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

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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 placebo[5]; 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 (≥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≤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 trial[126] 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 ≥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

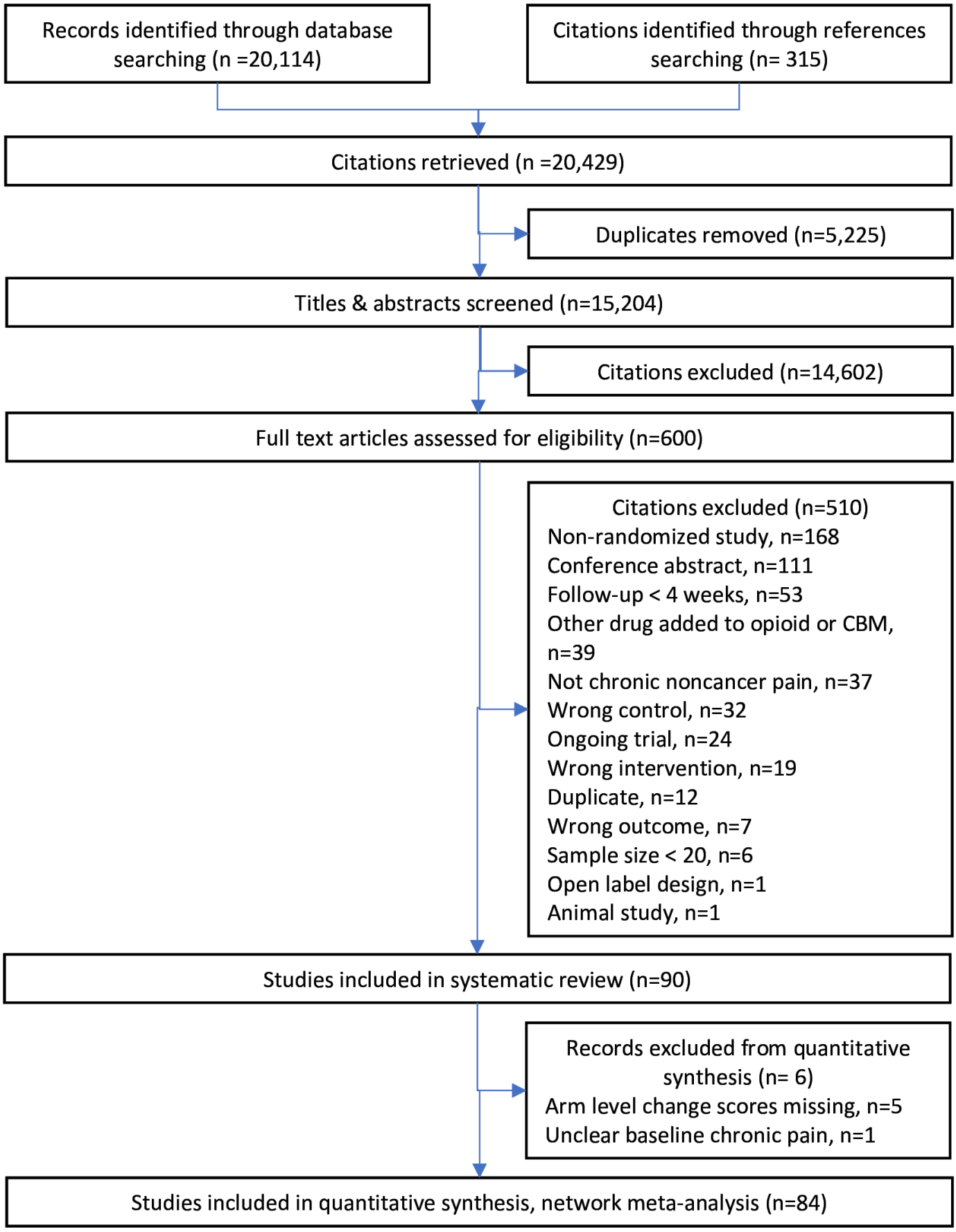

Figure 1 Study selection process for the systematic review and network meta-analysis.

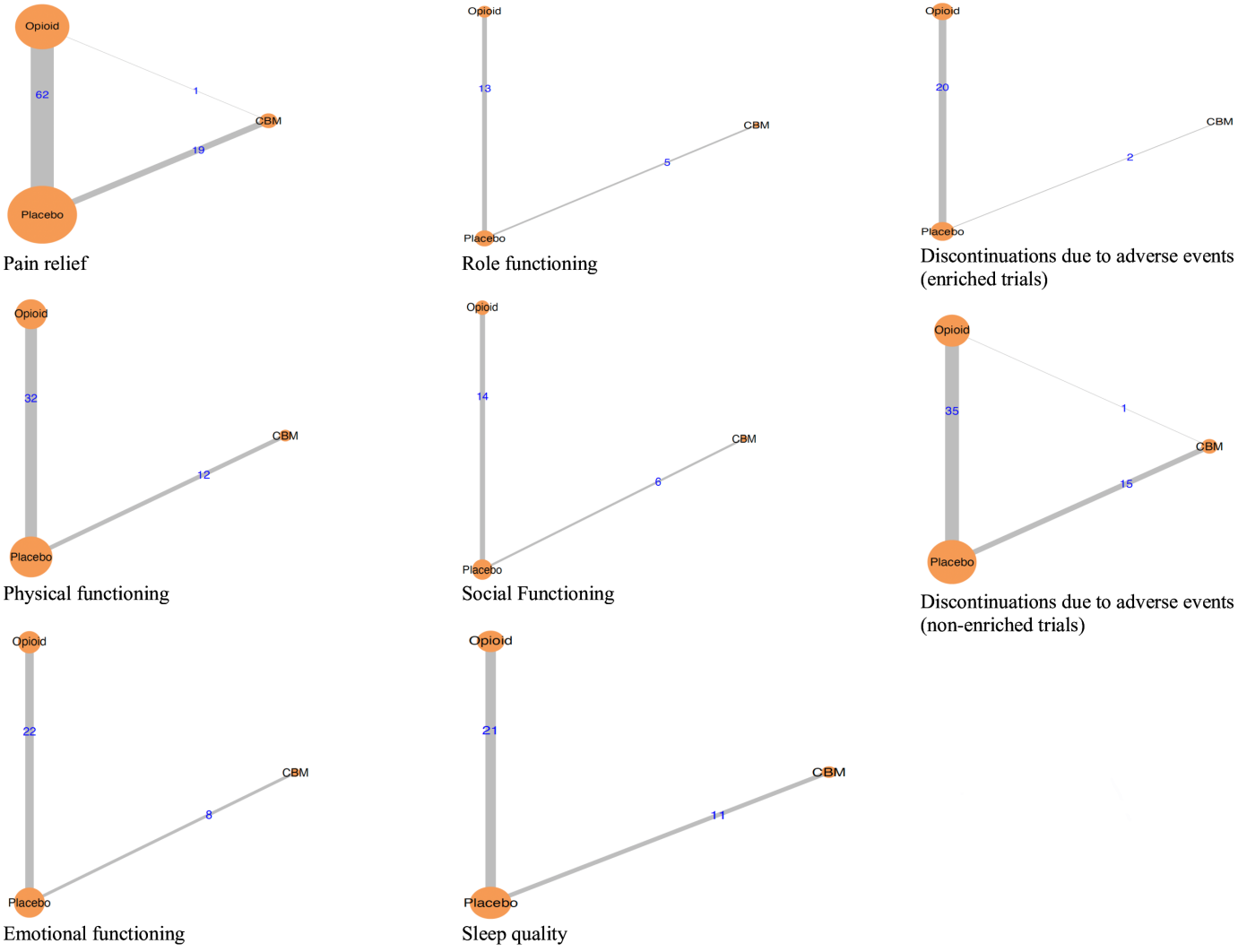

Figure 2 Evidence network for network meta-analysis outcomes.

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	18401	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				
	No of trials (patients)	Treatment effect WMD (95% CI)	No of trials (patients)	Treatment effect WMD (95% CI)	Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
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)	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)	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)	–	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)	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)	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)	–	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)		High
Cannabis for medical use versus placebo	8 (1515)	0.72 (−1.01 to 2.45)		–	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)		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)		Moderate
Cannabis for medical use versus placebo	5 (528)	1.27 (−12.39 to 14.93)		–	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)		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)		Moderate
Cannabis for medical use versus placebo	6 (795)	−1.82 (−5.79 to 2.15)		–	1.70 (−3.28 to 8.13)		Moderate

Continued

Table 2 Continued

Comparison	Direct evidence		Indirect evidence				
	No of trials (patients)	Treatment effect WMD (95% CI)	No of trials (patients)	Treatment effect WMD (95% CI)	Network estimate WMD (95% CrI)	RD for achieving the MID (95% CI)	GRADE
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: 100 mm VAS for sleep quality; higher is better; MID=10 mm							
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	Neuropathic	**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)
	Non-neuropathic	−0.12 (−0.55,0.30)	0.97 (−2.67, 4.72)	9.81 (−1.55,21.10)	1.01 (−3.01,4.75)	*0.34* (0.15, 0.67)
Length of follow-up	≤2 months	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* (0.20, 0.79)
	>2 months	0.41 (−0.04,0.85)	−0.75 (−3.83, 2.38)	−2.48 (−11.89, 5.23)	−2.26 (−9.50,2.29)	0.65 (0.37, 1.16)
Adequate randomisation	Yes	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)
	No	0.37 (−0.19,0.92)	0.01 (−10.42, 9.03)	−4.55 (−26.29,14.71)	−6.93 (−21.75,6.27)	0.77 (0.31, 1.86)
Adequate concealment	Yes	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)
	No	NA	NA	NA	NA	NA
Industry funded trials	Yes	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)
	No	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)
Loss to follow-up	High (≥20%)	*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)
	Low (<20%)	−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)
Study design	Enrichment	−0.65 (−1.65,0.35)	NA	−22.92 (−61.99,16.11)	−14.19 (−40.56,12.39)	NA
	Non-enrichment	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 opioids[130]; 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 compactor. 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.

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