooch C, Swenson M, *et al.* Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998;50:1842–6.
- 63 Huse E, Larbig W, Flor H, *et al.* The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001;90:47–55.
- 64 Katz N, Kopecky EA, O'Connor M, *et al.* A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain. *Pain* 2015;156:2458–67.
- 65 Katz N, Rauck R, Ahdieh H, *et al.* A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naïve patients with chronic low back pain. *Curr Med Res Opin* 2007;23:117–28.
- 66 Kawamata M, Iseki M, Kawakami M, *et al.* Efficacy and safety of controlled-release oxycodone for the management of moderate-to-severe chronic low back pain in Japan: results of an enriched enrollment randomized withdrawal study followed by an open-label extension study. *J Pain Res* 2019;12:363–75.

- 67 Khoromi S, Cui L, Nackers L, *et al.* Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 2007;130:66–75.
- 68 Langford R, McKenna F, Ratcliffe S, *et al.* Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. *Arthritis Rheum* 2006;54:1829–37.
- 69 Lin JC, Chu LF, Stringer EA, *et al.* One month of oral morphine decreases gray matter volume in the right amygdala of individuals with low back pain: confirmation of previously reported magnetic resonance imaging results. *Pain Med* 2016;17:1497–504.
- 70 Ma K, Jiang W, Zhou Q, *et al.* The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. *Int J Clin Pract* 2008;62:241–7.
- 71 Markenson JA, Croft J, Zhang PG, *et al.* Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain* 2005;21:524–35.
- 72 Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Med* 2005;6:357–66.
- 73 Mayorga AJ, Wang S, Kelly KM, *et al.* Efficacy and safety of fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: a randomised, placebo- and active-controlled trial. *Int J Clin Pract* 2016;70:493–505.
- 74 Moran C. MST continus tablets and pain control in severe rheumatoid arthritis. *Br J Clin Res* 1991;32:436–43.
- 75 Moulin DE, Iezzi A, Amireh R, *et al.* Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996;347:143–7.
- 76 Munera, PhD C, Drehobl, MD M, Sessler, PharmD NE, *et al.* A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *J Opioid Management* 2010;6:193–202.
- 77 Niesters M, Proto PL, Aarts L, *et al.* Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth* 2014;113:148–56.
- 78 Norrbrink C, Lundeberg T. Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. *Clin J Pain* 2009;25:177–84.
- 79 Peloso PM, Bellamy N, Bensen W, *et al.* Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000;27:764–71.
- 80 Raja SN, Haythornthwaite JA, Pappagallo M, *et al.* Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2002;59:1015–21.
- 81 Rauck R, Rapoport R, Thippahawong J. Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS® hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis. *Pain Pract* 2013;13:18–29.
- 82 Rauck RL, Nalamachu S, Wild JE, *et al.* Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: a randomized double-blind, placebo-controlled study. *Pain Med* 2014;15:975–85.
- 83 Rauck RL, Potts J, Xiang Q, *et al.* Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgrad Med* 2016;128:1–11.
- 84 Russell IJ, Kamin M, Bennett RM, *et al.* Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol* 2000;6:250–7.
- 85 Schimrigk S, Marziniak M, Neubauer C, *et al.* Dronabinol is a safe long-term treatment option for neuropathic pain patients. *Eur Neurol* 2017;78:320–9.
- 86 Schnitzer TJ, Gray WL, Paster RZ, *et al.* Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol* 2000;27:772–8.
- 87 Schwartz S, Etropolski M, Shapiro DY, *et al.* Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011;27:151–62.
- 88 Serrie A, Lange B, Steup A. Tapentadol prolonged-release for moderate-to-severe chronic osteoarthritis knee pain: a double-blind, randomized, placebo- and oxycodone controlled release-controlled study. *Curr Med Res Opin* 2017;33:1423–32.
- 89 Simpson RW, Włodarczyk JH. Transdermal buprenorphine relieves neuropathic pain: a randomized, double-blind, parallel-group, placebo-controlled trial in diabetic peripheral neuropathic pain. *Diabetes Care* 2016;39:1493–500.
- 90 Sindrup SH, Konder R, Lehmann R, *et al.* Randomized controlled trial of the combined monoaminergic and opioid investigational compound GRT9906 in painful polyneuropathy. *Eur J Pain* 2012;16:849–59.
- 91 Sindrup SH, Madsen C, Brøsen K, *et al.* The effect of tramadol in painful polyneuropathy in relation to serum drug and metabolite levels. *Clin Pharmacol Ther* 1999;66:636–41.
- 92 Steiner DJ, Sitar S, Wen W, *et al.* Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. *J Pain Symptom Manage* 2011;42:903–17.
- 93 Thorne C, Beaulieu AD, Callaghan DJ, *et al.* A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Res Manag* 2008;13:93–102.
- 94 Tominaga Y, Koga H, Uchida N, *et al.* Methodological issues in conducting pilot trials in chronic pain as randomized, double-blind, placebo-controlled studies. *Drug Res (Stuttg)* 2016;66:363–70.
- 95 Ueberall MA, Mueller-Schwefe GHH, Terhaag B. Efficacy and safety of flupirtine modified release for the management of moderate to severe chronic low back pain: results of SUPREME, a prospective randomized, double-blind, placebo- and active-controlled parallel-group phase IV study. *Curr Med Res Opin* 2012;28:1617–34.
- 96 Vinik AI, Shapiro DY, Rauschkolb C, *et al.* A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care* 2014;37:2302–9.
- 97 Vojtaššák J, Vojtaššák J, Jacobs A, *et al.* A phase IIIB, multicentre, randomised, parallel-group, placebo-controlled, double-blind study to investigate the efficacy and safety of OROS hydromorphone in subjects with moderate-to-severe chronic pain induced by osteoarthritis of the hip or the knee. *Pain Res Treat* 2011;2011:239501.
- 98 Vorsanger GJ, Xiang J, Gana TJ, *et al.* Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *J Opioid Manag* 2008;4:87–97.
- 99 Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998;50:1837–41.
- 100 Webster LR, Butera PG, Moran LV, *et al.* Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain* 2006;7:937–46.
- 101 Wen W, Sitar S, Lynch SY, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of single-entity, once-daily hydrocodone tablets in patients with uncontrolled moderate to severe chronic low back pain. *Expert Opin Pharmacother* 2015;16:1593–606.
- 102 Wu CL, Agarwal S, Tella PK, *et al.* Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008;109:289–96.
- 103 Andresen SR, Bing J, Hansen RM, *et al.* Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: a randomized, double-blind, placebo-controlled trial. *Pain* 2016;157:2097–103.
- 104 Blake DR, Robson P, Ho M, *et al.* Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:50–2.
- 105 de Vries M, van Rijckevorsel DCM, Vissers KCP, *et al.* Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. *Clin Gastroenterol Hepatol* 2017;15:1079–86.
- 106 Eibach L, Scheffel S, Cardebring M, *et al.* Cannabidivarin for HIV-associated neuropathic pain: a randomized, blinded, controlled clinical trial. *Clin Pharmacol Ther* 2021;109:1055–62.
- 107 Germini F, Coerezza A, Andreinetti L, *et al.* N-of-1 randomized trials of ultra-micronized palmitoylethanolamide in older patients with chronic pain. *Drugs Aging* 2017;34:941–52.
- 108 Hunter D, Oldfield G, Tich N, *et al.* Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. *Osteoarthritis Cartilage* 2018;26:S26.
- 109 Langford RM, Mares J, Novotna A, *et al.* A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260:984–97.
- 110 Marková J, Essner U, Akmaz B, *et al.* Sativex((R)) as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci* 2019;129:119–28.
- 111 NCT00710424. A study of Sativex® for pain relief due to diabetic neuropathy. 2006. Available: <https://ClinicalTrials.gov/show/NCT00710424>

- 112 Novotna A, Mares J, Ratcliffe S, *et al.* A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols® (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011;18:1122–31.
- 113 Nurmikko TJ, Serpell MG, Hoggart B, *et al.* Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007;133:210–20.
- 114 Pinsger M, Schimetta W, Volc D, *et al.* [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial]. *Wien Klin Wochenschr* 2006;118:327–35.
- 115 Rog DJ, Nurmikko TJ, Friede T, *et al.* Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65:812–9.
- 116 Selvarajah D, Gandhi R, Emery CJ, *et al.* Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care* 2010;33:128–30.
- 117 Serpell M, Ratcliffe S, Hovorka J, *et al.* A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain* 2014;18:999–1012.
- 118 Skrabek RQ, Galimova L, Ethans K, *et al.* Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;9:164–73.
- 119 Toth C, Mawani S, Brady S, *et al.* An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012;153:2073–82.
- 120 van Amerongen G, Kanhai K, Baakman AC, *et al.* Effects on spasticity and neuropathic pain of an oral formulation of Δ^9 -tetrahydrocannabinol in patients with progressive multiple sclerosis. *Clin Ther* 2018;40:1467–82.
- 121 Wissel J, Haydn T, Müller J, *et al.* Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol* 2006;253:1337–41.
- 122 Xu DH, Cullen BD, Tang M, *et al.* The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. *Curr Pharm Biotechnol* 2020;21:390–402.
- 123 Zajicek J, Fox P, Sanders H, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362:1517–26.
- 124 Zajicek JP, Sanders HP, Wright DE, *et al.* Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005;76:1664–9.
- 125 Zajicek JP, Hobart JC, Slade A, *et al.* Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry* 2012;83:1125–32.
- 126 Frank B, Serpell MG, Hughes J, *et al.* Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 2008;336:199–201.
- 127 Busse JW, Craigie S, Juurlink DN, *et al.* Guideline for opioid therapy and chronic noncancer pain. *CMAJ* 2017;189:E659–66.
- 128 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. *MMWR Recomm Rep* 2016;65:1–49.
- 129 National Institute for Health and Care Excellence (NICE). *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain*. 2021. Available: <http://www.ncbi.nlm.nih.gov/books/NBK569960/>
- 130 Mathieson S, Wertheimer G, Maher CG, *et al.* What proportion of patients with chronic noncancer pain are prescribed an opioid medicine? Systematic review and meta-regression of observational studies. *J Intern Med* 2020;287:458–74.
- 131 Choo EK, Feldstein Ewing SW, Lovejoy TI. Opioids out, cannabis in: negotiating the unknowns in patient care for chronic pain. *JAMA* 2016;316:1763.
- 132 Kaufman DE, Nihal AM, Leppo JD, *et al.* Opioid mortality following implementation of medical cannabis programs in the United States. *Pharmacopsychiatry* 2021;54:91–5.
- 133 Kim JH, Martins SS, Shmulewitz D, *et al.* Association between fatal opioid overdose and state medical cannabis laws in US national survey data, 2000–2011. *Int J Drug Policy* 2022;99:103449.
- 134 Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addiction and deaths related to pain killers? In: *RAND working paper*. 2015.
- 135 Hayes MJ, Brown MS. Legalization of medical marijuana and incidence of opioid mortality. *JAMA Intern Med* 2014;174:1673.
- 136 Harris M, Erridge S, Ergisi M, *et al.* UK medical cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. *Expert Rev Clin Pharmacol* 2022;15:473–85.
- 137 Tait J, Erridge S, Holvey C, *et al.* Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK medical cannabis registry. *Expert Rev Neurother* 2023;23:413–23.
- 138 Meng H, Page MG, Ajrawat P, *et al.* Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients. *Can J Anaesth* 2021;68:633–44.
- 139 Vickery AW, Roth S, Ernenwein T, *et al.* A large Australian longitudinal cohort registry demonstrates sustained safety and efficacy of oral medicinal cannabis for at least two years. *PLoS One* 2022;17:e0272241.
- 140 Kvamme SL, Pedersen MM, Rømer Thomsen K, *et al.* Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample. *Harm Reduct J* 2021;18:72.
- 141 Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res* 2017;2:160–6.
- 142 Humphreys K, Saitz R. Should physicians recommend replacing opioids with cannabis? *JAMA* 2019;321:639.
- 143 Noori A, Miroshnychenko A, Shergill Y, *et al.* Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open* 2021;11:e047717.
- 144 Goshua A, Craigie S, Guyatt GH, *et al.* Patient values and preferences regarding opioids for chronic noncancer pain: a systematic review. *Pain Med* 2018;19:2469–80.
- 145 Zeng L, Lytvyn L, Wang X, *et al.* Values and preferences towards medical cannabis among people living with chronic pain: a mixed-methods systematic review. *BMJ Open* 2021;11:e050831.
- 146 Ray WA, Chung CP, Murray KT, *et al.* Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. *JAMA* 2016;315:2415–23.
- 147 Mulla SM, Maqbool A, Sivanathan L, *et al.* Reporting of IMMPACT-recommended core outcome domains among trials assessing opioids for chronic non-cancer pain. *Pain* 2015;156:1615–9.
- 148 Noori A, Sadeghirad B, Wang L, *et al.* Comparative benefits and harms of individual opioids for chronic non-cancer pain: a systematic review and network meta-analysis of randomised trials. *Br J Anaesth* 2022;129:394–406.
- 149 Wang L, Hong PJ, May C, *et al.* Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ* 2021;374:1034.
- 150 Aviram J, Samuely-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. *Pain Phys* 2017;6:E755–96.
- 151 Connor JP, Stjepanović D, Le Foll B, *et al.* Cannabis use and cannabis use disorder. *Nat Rev Dis Primers* 2021;7:16.
- 152 Boscarino JA, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis* 2011;30:185–94.
- 153 Brignardello-Petersen R, Tomlinson G, Florez I, *et al.* Grading of recommendations assessment, development, and evaluation concept article 5: addressing intransitivity in a network meta-analysis. *J Clin Epidemiol* 2023;160:151–9.