Systematic Reviews and Meta-Analyses

PAIN®

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

Abstract

This review examines evidence for the effectiveness of cannabinoids in chronic noncancer pain (CNCP) and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL, and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 randomised controlled trials (RCTs) and 57 observational studies. Forty-eight studies examined neuropathic pain, 7 studies examined fibromyalgia, 1 rheumatoid arthritis, and 48 other CNCP (13 multiple sclerosis–related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, pooled event rates (PERs) for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo); significant effect for cannabinoids was found; number needed to treat to benefit was 24 (95% confidence interval [CI] 15-61); for 50% reduction in pain, PERs were 18.2% vs 14.4%; no significant difference was observed. Pooled change in pain intensity (standardised mean difference: −0.14, 95% CI −0.20 to −0.08) was equivalent to a 3 mm reduction on a 100 mm visual analogue scale greater than placebo groups. In RCTs, PERs for all-cause adverse events were 81.2% vs 66.2%; number needed to treat to harm: 6 (95% CI 5-8). There were no significant impacts on physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest that number needed to treat to benefit is high, and number needed to treat to harm is low, with limited impact on other domains. It seems unlikely that cannabinoids are highly effective medicines for CNCP.

Keywords: Cannabis, Chronic noncancer pain, Neuropathy, Systematic review, Meta-analysis, Number needed to treat

1. Introduction

There has been increasing attention to the use of cannabis and cannabinoids in the treatment of chronic noncancer pain (CNCP). Changes in legislation and use globally mean that it is likely that there will be an increase in the coming years in the availability and use of cannabis and cannabinoid products for CNCP. In the United States, these products are most commonly cited for use in CNCP.[48] Chronic noncancer pain conditions are prevalent and rank among the most significant causes of disability globally.[30]

Recent reviews of cannabis and cannabinoids for medicinal purposes have increased our knowledge in the understanding of their effectiveness on pain,[55,88,93] although they are limited in the case of CNCP management and conclusions have been conflicting, with some reviews reporting moderate to large effects,[48,93] whereas others have reported minimal[60] or no benefit.[3] Existing reviews have been limited in their searching for CNCP studies (eg, with a focus on specific types of cannabinoids[2] or study designs[60]), and no single review has considered the following: all types of evidence; different CNCP conditions individually; potential differential effects of different cannabinoids; and the safety of cannabis for patients with CNCP. Each of these limitations reduces our understanding of the evidence for the use of cannabinoids for CNCP.

Chronic noncancer pain conditions are varied, and many people with CNCP live with complex physical and mental health comorbidities.[9,70] Pain is considered by leading clinicians and researchers to be only one of a range of core outcomes that must be considered evaluating interventions for CNCP.[82] The current review addresses the limitations of previous reviews and is the first to examine the evidence for the effectiveness of cannabinoids for CNCP for all study designs, all CNCP types, all types of cannabis and cannabinoids, and using the outcomes specified in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[82]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] National Drug and Alcohol Research Centre, Faculty of Medicine, UNSW Sydney, Sydney, New South Wales, Australia, [b] Centre for Youth Substance Abuse Research, University of Queensland, Brisbane, Queensland, Australia, [c] National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, London, United Kingdom, [d] Discipline of Addiction Medicine, Faculty of Medicine, University of Sydney, Sydney, New South Wales, Australia, [e] Drug Health Services, Concord Repatriation General Hospital, Sydney Local Health District, NSW Health, Sydney, New South Wales, Australia

**Corresponding author. Address: 22-32 King St, Randwick 2031, New South Wales, Australia. Tel.: +61(2) 9385 0162; fax: +61 (2) 9385 0222. E-mail address: e.stockings@unsw.edu.au (E. Stockings).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 159 (2018) 1932–1954

http://dx.doi.org/10.1097/j.pain.0000000000001293

2. Methods

2.1. Search strategy and study eligibility

To ensure full coverage of the literature, we conducted a multiphase search, comprising an initial review of reviews for cannabis and cannabinoids to treat CNCP, followed by 4 condition-specific systematic reviews.

A systematic review of reviews in October 2016 in the electronic databases MEDLINE, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews to identify all reviews (and empirical studies contained within) that evaluated the evidence base for the administration of cannabis and cannabinoids to treat CNCP (PROSPERO registration CRD42016049475).

This search was supplemented by 4 systematic searches of empirical studies in July 2017 in the electronic databases MEDLINE, Embase, PsycINFO, the Cochrane Database of Systematic Reviews and clinicaltrials.gov to identify any trial that evaluated cannabis or cannabinoids in treating the specific pain conditions: neuropathic pain (PROSPERO registration: CRD42017065248), fibromyalgia (PROSPERO registration: CRD42017067057), arthritis (PROSPERO registration: CRD42017067059), and other or mixed groups of CNCP (Supplementary Material, page 6). Date of publication was restricted to between 1980 and July 2017. No restrictions were placed on language or publication type. Medline search strategies are shown in Appendix A of the supplementary appendix (available online at http://links.lww.com/PAIN/A592). Corresponding subject headings were used in each database where specialised thesauri existed.

Individual studies that were identified (N = 107) in the systematic review of reviews of cannabinoids for the treatment of pain were screened for eligibility in full by 2 independent reviewers. For reviews of empirical studies for neuropathic pain, fibromyalgia, arthritis, and CNCP, 2 reviewers independently examined titles and abstracts using the web-based systematic review program Covidence.[84] All articles identified as potentially relevant (including review articles) were obtained in full and screened by 2 independent reviewers. Study screening was conducted in duplicate by 2 independent reviewers (any of G.C., E.S., M.W., D.Z., S.N., and R.R.). Interrater disagreement was resolved via consultation with an independent third reviewer (any of L.D., G.C., E.S., M.W., D.Z., and R.R.).

2.2. Types of pain conditions

We included studies that examined impacts of cannabis and cannabinoids on any CNCP condition. We followed Cochrane protocols determining studies for inclusion and extracting data; at least 80% of the patient population was required to be experiencing one of the included pain conditions (neuropathic pain, CNCP, arthritis, or fibromyalgia). If less than 80% of the sample had one of the target pain conditions but results were presented separately for the subsample experiencing one of these pain conditions, we included the study and extracted data for the target subgroup. Studies were required to examine cannabis and cannabinoids as a primary or secondary indication for pain and to measure at least 1 of our 3 primary pain outcomes: pain intensity and 30% or 50% reduction in pain.

2.3. Types of interventions

We considered studies examining tetrahydrocannabinol; cannabidiol; combination of tetrahydrocannabinol + cannabidiol; plant-based cannabis (eg, *Cannabis sativa*); and other cannabinoids, eg, tetrahydrocannabinolic acid (THCA), cannabidiolic acid, cannabidivarin, and the synthetic delta-9-tetrahydrocannabinol formulations nabilone and dronabinol.

2.4. Types of studies

We included randomised controlled trials (RCTs), nonrandomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case–control studies, analytical cross-sectional studies, observational studies, self-report, and N-of-1 studies. For studies with a comparison group, we considered any type of comparator, including placebo groups, waitlist controls, and other interventions.

2.5. Outcomes

Guided by the IMMPACT core outcome domains for clinical trials in CNCP,[82] we grouped the outcomes of interest into 6 categories: pain intensity, physical functioning, emotional functioning, global impression of change, adverse events (AEs), and withdrawals. We assessed the clinical significance of the changes by extracting data for a 30% reduction in pain (a "moderate" effect) and a 50% reduction in pain (a "substantial" effect).[24]

2.6. Assessment of risk of study bias

We used the Cochrane Collaboration risk of bias tool for RCTs.[36] Randomised controlled trials were judged to have an overall "low risk" of bias if they had 6 to 8 risk domains rated as having a low risk of bias, "unclear risk" if 4 or more domains were judged as being unclear, and "high risk" if 3 or more domains were judged as being high risk. We additionally examined risk of bias because of sample size, where studies comprising at least 100 participants per treatment arm were classified as "low risk," studies comprising 30 to 100 per arm were classified as "unclear risk," and studies comprising <30 participants per arm were classified as "high risk." Observational studies or case study reports were evaluated using an adapted version of the Cochrane Collaboration risk of bias in nonrandomised studies of interventions (ROBINS-I) assessment tool.[76] Overall, risk of bias was determined by the most serious risk of bias allocated to that study across the tool.

2.7. Grading of evidence

As the review included RCTs and observational trials, we used an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool to grade the overall study methodology.[63] Randomised controlled trials began with a high rating that was downgraded if important limitations were identified in the study methodology. Observational trials began with a low rating and were upgraded if important strengths were identified. We additionally conducted a GRADE assessment using GRADEPro (https://gradepro.org/) for each reported pooled estimate that evaluated the risk of bias, inconsistency, indirectness, imprecision, and publication bias (through visual inspection of funnel plots).

2.8. Data extraction

We extracted details on the participants, interventions, comparisons, outcomes, and study design (PICOS) of each study, including: sample N, age, sex, medical and pain condition(s),

length and type of treatment (including route of administration, place in therapeutic hierarchy, dose, and cointerventions), comparator type, study country, year, and design. Outcomes were extracted following IMMPACT recommendations. When data were not reported in full, we contacted authors for additional information. When studies reported multiple measures of a single domain (eg, pain intensity), we applied a hierarchy of evidence. When authors reported multiple analyses (eg, intention to treat [ITT], available case, or per protocol), we extracted the more conservative with a preference for ITT analyses. We reported AEs according to high-level Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/) categories and report the 18 most common single AEs.

Data extraction, risk of bias, and GRADE assessments were conducted in duplicate by 2 independent reviewers (any of G.C., E.S., M.W., D.Z., S.N., and R.R.). Interrater disagreement was resolved via consultation with an independent third reviewer (any of L.D., G.C., E.S., M.W., D.Z., and R.R.).

2.9. Data analysis

We extracted data from all reported time points in each trial. Our primary analysis included data from the primary endpoint (or longest follow-up) in each trial. If multiple assessments were made on participants on the same day, we analysed the data taken from the longest follow-up.

Data were analysed separately for RCTs and observational study designs. All analyses were conducted using Review Manager (RevMan) version 5.3[79] and Stata 15.0.[75] Continuous outcomes were pooled using fixed-effect generic inverse variance meta-analysis and expressed as standardised mean differences (SMDs) with 95% confidence intervals (CIs). To aid clinical interpretation of the continuous outcome of change in pain intensity, we additionally reexpressed the SMD for overall change in pain intensity as a mean difference on a 100 mm visual analogue scale (VAS) by multiplying the pooled SMD by a typical baseline among-person SD on a 100 mm VAS, obtained from the included studies.[36,38] Dichotomous outcomes were summarised as odds ratios (ORs) using the Mantel–Haenszel fixed-effect model.[22] For observational studies, we pooled event rates using the Stata metaprop command.[57] Heterogeneity was assessed using the I^2 statistic and described as low (≤25%), moderate (>25% and ≤50%), or high (≥75%).[35] When data permitted, we assessed publication bias in the pooled estimates using the Stata15.0 metabias command to detect small study effects.[33] If the test of small study effects was significant, we used the Stata15.0 metatrim command to conduct Duval and Tweedie's[23] nonparametric trim and fill procedure and provide an adjusted treatment effect. We conducted sensitivity analyses using the inverse variance random effects model where I^2 values exceeded 50%. For the primary pain intensity outcomes (30% reduction in pain, 50% reduction in pain, and change in pain intensity), we conducted subgroup analyses to assess for differences in RCT-pooled estimates based on overall study risk of bias (low, unclear, or high), study risk of bias due to sample size (low [100+ participants per treatment arm], unclear [30-100 per arm], and high [<30 per arm]), intervention length (1-day studies, very short term [<4 weeks], short term [4-12 weeks], intermediate term [13-26 weeks], or long term [>26 weeks]), and imputation method (none/ITT, completer-only, or last observation carried forward). We followed Cochrane Collaboration methods to overcome unit-of-analysis errors for multiarm studies.[35] When raw data were not reported, we used the Generic Inverse Variance fixed-effect model to pool effect estimates and their standard errors.[35]

For dichotomous outcomes with at least a moderate GRADE rating, we calculated numbers needed to treat to benefit (NNTBs) and numbers needed to treat to harm (NNTHs) and their 95% CIs. We used pooled estimates of relative effect measures (ORs) to take into account the event rate in control groups.[11] Number needed to treat to benefit was calculated for the outcomes 30% reduction in pain, 50% reduction in pain, and change in patient global impression of change (PGIC). Number needed to treat to harm was calculated for all-cause AEs and study withdrawals due to AEs. Panel G1 in Appendix G summarises the core statistics and metrics used in this article (available online at http://links.lww.com/PAIN/A592).

3. Results

The combined searches resulted in 2525 results. In total, 91 publications were eligible and included in the review, which reported on 104 distinct studies (**Fig. 1**, Figure B1 Appendix B, available online at http://links.lww.com/PAIN/A592). **Table 1** (RCTs) and Table B1 in Appendix B (available online at http://links.lww.com/PAIN/A592) (observational studies) contain the list of included studies. The search additionally identified 17 ongoing studies for which results are yet to be reported (Appendix Table B2, available online at http://links.lww.com/PAIN/A592). Excluded studies are listed in Appendix Table B3 (appendices available online at http://links.lww.com/PAIN/A592).

3.1. Study characteristics

Characteristics of included studies, including sample characteristics, pain classification, cannabinoid classification, treatment length, dose, study outcomes, risk of bias rating, and imputation method are provided in **Table 1** (RCTs) and Appendix Table B1 (observational studies, available online at http://links.lww.com/PAIN/A592). The 104 studies comprised 47 RCTs (24 parallel RCTs and 23 cross-over RCTs), and 57 observational studies, comprising a total of 9958 participants (n = 4271 RCTs; 5687 observational studies). We contacted 9 authors for additional information; 6 responded and 2 provided data that were used in analyses. Most studies were conducted in Western Europe (n = 47) or the United States (n = 34, **Table 2**).

When possible, we have examined CNCP categories separately. Overall, we found 48 studies of neuropathic pain (of which 16 were multiple sclerosis [MS]-related and 32 were non–MS-related), 7 studies for fibromyalgia, 1 for arthritis (specifically rheumatoid arthritis), and 48 studies for other CNCP (of which 13 were MS-related pain, 6 were visceral pain, and 29 were studies of samples with mixed or undefined non–MS-related CNCP, and **Table 3**).

3.2. Characteristics of participants

Detailed characteristics of participants in the studies are provided in **Table 1** (RCTs) and Appendix Table B1 (available online at http://links.lww.com/PAIN/A592) (observational studies). Details of ongoing studies with no data available at time of current review are detailed in Appendix Table B2 (available online at http://links.lww.com/PAIN/A592). Details of studies excluded at the full-text review stage are presented in Appendix Table B3 (available online at http://links.lww.com/PAIN/A592). The number of participants ranged from 1 to 649, with a median of 42 (mean 136.8). All studies were conducted in adult samples, except for 2 case series of 2 adolescents (aged 14 and 15 years)[67] and an open-label trial in young girls with adverse drug effects after vaccination.[59] Where reported, mean age of adult participants ranged from 28[43] to 67[10] years (median 49.2, mean 50.5), and percentage of males ranged

from 0% to 100% (median 46.7%; mean 45.1%). Mean baseline pain intensity scores were 59.6 (SD = 14.6; range: 30.1-87.5) on a 100 mm VAS, suggesting that patients had moderate to severe pain intensity at study intake.[34]

Pain was the primary indication in 76 studies and a secondary indication in 28 studies. Of the 104 included studies, 4[12,64,69,77] (n = 47 participants) examined cannabinoids as a first-line therapy, and 87 examined cannabinoids as a second-line therapy in addition to existing medication regimens. In 13 studies, the place of cannabinoids in the therapeutic hierarchy was not reported or unclear. The most common other adjunct medications were opioids, nonsteroidal anti-inflammatory drugs, and antispasticity medications. In nearly all RCT studies, patients were required to be on a stable dose of current medication before commencement of the trial.

The most commonly studied cannabinoid was nabiximols, followed by *C. sativa*. See Table B4 (available online at http://links.lww.com/PAIN/A592) for more information on the cannabinoids used in the included trials, including route of administration, duration, and dose.

3.3. Risk of bias ratings

Most parallel and cross-over RCTs were rated as unclear risk of bias across all domains because information was not fully reported or could not be obtained from the authors (see Appendix C for ratings of risk of bias, available online at http://links.lww.com/PAIN/A592). Several were rated as at high risk of bias because of selective reporting or other biases, such as omission of data and CIs, changes in selection of the primary endpoint, or a failure to take account of within-subject effects in cross-over studies (Appendix C, Figures C1, C2, available online at http://links.lww.com/PAIN/A592). Observational studies were judged to be at serious or critical risk of bias for key domains because of confounding, intervention measurement, high dropout, and selection of the reported result (Figure C3, available online at http://links.lww.com/PAIN/A592).

3.4. Outcomes

Tables D1 and D2 in Appendix D (available online at http://links.lww.com/PAIN/A592) describe IMMPACT outcomes collected in RCTs and observational studies, respectively. The most commonly studied outcomes were pain intensity (n = 100), AEs (n = 81), and withdrawals (n = 71). Fewer studies reported on physical functioning (n = 52), emotional functioning (n = 43), and patient's global impression of change (n = 24). Only 2 studies in which pain was the primary indication reported on all 6 outcomes.[40,80]

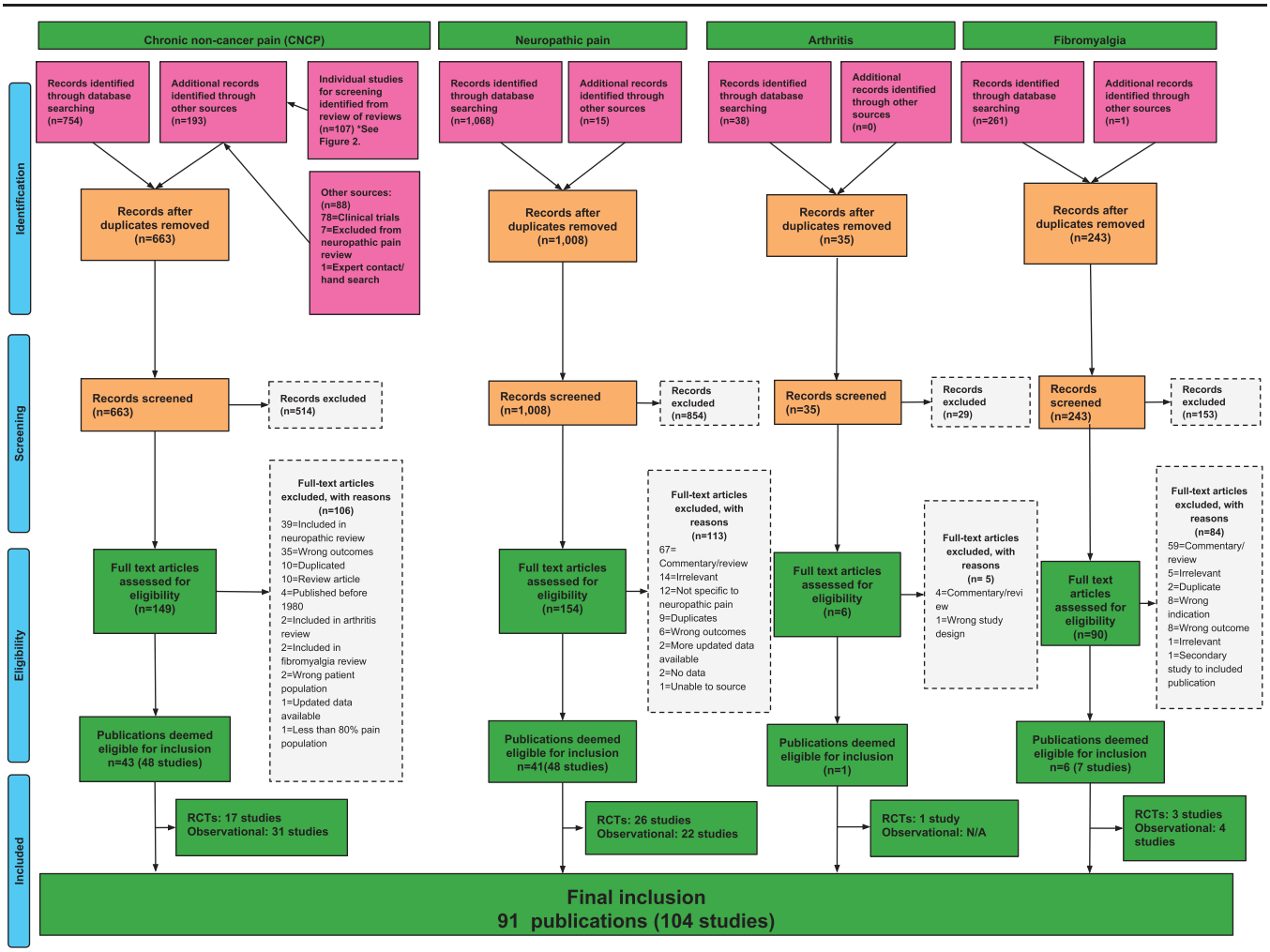

Figure 1. PRISMA flowchart showing the process of selection of studies into the review. See Figure B1 in Supplementary Appendix B (available online at http://links.lww.com/PAIN/A592) for the PRISMA flowchart of the systematic review of reviews. RCT, randomised controlled trial.

Table 1

Characteristics of included randomised controlled trials, n = 47.

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Abrams et al. (United States)[1]	Total N: 55 Age: 48.5 (6.5) Male %: 85.7	Neuropathic pain (HIV-related)	Analgesic Adjuvant Analgesics	*Cannabis sativa* (smoked)	5 d (very short-term study)	3.56% THC	50%: not assessed 30%: significant, positive effect* Pain intensity: significant, positive effect (data not reported in usable manner)	High/low risk All patients who remained in the study at each time point were included in the analysis
Ball et al. (United Kingdom—multicentre)[4]	Total N: 493 Age: 52.19 (7.8) Male %: 40.8	CNCP (MS-related)	Antispasticity and analgesic Adjuvant Paracetamol; NSAIDs; opioids; and antiepileptics	Dronabinol (oral)†	156 wk (long-term study)	15.085 mg (14-28 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	High/low risk ITT analysis
Berman et al. (United Kingdom)[6]	Total N: 48 Age: 39 (NR) Male %: 95.8	Neuropathic pain (Brachial plexus avulsion)	Analgesic Adjuvant Cointerventions: NR	(1) THC extract (oromucosal spray)† (2) Nabiximols (oromucosal spray)†	14 d (very short-term study) 14 d (very short-term study)	NR (max dose of 129.6 mg THC) NR (max dose of 129.6 mg THC and 120 mg CBD)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/high risk ITT analysis
Blake et al. (United Kingdom)[8]	Total N: 58 Age: 62.8 (9.8) Male %: 21	Rheumatoid arthritis	Analgesic; stiffness; and sleep Adjuvant Cointerventions: NSAIDs; prednisolone; and DMARDS	Nabiximols (oromucosal spray)†	5 wk (short-term study)	14.58 mg THC (2.7-16.2 mg) and 13.5 mg CBD (2.5-15 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/unclear risk ITT analysis
Carroll et al. (United Kingdom)[10]	Total N: 19 Age: 67 (NR) Male %: 63.2	CNCP (Parkinson disease–related)	Dyskinesia Adjuvant Cointerventions: antiparkinsonian medication	THC:CBD (oral)†	4 wk (short-term study)	Minimum dose of 5 mg THC and 2.5 mg CBD	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk NR
Chung et al. (Canada)[12]	Total N: 6 Age: NR Male %: 0	Fibromyalgia	Analgesic and sleep NR Cointerventions: NR	Nabilone (oral)†	4 wk (short-term study)	NR	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (data not reported, only *P* value given)	Low/unclear risk NR

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Collin et al. (multicentre—15 centres in United Kingdom and 8 in Czech Republic)[14]	Total N: 337 Age: 48 (9.61) Male %: 39	CNCP (MS-related)	Spasticity (primary); tremor; analgesic; fatigue; sleep quality; bladder function; and quality of life Adjuvant Cointerventions: antispasticity agents	Nabiximols (oromucosal spray)†	14 wk (intermediate-term study)	22.95 mg THC (2.7-59.4 mg) and 21.25 mg CBD (2.5-55 mg)	50%: not assessed 30%: no benefit (data for control group not presented) Pain intensity: no benefit*	High/unclear risk ITT analysis
Corey-Bloom et al. (United States)[15]	Total N: 37 Age: 51 (8) Male %: 37	CNCP (MS-related)	Antispasticity and analgesic Adjuvant Cointerventions: antispasticity agents	*C. sativa* (smoked)	3 d (very short-term study)	4% THC (800 mg plant material)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/unclear risk Other: worst-case scenario sensitivity analysis
de Vries et al. (Netherlands)[18]	Total N: 25 Age: 51.8 (9.3) Male %: 62.5	CNCP—visceral (Visceral—due to chronic pancreatitis)	Analgesic Adjuvant Cointerventions: 23/24 (95.8%) of participants used concomitant medications, including opioids, NSAIDs, paracetamol, anticonvulsants, antidepressants, and pancreatic enzymes	Dronabinol (oral)†	1 d (very short-term study)	8 mg	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk Patients who withdrew were replaced
de Vries et al. (Netherlands)[19]	Total N: 65 Age: 52.9 (9.65) Male %: 50	CNCP—visceral (Visceral—due to chronic pancreatitis)	Analgesic; health-related quality of life; sleep; and change in functioning Adjuvant Cointerventions: paracetamol; NSAIDs; opioids; and antiepileptics	Dronabinol (oral)†	50-52 d (short-term study)	NR (9-24 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk Patients who withdrew were replaced
Ellis et al. (United States)[26]	Total N: 34 Age: 49.1 (6.9) Male %: 97	Neuropathic pain (HIV-related)	Analgesic Adjuvant Cointerventions: opioids; NSAIDs; antidepressants; and anticonvulsants	*C. sativa* (smoked)	5 d (very short-term study)	NR (1-8% THC)	50%: not assessed 30%: significant, positive effect (cross-over data not presented in usable format) Pain intensity: significant, positive effect (cross-over data not presented in usable format)	Moderate/unclear risk Other: missing values were imputed from the most unfavourable (ie, highest) 50% of the observed (completers) values

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Frank et al. (United Kingdom)[29]	Total N: 96 Age: 50.15 (13.69) Male %: 52	Neuropathic pain (Mixed aetiologies: pain after injury or surgery; demyelination; complex regional pain syndrome; diabetic neuropathy; postherpetic neuralgia, and others)	Analgesic Adjuvant Cointerventions: analgesics	Nabilone (oral)†	6 wk (short-term study)	NR (0.25-2 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit (dihydrocodeine superior to nabilone)*	High/unclear risk Other: missing data from the past 2 weeks were substituted with data from the preceding week (if no data, then the treatment period was excluded)
Hagenbach et al. (c) (Switzerland)[31]	Total N: 13 Age: 42.6 (NR) Male %: 92	CNCP (Spinal cord injury)	Antispasticity and analgesic Adjuvant Cointerventions: NR	Dronabinol (oral)†	NR	NR (20-60 mg)	50%: not assessed 30%: not assessed Pain intensity: assessed but outcomes not reported	High/unclear risk NR
Karst et al. (Germany)[39]	Total N: 21 Age: 50.86 (11.69) Male %: 61.9	Neuropathic pain (Mixed aetiologies, including lesions to cervicobrachial plexus, left maxillary nerve, left trigeminal nerve, etc.)	Analgesic Adjuvant Cointerventions: analgesics; NSAIDs; opioids; anticonvulsant; and tricyclic antidepressants	CT-3 (oral)†	1 wk (very short-term study)	NR (40-80 mg)	50%: no benefit* 30%: no benefit* Pain intensity: significant, positive effect*	Moderate/low risk Other: 2 patients whom dropped out early in the study had their data excluded
Langford et al. (multicentre—12 centres in United Kingdom, 7 in Czech Republic, 5 in Canada, 5 in Spain, and 4 in France)[40]	Total N: 339 Age: 48.97 (10.47) Male %: 32	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: anticonvulsant; NSAID; analgesics; tricyclic antidepressants; opioids; and antiarrhythmic	Nabiximols (oromucosal spray)†	14 wk (intermediate-term study)	23.76 mg THC and 22 mg CBD (max dose of 32.4 mg THC and 30 mg CBD)	50%: no benefit* 30%: no benefit* Pain intensity: no benefit*	High/low risk ITT analysis
Lynch et al. (Canada)[42]	Total N: 18 Age: 56 (10.8) Male %: 16.7	Neuropathic pain (Chemotherapy-induced)	Analgesic Adjuvant Cointerventions: analgesics	Nabiximols (oromucosal spray)†	4 wk (short-term study)	21.6 mg THC (8.1-32.4 mg) and 20 mg CBD (7.5-30 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit (cross-over data not reported in usable format)	Moderate/low risk LOCF

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Narang et al. (United States)[47]	Total N: 30 Age: 43.76 (11.8) Male %: 46.7	CNCP (Neuropathic pain [n = 7]; nociceptive pain [n = 7]; mixed neuropathic and nociceptive [n = 11]; and uncategorised pain [n = 6])	Analgesic Adjuvant Cointerventions: opioids	(1) Dronabinol (oral)† 10 mg (2) Dronabinol (oral)† 20 mg	1 d (very short-term study) 1 d (very short-term study)	10 mg 20 mg	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (incomplete data reported)	Moderate/low risk LOCF
NCT00710424 (GW Pharmaceuticals 2008) (United Kingdom, Czech Republic, and Romania)[49]	Total N: 297 Age: 59.5 (10.54) Male %: 61.6	Neuropathic pain (Diabetes-related)	Analgesic Adjuvant Cointerventions: analgesics	Nabiximols (oromucosal spray)†	14 wk (intermediate-term study)	Max dose of 65 mg THC and 60 mg CBD	50%: not assessed 30%: no benefit* Pain intensity: no benefit*	High/unclear risk NR
NCT01606176 (GW Pharmaceuticals 2012) (United Kingdom)[51]	Total N: 70 Age: 54.58 (11.57) Male %: 41.4	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: analgesics	Nabiximols (oromucosal spray)†	3 wk (very short-term study)	Max dose of 120 mg THC and 120 mg CBD	50%: not assessed 30%: not assessed Pain intensity: no benefit*	High/unclear risk NR
NCT01606202 (GW Pharmaceuticals 2012b) (United Kingdom and Romania)[50]	Total N: 116 Age: 48.1 (12.69) Male %: 78.4	Neuropathic pain (Spinal cord injury)	Analgesic Adjuvant Cointerventions: NR	Nabiximols (oromucosal spray)†	3 wk (very short-term study)	NR (max dose of 130 mg THC and 120 mg CBD)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk NR
Novotna et al. (multicentre—18 centres in United kingdom, 11 in Spain, 10 in Poland, 8 in Czech Republic, and 5 in Italy)[54]	Total N: 241 Age: 48.6 (9.33) Male %: 40	CNCP (MS-related)	Antispasticity Adjuvant Cointerventions: antispasticity agents and disease-modifying medications	Nabiximols (oromucosal spray)†	12 wk (short-term study)	22.41 mg THC and 20.75 mg CBD (max dose of 32.4 mg THC and 30 mg CBD)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/high risk ITT analysis
Nurmikko et al. (multicentre—5 centres in United Kingdom and 1 in Belgium)[56]	Total N: 125 Age: 53.34 (15.5) Male %: 40.8	Neuropathic pain (Mixed aetiologies, eg, focal nerve lesion; peripheral neuropathy; postherpetic neuralgia; complex regional pain syndrome, etc).	Analgesic Adjuvant Cointerventions: antiepileptic; tricyclic; opioids; analgesics; and anti-inflammatory	Nabiximols (oromucosal spray) †	5 wk (short-term study)	29.403 mg THC (3.51-84.78 mg) and 27.225 mg CBD (3.25-78.5 mg)	50%: no benefit* 30%: no benefit* Pain intensity: significant, positive effect*	High/low risk ITT analysis

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Pini et al. (Italy)[61]	Total N: 30 Age: 52.7 (9.6) Male %: 33.3	CNCP (Medication overuse headache pain)	Analgesic Adjuvant Cointerventions: analgesics	Nabilone (oral)†	8 wk (short-term study)	0.5 mg	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (cross-over data not presented in usable format)	Moderate/low risk NR
Pinsger et al. (Austria)[62]	Total N: 30 Age: NR Male %: 71	CNCP (Mixed conditions, eg, cervical syndrome; lumbago and thoracic syndrome; intervertebral disk prolapse; etc.)	Analgesic Adjuvant Cointerventions: NR	Nabilone (oral)†	4 wk (short-term study)	NR (0.25-1 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit (cross-over data not presented in usable format)	Moderate/unclear risk ITT analysis
Rintala et al. (United States)[64]	Total N: 7 Age: 50.1 (8.3) Male %: 71.4	Neuropathic pain (Spinal cord injury)	Analgesic Primary Cointerventions: not applicable	Dronabinol (oral)†	8 wk (short-term study)	NR (5-20 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk NR
Riva et al. (4 centres in Italy)[65]	Total N: 60 Age: NR Male %: NR	CNCP (Amyotrophic lateral sclerosis–related)	Antispasticity; sleep; analgesic; change in functioning; and appetite adjuvant Cointerventions: antispasticity therapy	Nabiximols (oromucosal spray)†	6 wk (short-term study)	NR	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (data not reported)	Moderate/unclear risk NR
Rog et al. (United Kingdom)[66]	Total N: 66 Age: 49.2 (8.3) Male %: 21.2	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: analgesics (eg, acetaminophen; opioids; NSAIDs; etc.)	Nabiximols (oromucosal spray) †	4 wk (short-term study)	25.92 mg THC (5.4-67.5 mg) and 24 mg CBD (5-62.5 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	High/low risk ITT analysis
Schimrigk et al. (a) (Germany)[68]	Total N: 240 Age: 47.7 (9.7) Male %: 27.1	Neuropathic pain (MS-related)	Analgesic and quality of life Adjuvant Cointerventions: analgesics (most common was gabapentin [20.8% of patients])	Dronabinol (NR)†	16 wk (intermediate-term study)	12.7 mg (0-15.9 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/low risk ITT analysis

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Selvarajah et al. (United Kingdom)[71]	Total N: 30 Age: 56.3 (10.29) Male %: 63.3	Neuropathic pain (Diabetes-related)	Analgesic; health-related quality of life; and mental health Adjuvant Cointerventions: preexisting neuropathic pain treatment	Nabiximols (oromucosal spray)†	12 wk (short-term study)	NR	50%: not assessed 30%: no benefit* Pain intensity: no benefit*	Moderate/unclear risk ITT analysis
Serpell et al. (multicentre—21 centres in United Kingdom, 7 in Czech Republic, 6 in Romania, 4 in Belgium, and 1 in Canada)[72]	Total N: 246 Age: 57.3 (14.2) Male %: 39	Neuropathic pain (Focal nerve lesion [n = 96]; postherpetic neuralgia [n = 64]; peripheral neuropathy [n = 60]; and complex regional pain syndrome type II [n = 31])	Analgesic; health-related quality of life; and sleep Adjuvant Cointerventions: analgesics (eg, tricyclic antidepressants; antiepileptics; natural opium alkaloids; opioids; etc.)	Nabiximols (oromucosal spray)†	14 wk (intermediate-term study)	24.03 mg THC and 22.25 mg CBD (max dose of 64.8 mg THC and 60 mg CBD)	50%: no benefit* 30%: significant, positive effect* Pain intensity: no benefit*	High/low risk ITT analysis—however, 6 patients were not included in the analysis, as they had no on-treatment efficacy data
Skrabek et al. (Canada)[74]	Total N: 40 Age: 47.6 (9.13) Male %: 7	Fibromyalgia	Analgesic and quality of life Adjuvant Cointerventions: NR	Nabilone (oral)†	4 wk (short-term study)	NR (0.5-2 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (data not presented)	Moderate/unclear risk NR
Svendsen et al. (Denmark)[77]	Total N: 24 Age: NR Male %: 41.7	Neuropathic pain (MS-related)	Analgesic Primary Cointerventions: not applicable	Dronabinol (oral)†	20 d (very short-term study)	NR (2.5-10 mg)	50%: no benefit* 30%: not assessed Pain intensity: significant, positive effect*	Moderate/low risk ITT analysis
Turcotte et al. (Canada)[81]	Total N: 15 Age: 45.5 (10.84) Male %: 13.3	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: gabapentin	Nabilone (oral) †	9 wk (short-term study)	NR (0.5-2 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (data not presented)	Moderate/low risk Other: missing data were imputed separately for each study group by calculating the midpoint of the average group scores
van Amerongen et al. (a) (Netherlands)[83]	Total N: 24 Age: 54.3 (8.9) Male %: 33.3	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: spasmolytic therapy	THC extract (oral)†	NR	16 mg	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk NR

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
van Amerongen et al. (b) (Netherlands)[83]	Total N: 24 Age: 54.3 (8.9) Male %: 33.3	Neuropathic pain (MS-related)	Analgesic Adjuvant Cointerventions: spasmolytic therapy	THC extract (oral)†	4 wk (short-term study)	21.75 mg (9-29 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/unclear risk NR
Wade et al. (United Kingdom)[87]	Total N: 20 Age: 48 (NR) Male %: 50	Neuropathic pain (Mixed aetiologies: MS-related [n = 14]; spinal cord injury [n = 4]; brachial plexus lesion and neuropathy [n = 1]; and phantom limb pain [n = 1])	Neurogenic symptoms: analgesic; antispasticity; impaired bladder control; and tremor Adjuvant Cointerventions: NR	(1) THC extract (sublingual spray)† (2) CBD extract (sublingual spray)† (3) THC:CBD extract (sublingual spray)†	8 wk (short-term study) 8 wk (short-term study) 8 wk (short-term study)	NR (2.5-120 mg) NR (2.5-120 mg) NR (2.5-120 mg THC and 2.5-120 mg CBD)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect (cross-over data not presented in usable format)	Moderate/unclear risk NR
Wade et al. (United Kingdom)[86]	Total N: 160 Age: 50.7 (NR) Male %: 38	CNCP (MS-related)	Antispasticity; analgesic Adjuvant Cointerventions: NR	Nabiximols (oromucosal spray)†	6 wk (short-term study)	Max dose of 120 mg THC and 120 mg CBD	50%: not assessed 30%: not assessed Pain intensity: no benefit*	High/high risk NR
Wallace et al. (United States)[89]	Total N: 16 Age: 56.9 (8.2) Male %: 56	Neuropathic pain (Diabetes-related)	Analgesic Adjuvant Cointerventions: other diabetes medication; opioids; and NSAIDs	*C. sativa* (vaporised)†	1 d (very short-term study)	(1) 1% (2) 4% (3) 7%	50%: not assessed 30%: no benefit (cross-over data not presented in usable format) Pain intensity: significant, positive effect (cross-over data not presented in usable format)	Moderate/unclear risk NR
Ware et al. (Canada)[90]	Total N: 31 Age: 49.5 (11.2) Male %: 16	Fibromyalgia	Sleep; analgesic; mood; quality of life; and global satisfaction Adjuvant Cointerventions: NR	Nabilone (oral)†	2 wk (very short-term study)	NR (0.5-1 mg)	50%: not assessed 30%: not assessed Pain intensity: no benefit*	Moderate/low risk NR
Ware et al. (Canada)[92]	Total N: 23 Age: 45.4 (12.3) Male %: 47.8	Neuropathic pain (Due to trauma or surgery)	Analgesic Adjuvant Cointerventions: opioids; antidepressants; anticonvulsants; and NSAIDs	*C. sativa* (smoked)†	5 d (very short-term study)	(1) 2.5% (2) 6.0% (3) 9.4%	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/unclear risk ITT analysis

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N Age: mean (SD) Male %	Pain classification (Specific condition)	Indication(s) Place in therapeutic hierarchy Cointerventions	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB Analysis method
Wilsey et al. (United States)[95]	Total N: 38 Age: NR Male %: 52.6	Neuropathic pain (Mixed aetiologies: spinal cord injury; complex regional pain syndrome; diabetic neuropathy; multiple sclerosis; etc)	Analgesic Adjuvant Cointerventions: NR	*C. sativa* (vaporised)	1 d (very short-term study)	(1) 3.5% (2) 7%	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/unclear risk ITT analysis
Wilsey et al. (United States)[94]	Total N: 39 Age: 50 (11) Male %: 71.7	Neuropathic pain (Mixed aetiologies: spinal cord injury; complex regional pain syndrome; diabetic neuropathy; multiple sclerosis; etc.)	Analgesic Adjuvant Cointerventions: NR	*C. sativa* (vaporised)	1 d (very short-term study)	(1) 1.29% (2) 3.53%	50%: not assessed 30%: significant, positive effect (data not presented) Pain intensity: significant, positive effect (data not presented)	Moderate/unclear risk ITT analysis
Wilsey et al. (United States)[96]	Total N: 42 Age: 46.4 (13.6) Male %: 69	Neuropathic pain (Spinal cord injury)	Analgesic Adjuvant Cointerventions: analgesics	*C. sativa* (vaporised)	1 d (very short-term study)	(1) 2.9% (2) 6.7%	50%: not assessed 30%: significant, positive effect (data not presented) Pain intensity: significant, positive effect	Moderate/high risk NR
Wissel et al. (Switzerland)[97]	Total N: 13 Age: 44.8 (14.38) Male %: 30.7	CNCP (Upper motor neuron syndrome)	Analgesic Adjuvant Cointerventions: premedication and physical therapy	Nabilone (oral)†	4 wk (short-term study)	NR (0.5-1 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	Moderate/unclear risk NR
Wong et al. (United States)[98]	Total N: 75 Age: 41 (NR) Male %: NR	CNCP—visceral (IBS-related)	Anticolonic NR Cointerventions: NR	Dronabinol (NR)†	1 d (very short-term study)	(1) 2.5 mg (2) 5 mg	50%: not assessed 30%: not assessed Pain intensity: no benefit (incomplete data reported)	High/unclear risk Other: missing data were imputed using the overall subjects' mean (or median)
Zajicek et al. (United Kingdom)[99]	Total N: 630 Age: 50.55 (7.9) Male %: 33.65	CNCP (MS-related)	Antispasticity and analgesic Adjuvant Cointerventions: antispasticity agents	(1) Dronabinol (oral)† (2) THC:CBD extract (oral)†	14 wk (intermediate-term study) 14 wk (intermediate-term study)	NR (10-25 mg) NR (10-25 mg THC and 5-12.5 mg CBD)	50%: not assessed 30%: significant, positive effect* Pain intensity: not assessed	High/low risk ITT analysis

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Sample N	Pain classification	Indication(s)	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)	Pain outcomes	GRADE methodology rating/RoB
	Age: mean (SD)	(Specific condition)	Place in therapeutic hierarchy					Analysis method
	Male %		Cointerventions					
Zajicek et al. (22 centres in United Kingdom)[100]	Total N: 277 Age: 51.94 (7.8) Male %: 36.8	CNCP (MS-related)	Antispasticity and analgesic Adjuvant Cointerventions: physiotherapy; antispasticity agents; and analgesics	THC extract (oral)†	12 wk (short-term study)	17.1 mg (5-25 mg)	50%: not assessed 30%: not assessed Pain intensity: significant, positive effect*	High/low risk LOCF

* Study had sufficient data and was used in meta-analysis. Reasons are provided in parentheses for why studies reporting an outcome were not used in meta-analysis.
† Cannabinoid was pharmaceutical grade.
CBD, cannabidiol; CNCP, chronic noncancer pain; DMARDs, disease-modifying antirheumatic drugs; IBS, inflammatory bowel syndrome; ITT, intention to treat; LOCF, last observation carried forward; MS, multiple sclerosis; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; RoB, risk of bias; THC, Δ-9-tetrahydrocannabinol.

3.5. Pain

3.5.1. Thirty percent reduction in pain

3.5.1.1. Randomised controlled trial evidence

Of the 47 included RCTs, 13 assessed 30% reduction in pain (Table D1 in Appendix D, available online at http://links.lww.com/PAIN/A592), of which 8 RCTs (based on 9 data points) reported sufficient data and were used in the meta-analysis. Across all cannabinoids and CNCP conditions, cannabinoids were more likely than placebo groups to produce a 30% reduction in pain[1,37,39,40,56,71,72,99] (n = 1734, OR 1.46, 95% CI 1.16-1.84, **Table 4** and Table E1 and Figure E1 in Appendix E, available online at http://links.lww.com/PAIN/A592). A summary of key outcomes, including NNTB is shown in **Table 6**. No evidence of small study effects was detected ($P = 0.08$). We found significant effects for plant-based cannabis, THC:CBD extract, and ajulemic acid, but these were each based on a single study and our GRADE ratings for these estimates was moderate to very low. Among the specific pain conditions, we found effects for neuropathic pain and MS-related CNCP (**Table 4** and Figure E1, available online at http://links.lww.com/PAIN/A592). Of the remaining 5 studies that assessed 30% reduction in pain but for which data were not reported or obtained from study authors, 3 reported a significant positive effect and 2 reported no benefit. When examined by overall study risk of bias rating and risk of bias due to sample size, the effect estimate remained significant for studies classified as having low risk and for studies with more than 100 participants per treatment arm, but was not significant for studies at unclear risk of bias, or for studies with less than 100 participants per arm, with notably larger but nonsignificant effects for the smallest studies (<30 participants per arm; Figures E1.1 and E1.1a, available online at http://links.lww.com/PAIN/A592). No significant differences in effect sizes were identified between studies with interventions of very short term (<4 weeks), short term (4-12 weeks), and intermediate term (13-26 weeks, Figure E1.2, available online at http://links.lww.com/PAIN/A592). All studies assessed outcomes using ITT analyses without imputation.

3.5.1.2. Observational evidence

In observational studies with a comparison group, one small open-label study with a randomised withdrawal phase (n = 26[80]) found that nabilone was significantly more likely to produce a 30% reduction in pain relative to placebo (**Table 4**). In observational studies with no comparison group, the pooled prevalence of receiving cannabinoids reported achieving a 30% reduction in pain was 72% (95% CI 66%-78%) (Figure E5 and Appendix F, available online at http://links.lww.com/PAIN/A592).

3.5.2. Fifty percent reduction in pain

3.5.2.1. Randomised controlled trial evidence

Five of the 47 included RCTs assessed 50% reduction in pain, all of which provided sufficient data for meta-analysis. We found no significant evidence that cannabinoids reduced pain by 50% compared with placebo groups (OR 1.43, 95% CI 0.97-2.11, **Table 4** and Table E1 and Figure E2 in Appendix E, available online at http://links.lww.com/PAIN/A592). We found no effect for any of the specific cannabinoids; however, among pain conditions, a significant effect was found for non–MS-related neuropathic pain (**Table 4**). No evidence of small study effects was detected

($P = 0.12$). No subgroup analysis was able to be conducted for overall study risk of bias, as all studies were classified as low risk. When examined by risk of bias due to sample size, effects were larger and had substantial uncertainty for studies of <100 participants per treatment arm compared with studies with 100+ participants, but all estimates fell within overlapping bounds of uncertainty and were nonsignificant (Figure E2.1.a, available online at http://links.lww.com/PAIN/A592). No differences were detected between studies with interventions of very short term (<4 weeks), short term (4-12 weeks), and intermediate term (13-26 weeks, Figures E2.1 and E2.2, available online at http://links.lww.com/PAIN/A592). All studies assessed outcomes using ITT analyses without imputation.

3.5.2.2. Observational evidence

Two observational studies with a comparison group found evidence of a significant effect for 50% reduction in pain; however, the GRADE rating for this outcome was very low (**Table 4** and Table E1 in Appendix E, available online at http://links.lww.com/PAIN/A592). Outcomes for observational studies with no comparison group were equivocal and are summarised narratively in Appendix F (available online at http://links.lww.com/PAIN/A592).

3.5.3. Change in pain intensity

3.5.3.1. Randomised controlled trial evidence

Of the 47 RCTs included in the review, 45 reported data on pain intensity, of which 30 (comprising 34 data points) reported sufficient data and were used in the meta-analysis for change in pain intensity. We found that cannabinoids overall produced a larger reduction in pain intensity than placebo groups (SMD −0.14, 95% CI −0.20 to −0.08, **Table 4** and Table E1 and Figure E3 in Appendix E, available online at http://links.lww.com/PAIN/A592). We calculated this to be roughly equivalent to a reduction of 2.9 mm on a 100 mm VAS (95% CI −4.61 to −1.46) greater than placebo groups. Among the cannabinoids, there were significant effects for nabiximols and THC extract, both with a moderate GRADE rating (Table E1, available online at http://links.lww.com/PAIN/A592). We found an effect for neuropathic pain (MS and non–MS-related) and rheumatoid arthritis, but the latter was based on 1 small study and had a very low-grade rating (**Table 4**). No evidence of small study effects was detected ($P = 0.49$). Of the remaining 15 studies that assessed pain intensity but for which data were not reported or obtained from study authors, 12 reported a significant positive effect and 3 reported no benefit. When examined by overall risk of bias rating, the effect estimate remained significant for studies classified as low risk but was not significant for studies at unclear or high risk of bias (Figure E3.1, available online at http://links.lww.com/PAIN/A592), and effect sizes were larger for studies with smaller sample sizes (Figure E3.1a, available online at http://links.lww.com/PAIN/A592). When examined by study, intervention length effects seemed to dissipate with increasing study length: 1-day and very short term (<4 weeks) studies remained significant; however, studies conducted in the short (4-12 weeks), intermediate (13-26 weeks), or long term (>26 weeks) did not, with decreasing effect sizes as study length increased (Figure E3.2, available online at http://links.lww.com/PAIN/A592). The effect remained significant for studies using ITT analyses, however, was smaller and not significant for studies using last observation carried forward imputation methods, or where the handling of missing data was not reported (Figure E3.3, available online at http://links.lww.com/PAIN/A592).

3.5.3.2. Observational evidence

In the observational studies with a comparison group, we found no significant evidence of effect for cannabinoids in reducing pain intensity (**Table 4**). A significant reduction in pain intensity was identified in within-person pre–post assessments of pain in observational studies with no comparison group (Appendix F, available online at http://links.lww.com/PAIN/A592). Five RCTs examined reductions in analgesic use. People taking nabiximols had a greater reduction in the frequency and quantity of use of rescue analgesics compared with placebo groups (SMD −0.13, 95% CI −0.26 to −0.01, $I^2 = 48\%$); this had a moderate GRADE rating.

3.6. Physical functioning

No significant effect of cannabinoids on overall physical functioning in 18 RCTs, Table E2 and Figure E6 (available online at http://links.lww.com/PAIN/A592) or quality of life (n = 11 RCTs) compared with placebo groups was found (Table E2 and Figure E8, available online at http://links.lww.com/PAIN/A592). There was a significant effect of cannabinoids in reducing sleep problems when compared with placebo groups (SMD −0.29, 95% CI −0.40 to −0.19), but the GRADE assessment for this was low (Table E2 and Figure E7, available online at http://links.lww.com/PAIN/A592). We found a reduction in sleep problems when compared with placebo groups for nabiximols with a moderate GRADE rating (SMD −0.32, 95% CI −0.44 to −0.20, Table E3 in Appendix E, available online at http://links.lww.com/PAIN/A592). No small study effects were detected for any of these outcomes (P's range from 0.14 to 0.84).

3.7. Emotional functioning

Patients receiving any cannabinoids did not report any difference compared with comparator groups in overall emotional functioning, or in depressive or anxiety symptoms specifically (Table E2 and Figures E9–E11, available online at http://links.lww.com/PAIN/A592). No evidence of small study effects was identified for overall emotional functioning ($P = 0.10$) or anxiety symptoms ($P = 0.06$); however, a significant effect was detected for depression ($P = 0.01$). The trim and fill procedure to account for small study effects revealed that the adjusted estimate did not differ significantly from the original estimate (SMD 0.04, 95% CI −0.14 to 0.22, Table E2, available online at http://links.lww.com/PAIN/A592). A significant improvement in emotional functioning was identified for dronabinol compared with placebo based on a single study; we had low confidence in this effect (Table E3 in Appendix E, available online at http://links.lww.com/PAIN/A592).

3.8. Patient global impression of change

In the 4 RCTs which reported PGIC as a continuous outcome on the 7-item PGIC scale, there were significant increases among patients receiving any cannabinoid compared with placebo (Table E2 and Figure E12, available online at http://links.lww.com/PAIN/A592), with no evidence of small study effects ($P = 0.28$). Nine RCTs reported PGIC scores as a dichotomous outcome (much or very much improved vs slightly improved, no change, or worse), with significant improvement among patients receiving any cannabinoid compared with placebo (**Table 4** and Figure E13, available online at http://links.lww.com/PAIN/A592), and no evidence of small study effects ($P = 0.3$). Confidence in these outcomes was low to very low. Most of the evidence was for nabiximols, with some evidence for nabilone, *C. sativa*, and THC extract.

Table 2

Characteristics of included studies.

	N studies
Study design	
Randomised controlled trials (RCTs)	47
Parallel RCT	24
Cross-over RCT	23
Observational studies	57
Open-label trial	29
Prospective study	9
Survey—cross-sectional or retrospective	9
Chart review	4
Case series	6
GRADE ranking of study quality	
Very low	22
Low	24
Moderate	43
High	15
Region	
North America	34
Western Europe	47
Other and multiple regions	23
Year of study	
1980-1990	1
1991-2000	1
2001-2010	45
2011-2017	16
Not recorded	41
Conflict of interest declared by authors	
Yes—none	36
Yes—potential conflict	35
Not declared	33
Outcomes collected according to IMMPACT recommendations	
Pain intensity	100
30% reduction in pain	18
50% reduction in pain	10
Reduction in use of rescue analgesics	8
Physical functioning	52
Emotional functioning	43
Global impression of change	24
Adverse events	81
Study withdrawals	71

GRADE, Grades of Recommendation, Assessment, Development and Evaluation tool; IMMPACT, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

Table 3

Characteristics of participants and interventions.

Characteristics of participants, where reported in studies	
Median no. of participants	40
Median % women	53.3
Median age of participants	49.5
Pain condition	N studies
Neuropathic pain	48
MS-related	16
Non–MS-related	32
Fibromyalgia	7
Arthritis (rheumatoid)	1
Chronic noncancer pain	48
MS-related	13
Non–MS-related	29
Visceral pain	6
Reported % previously cannabinoid-naive	3
Cannabinoid used	
Cannabis sativa	26
THC extract	11
Nabiximols	24
THC:CBD extracts	3
CBD extract	2
Dronabinol	18
Nabilone	17
THC-HS	1
Unknown	1
Pharmaceutical grade product	
Yes	74
No	19
Unsure/unknown	11
Route of administration	
Vapourised	6
Smoked	7
Oral	42
Oral mucosal spray	30
Mixed routes	9
Not recorded	9
Rectal	1
Median duration of treatment (wk)	8
Primary indication for cannabinoid	
Analgesia	76
Spasticity	19
Other including mixed or physical, social functioning, and quality of life	9
Place in therapeutic hierarchy	
Primary	4
Adjuvant	87
Not reported and could not be determined	13

CBD, cannabidiol; MS, multiple sclerosis; THC, Δ-9-tetrahydrocannabinol; THC-HS, THC-hemisuccinate.

3.9. Study withdrawals

Patients with CNCP who received a cannabinoid had 2 times the odds of withdrawing from a trial for any reason than patients who received placebo (Table E4 in Appendix E, available online at http://links.lww.com/PAIN/A592). They had 3.47 times the odds of withdrawing because of AEs (**Table 5**); no evidence of small study effects was found ($P = 0.44$). Patients with CNCP who received placebo were slightly more likely to withdraw from trials because of a lack of efficacy than those receiving cannabinoids. There was some variation between cannabinoids in reasons for withdrawal (Table E4 in Appendix E, available online at http://links.lww.com/PAIN/A592).

3.10. Adverse events

Patients with CNCP receiving cannabinoids had 2.33 times the odds of experiencing an AE compared with placebo groups (**Table 5** and Table E4 in Appendix E, available online at http://links.lww.com/PAIN/A592). Significant evidence of small study effects was detected ($P = 0.01$); however, the adjusted estimate did not differ significantly from the original (OR = 2.22, 95% CI 1.60-3.01). Serious AEs were reported in a smaller number of studies (**Table 5**), and patients receiving cannabinoids had higher rates of serious AEs, but this did not reach statistical significance. No small study effects were detected ($P = 0.52$). Compared with placebo groups, patients receiving cannabinoids were more likely to report individual AEs such as dizziness (OR 5.52, 95% CI 4.47-6.83), cognitive attention or disturbance (OR 5.67, 95% CI 2.72-11.79), and confusion and disorientation (OR 5.35, 95% CI 2.31-12.39, **Table 5**).

Table 4

Effect sizes for pain-related outcomes from meta-analyses of RCTs and observational studies of any cannabinoid in CNCP, by outcome type, CNCP condition, and comparator, with associated GRADE rating.

Outcome study type	Refs	N studies (N part.)	Medical condition	Comparator	Summary estimate (95% CI)	Favours	I^2	GRADE rating*
30% reduction in pain								
Parallel RCT; and cross-over RCT†	**1,39,40,49,56,71,72,80**	**7 (1105)**	**Neuropathic pain**	**Placebo**	**OR 1.31 (1.02 to 1.69)**	**Cannabinoid**	**48%**	⊕⊕◯◯ **Low**
Parallel RCT; and cross-over RCT†		6 (766)	Non–MS-related	Placebo	OR 1.36 (0.99 to 1.86)‡	Neither‡	57%‡	⊕◯◯◯ Very low
Parallel RCT	40	1 (339)	MS-related	Placebo	OR 1.22 (0.80 to 1.87)	Neither	n/a	⊕⊕⊕◯ Moderate
—		0 (0)	Fibromyalgia	Placebo	No studies	—	—	—
—		0 (0)	Arthritis	Placebo	No studies	—	—	—
Parallel RCT	**99**	**2 (502)**	**CNCP—mixed**	**Placebo**	**OR 2.38 (1.35 to 4.22)**	**Cannabinoid**	**0%**	⊕⊕⊕◯ **Moderate**
Parallel RCT	**99**	**2 (502)**	**MS-related CNCP**	**Placebo**	**OR 2.38 (1.35 to 4.22)**	**Cannabinoid**	**0%**	⊕⊕⊕◯ **Moderate**
—		0 (0)	Non–MS-related	Placebo	No studies	—	—	—
—		0 (0)	Visceral pain	Placebo	No studies	—	—	—
All RCTs	**1,39,40,56,71,72,78,99**	**9 (1734)**	**All pain types**	**Placebo**	**OR 1.46 (1.16 to 1.84)‡**	**Cannabinoid‡**	52%‡	⊕⊕⊕◯ **Moderate**
Observational§	**80**	**1 (26)**	**Non–MS-related neuropathic pain**	**Placebo**	**OR 8.80 (1.35 to 57.43)**	**Cannabinoid**	n/a	⊕◯◯◯ **Very low**
50% reduction in pain								
Parallel RCT	39,40,56,72,77	5 (753)	Neuropathic pain	Placebo	OR 1.43 (0.97 to 2.11)	Neither	25%	⊕⊕⊕◯ Moderate
Parallel RCT	40,77	2 (363)	MS-related	Placebo	OR 1.19 (0.75 to 1.89)‖	Neither‖	61%‖	⊕⊕◯◯ Low
Parallel RCT	**39,56,72**	**3 (390)**	**Non–MS-related**	**Placebo**	**OR 2.22 (1.09 to 4.49)**	**Cannabinoid**	**0%**	⊕⊕◯◯ **Low**
—		0 (0)	Fibromyalgia	Placebo	No studies	—	—	—
—		0 (0)	Arthritis	Placebo	No studies	—	—	—
—		0 (0)	CNCP	Placebo	No studies	—	—	—
—		0 (0)	MS-related	Placebo	No studies	—	—	—
—		0 (0)	Non–MS-related	Placebo	No studies	—	—	—
—		0 (0)	Visceral pain	Placebo	No studies	—	—	—
All RCTs	39,40,56,72,77	5 (753)	All pain types	Placebo	OR 1.43 (0.97 to 2.11)	Neither	25%	⊕⊕⊕◯ Moderate
Observational§	**53,80**	**2 (74)**	**Non–MS-related neuropathic pain**	**Placebo**	**OR 5.54 (1.75 to 17.49)**	**Cannabinoid**	**0%**	⊕◯◯◯ **Very low**
Change in pain scores								
Parallel RCT; and cross-over RCT†	**5,6,29,39,40,52,56,64,66,68,71,72,77,78,83,92,95**	**22 (2226)**	**Neuropathic pain**	**Placebo; dihydrocodeine; and diphenhydramine**	**SMD −0.20 (−0.28 to −0.12)¶**	**Cannabinoid¶**	**57%¶**	⊕⊕⊕◯ **Moderate**
Parallel RCT; and cross-over RCT†	**40,52,66,68,77,83**	**7 (808)**	**MS-related**	**Placebo**	**SMD −0.23 (−0.36 to −0.09)**	**Cannabinoid**	**37%**	⊕⊕⊕⊕ **High**
Parallel RCT; and cross-over RCT†	**6,29,39,52,56,64,71,72,78,92,95**	**15 (1418)**	**Non–MS-related**	**Placebo; dihydrocodeine; and diphenhydramine**	**SMD −0.19 (−0.29 to −0.08)#**	**Cannabinoid#**	**64%#**	⊕◯◯◯ **Very low**
Cross-over RCT	91	1 (64)	Fibromyalgia	Amitriptyline	SMD −0.24 (−0.73 to 0.25)	Neither	n/a	⊕⊕◯◯ Low
Parallel RCT	**8**	**1 (58)**	**Rheumatoid arthritis**	**Placebo**	**SMD −0.62 (−1.14 to −0.09)**	**Cannabinoid**	**n/a**	⊕◯◯◯ **Very low**
Parallel RCT; and cross-over RCT†	4,10,14,15,18,19,54,86,97,100	8 (1423)	CNCP	Placebo	SMD −0.01 (−0.11 to 0.10)**	Neither**	73%**	⊕⊕◯◯ Low
Parallel RCT; and cross-over RCT†	4,14,15,54,86,100	6 (1363)	MS-related	Placebo	SMD −0.01 (−0.12 to 0.10)††	Neither††	78%††	⊕◯◯◯ Very low

(*continued on next page*)

Table 4 (*continued*)

Outcome study type	Refs	N studies (N part.)	Medical condition	Comparator	Summary estimate (95% CI)	Favours	I^2	GRADE rating*
Parallel RCT; and cross-over RCT†	10,18,19,97	2 (60)	Non–MS-related	Placebo	SMD 0.08 (−0.43 to 0.60)‡‡	Neither	69%‡‡	⊕⊕◯◯ Low
Parallel RCT; and cross-over RCT†	18,19	2(98)	Visceral pain	Diazepam	SMD −0.29 (−0.69 to 0.11)	Neither	0%	⊕◯◯◯ Very low
All RCTs	**4–6,8,10,14,15,18,19,29,39,40,52,54,56,64, 66,68,71,72,77,78,83,85,86,90,92,95,97,100**	**34 (3869)**	**All pain types**	**Placebo**	**SMD −0.14 (−0.20 to −0.08)§§**	**Cannabinoid‡‡**	**62%§§**	**⊕⊕⊕◯ Moderate**
Observational§	7,21,62,73,80,91	7 (1262)	All pain types	Gabapentin; placebo; and noncannabis users	SMD −0.02 (−0.10 to 0.06)‖‖	Neither	76%‖‖	⊕◯◯◯ Very low

CI, confidence interval; MS, multiple sclerosis; N, number; OR, odds ratio; part., participants; RCT, randomised controlled trial.

Bold font indicates a statistically significant result.

* High: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate: We are moderately confident in the effect estimate that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality: Our confidence in the effect estimate is limited that the true effect may be substantially different from the estimate of the effect; Very low quality: We have very little confidence in the effect estimate that the true effect is likely to be substantially different from the estimate of effect.

† Only those cross-over trials where data were amenable to meta-analysis were included (ie, where appropriate paired analyses were conducted and could be extracted or obtained from study authors; or where results were presented separately for each period of the trial and participants were not double counted).[16,25] Where results from paired analyses were amenable to meta-analyses, we have analysed these data; otherwise, to avoid carry-over effects, we analysed data from the first period only.[17]

‡ Sensitivity analysis indicated that this effect did not differ when using the random effects model (OR 1.63, 95% CI 0.92-2.89).

§ Only observational studies with a comparator group are included here. For observational groups with no comparator, the proportion reporting improvement is presented in Appendix F (available online at http://links.lww.com/PAIN/A592).

‖ Sensitivity analysis indicated that this effect did not differ when using the random effects model (OR 2.07, 95% CI 0.34-12.50).

¶ Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD −0.24, 95% CI 0.38 to −0.10).

Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD −0.20, 95% CI −0.38 to −0.10).

** Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD 0.08, 95% CI −0.15 to 0.32).

†† Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD 0.08, 95% CI −0.17 to 0.33).

‡‡ Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD 0.18, 95% CI −0.77 to 1.14).

§§ Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD −0.17, 95% CI −0.28 to −0.05).

‖‖ Sensitivity analysis indicated that this effect did not differ when using the random effects model (SMD −0.10, 95% CI −0.32 to 0.12).

CNCP, chronic noncancer pain; SMD, standardised mean difference.

3.11. Summary statistics

Table 6 summarises the pooled ORs, pooled event rates for cannabinoids vs placebo groups, and NNTB or NNTH for dichotomous outcomes with a moderate or higher GRADE rating in RCTs. Note: because we only had continuous measures of sleep outcomes, cannabinoids' impacts on improving sleep cannot be included in these summary statistics.

For cannabinoids' impact on pain outcomes, pooled event rates for 30% reduction in pain intensity were 29.0% vs 25.9%, respectively. The NNTB was 24 (95% CI 15-61, **Table 6**). For a 50% reduction in pain, the pooled event rate for cannabinoids

Table 5

Pooled estimates of odds of individual adverse events from parallel and cross-over† randomised controlled trials cannabinoids in chronic noncancer pain (AEs; cannabinoid vs comparator).

Adverse event categories	No. of studies (no. of patients) [Refs]	Summary OR (95% CI)	I^2	GRADE rating*
Any	**10 (1959)[14,39,40,49–51,54,68,83,100]**	**OR 2.33 (1.88-2.89)‡**	**62%‡**	⊕⊕⊕◯ **Moderate**
Serious	11 (1974)[8,40,49–51,65,68,81,99,100]	OR 1.82 (0.93-3.59)	48%	⊕⊕◯◯ Low
Withdrawal due to AE	**19 (3265) [1,4,8,14,19,40,49–51,54,56,66,68,72,74,81,83,86,100]**	**OR 3.47 (2.64-4.56)**	21%	⊕⊕⊕◯ **Moderate**
MedDRA high-level grouping				
Gastrointestinal disorders	**4 (1163)[14,40,54,72]**	**OR 1.70 (1.30-2.22)**	**0%**	⊕⊕⊕◯ **Moderate**
Infections and infestations	5 (1279)[14,40,50,54,72]	OR 1.12 (0.85-1.47)	23%	⊕⊕◯◯ Low
Psychiatric disorders	5 (1288)[14,40,54,56,72]	OR 2.40 (1.67-3.46)	0%	⊕⊕◯◯ Low
Nervous system disorders	**4 (1163)[14,40,54,72]**	**OR 2.75 (2.13-3.54)‡**	**78%‡**	⊕⊕◯◯ **Low**
Musculoskeletal and connective tissue disorder	**4 (1410)[4,14,40,54]**	**OR 0.82 (0.61-1.11)§**	**64%§**	⊕◯◯◯ **Very low**
Metabolism and nutrition disorders	1 (246)[72]	OR 2.48 (0.93-6.62)	n/a	⊕⊕⊕◯ Moderate
Cardiac Disorders	1 (246)[72]	OR 0.92 (0.13-6.64)	n/a	⊕⊕◯◯ Low
Skin and subcutaneous tissue disorders	1 (246)[72]	OR 0.92 (0.35-2.39)	n/a	⊕⊕⊕◯ Moderate
Eye disorders	1 (236)[72]	OR 1.18 (0.38-3.61)	n/a	⊕⊕⊕◯ Moderate
Ear and labyrinth disorders	**3 (826)[40,54,72]**	**OR 3.24 (1.60-6.57)**	**0%**	⊕◯◯◯ **Very low**
General disorders and administration site conditions	**4 (1163)[14,40,54,72]**	**OR 1.79 (1.36-2.35)**	**0%**	⊕⊕◯◯ **Low**
Death	1 (493)[4]	OR 3.03 (0.36-25.36)	n/a	⊕◯◯◯ Very low
Respiratory, thoracic, and mediastinal disorders	2 (585)[40,72]	OR 0.80 (0.45-1.44)	0%	⊕⊕⊕◯ Moderate
Vascular disorders	1 (246)[72]	OR 0.60 (0.17-2.19)	n/a	⊕⊕⊕◯ Moderate
Injury poisoning and procedural complications	1 (246)[72]	OR 1.41 (0.49-4.09)	n/a	⊕⊕⊕◯ Moderate
Renal and urinary disorders	1 (246)[72]	OR 1.39 (0.23-8.48)	n/a	⊕⊕⊕◯ Moderate
Individual AEs				
Dizziness	**23 (3879) [1,4,8,14,19,40,49–51,54,56,66,68,72,74,80,83,86,90,98–100]**	**OR 5.52 (4.47-6.83)**	**0%**	⊕⊕◯◯ **Low**
Depressed mood	**6 (1470)[4,19,40,49,72,74]**	**OR 1.60 (1.04-2.48)**	**0%**	⊕⊕◯◯ **Low**
Anxiety	2 (301)[1,72]	OR 2.45 (0.46-12.96)	0%	⊕◯◯◯ Very low
Cognitive or attention disturbance	**11 (1946)[19,40,49,51,56,66,72,74,86,99]**	**OR 5.67 (2.72-11.79)**	**0%**	⊕⊕◯◯ **Low**
Nausea	**14 (2381)[8,14,18,40,49–51,54,56,66,68,72,80,83,86]**	**OR 2.28 (1.73-3.00)**	**0%**	⊕⊕◯◯ **Low**
Vomiting	8 (1317)[8,40,49–51,56,66,72]	OR 1.57 (0.98-2.52)	0%	⊕⊕⊕◯ Moderate
Diarrhoea	10 (2099)[4,19,40,49,51,54,56,66,72,86]	OR 1.26 (0.90-1.76)	17%	⊕⊕◯◯ Low
Constipation	7 (1604)[4,8,19,50,72,99]	OR 1.32 (0.84-2.07)	0%	⊕⊕◯◯ Low
Drowsiness	**18 (2724)[8,14,19,40,49–51,54,56,66,72,74,83,86,98,99]**	**OR 2.18 (1.59-2.98)**	**42%**	⊕⊕◯◯ **Low**
Thought disturbance	**6 (539)[49,51,72,74,98]**	**OR 7.35 (1.95-27.72)**	**0%**	⊕◯◯◯ **Very low**
Insomnia	6 (582)[40,49–51,74,83]	OR 0.23 (0.07-0.76)	0%	⊕⊕◯◯ Low
Confusion and disorientation	**7 (984)[19,49–51,72,74,86]**	**OR 5.35 (2.31-12.39)**	**0%**	⊕⊕◯◯ **Low**
Intoxication	**10 (1476)[40,46–51,66,72,74,83,86]**	**OR 3.44 (1.74-6.83)**	**0%**	⊕⊕◯◯ **Low**
Appetite change	**7 (626)[19,50,56,66,72,74,83]**	**OR 3.00 (1.37-6.57)**	**0%**	⊕⊕◯◯ **Low**
Cardiovascular symptoms	4 (667)[8,49,66,72]	OR 0.80 (0.28-2.30)	0%	⊕⊕◯◯ Low
Respiratory tract infections	**7 (1384)[40,49,50,54,56,66,72]**	**OR 1.06 (0.63-1.78)**	**0%**	⊕⊕◯◯ **Low**
Dry mouth	19 (3117) [8,10,14,18,19,40,49–51,54,56,66,68,72,74,80,83,99,100]	OR 3.63 (2.61-5.05)	0%	⊕⊕◯◯ Low
Headaches and migraines	17 (2428)[8,19,40,49–51,54,56,66,68,72,74,83,86,98,100]	OR 0.86 (0.64-1.15)	0%	⊕⊕◯◯ Low

Bold font indicates a statistically significant result.

* High: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate: We are moderately confident in the effect estimate that the true effect is likely to be close to space the estimate of the effect, but there is a possibility that it is substantially different; Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect; Very low quality: We have very little confidence in the effect estimate that the true effect is likely to be substantially different from the estimate of effect.

† Only those cross-over trials where data were amenable to meta-analysis were included (ie, where appropriate paired analyses were conducted and could be extracted or obtained from study authors; or where results were presented separately for each period of the trial and participants were not double counted).[16,25] Where results from paired analyses were amenable to meta-analyses, we have analysed these data; otherwise, to avoid carry-over effects, we analysed data from the first period only.[17]

‡Sensitivity analysis indicated that this effect did not differ when using the random effects model (OR 2.73, 95% CI 1.82-4.09).

‡ Sensitivity analysis indicated that this effect did not differ when using the random effects model (OR 2.59, 95% CI 1.48-4.54).

§ Sensitivity analysis indicated that this effect did not differ when using the random effects model (OR 0.89, 95% CI 0.53-1.50).

AE, adverse event; CI, confidence interval; OR, odds ratio.

Table 6

Summary of key statistics on the effectiveness of cannabinoids for chronic noncancer pain in randomised controlled trials.

Outcome	Pooled odds ratio (95% CI)	Pooled event rate (%), cannabinoid vs placebo	Number needed to treat to benefit (NNTB) (95% CI)
Pain outcomes			
30% reduction in pain	**1.46 (1.16-1.84)**	**29.0% vs 25.9%**	**24 (15-61)**
50% reduction in pain	1.43 (0.97-2.11)	18.2% vs 14.4%	*
Patient global impression of change			
Perceived "much" to "very much" improved	**1.62 (1.34-1.96)**	**18.9% vs 11.8%**	**38 (27-62)**
	Pooled odds ratio (95% CI)	**Pooled event rate (%), cannabinoid vs placebo**	**Number needed to treat to harm (NNTH) (95% CI)**
Adverse events			
All-cause adverse events	**2.33 (1.88-2.89)**	**81.2% vs 66.2%**	**6 (5-8)**
Study withdrawals—adverse events	**3.47 (2.64-4.56)**	**15.8% vs 4.6%**	**40 (35-49)**

Bold font indicates a statistically significant result. Only categorical outcomes with a moderate or higher GRADE rating are reported here.

* Number needed to treat to benefit unable to be calculated as the pooled odds ratio crossed the line of no effect.

CI, confidence interval.

was 18.2%, compared with 14.4% for placebo groups (**Table 6**). The NNTB for 50% reduction in pain was unable to be calculated, as the estimate crossed the line of no effect.

For studies where outcomes were presented dichotomously, participants receiving cannabinoids had slightly increased odds of reporting global improvements (PGIC) than patients who received placebo (**Table 6**). In participants receiving cannabinoids, the pooled percentage reporting "much" or "very much" global improvement was 18.9% compared with 11.8%; the NNT was 38 (95% CI 27-62).

Pooled statistics for AEs and study withdrawals are also presented in **Table 6**. The estimated pooled rate of all-cause AEs was 81.2% among people receiving cannabinoids, compared with 66.2% of those receiving placebo; the NNTH was 6 (95% CI 5-8). The pooled event rate for study withdrawals due to AEs was 15.8% in those receiving cannabinoids compared with 4.6% of those receiving placebo, and the NNTH was 40 (35-49).

4. Discussion

To the best of our knowledge, this is the first systematic review of the evidence for the effectiveness and safety of cannabinoids for CNCP that included all cannabinoids, all study designs, and considered all outcomes recommended by the IMMPACT group. We also assessed the clinical relevance of these findings using event rates, NNTB, and NNTH.

We found moderate evidence for a reduction in pain for cannabinoids when compared with placebo groups. Pooled analyses suggested that 30% reduction in pain was reported by 29.0% in cannabinoids, compared with 25.9% in placebo groups. A 50% reduction in pain was reported by 18.2% in cannabinoid groups and 14.4% in placebo groups; however, this did not reach statistical significance. The NNTB to achieve a 30% reduction in pain for 1 person using cannabis or cannabinoids (compared with placebo groups) was estimated at 24 (95% CI 15-61), and the NNTH for 1 person to experience any AE was 6 (95% CI 5-8). Although caution needs to be used in comparing NNTs across studies involving different groups and timeframes,[44] these NNTBs are much higher than those for other analgesics: previous studies in neuropathic pain suggested NNTs for strong opioids of 4.3 (95% CI 3.4-5.8), pregabalin (7.7, 95% CI 6.5-9.4), and tricyclic antidepressants (3.6, 95% CI 3.0-4.4).[28] The NNTH in our review was similar to that for opioids for CNCP, with a recent Cochrane review indicating that the NNTH for 1 person using opioids to experience any AE (compared with placebo) was 5 (95% CI 4-9).[27] When reexpressed as a mean change on the commonly used 100 mm VAS, the pooled SMD for the continuous outcome of change in pain intensity was equivalent to a 3 mm greater reduction on this scale compared with placebo, which is well below the 30 mm reduction regarded to represent a clinically important difference in pain intensity.[41,58] In contrast to more optimistic conclusions from earlier reviews,[2,48] our findings are largely consistent with a recent Cochrane review examining cannabinoids for neuropathic pain, indicating that these medicines are unlikely to be effective in the treatment of pain.[46] In their review, Mücke et al.[46] report an NNTB of 20 for 50% or greater reduction in pain, and NNTHs of 3 and 6 for AEs relating to nervous system and psychiatric disorders, respectively, suggesting a similar efficacy and safety profile of cannabinoids for pain as reported in our review.

The evidence on the effectiveness of cannabinoids for CNCP is limited for several reasons. First, sample size is an issue, with only 21 of the 104 included studies having at least 100 participants per treatment arm. Although we made multiple attempts to minimise risk of bias in the effect estimates due to small sample sizes, this risk cannot be fully mitigated. For some estimates, effect sizes were notably larger in studies with <30 participants per treatment arm compared with studies of 100+ per arm; however, these estimates fell within overlapping bounds of uncertainty. There is a growing body of evidence indicating that effect estimates tend to be larger in studies with small sample sizes,[20] and as such, caution should be taken when interpreting outcomes based on studies with small sample sizes in this review. Well conducted, large RCTs comprising at least 100 participants per treatment arm should be considered a priority in this space. Second, most studies were of limited duration (median of 8 weeks): given that CNCP is a chronic condition, this sheds little light on the appropriateness of long-term use of cannabinoids in CNCP, in terms of both treatment efficacy and safety. Of the little evidence available, we found that reductions in pain intensity were largest for 1-day studies, and smaller and nonsignificant in studies of 13-week duration or longer, providing some initial suggestion that the effectiveness of cannabinoids for CNCP may diminish over time. Third, the issues of cannabinoid tolerance, risks of iatrogenic dependence, and of withdrawal symptoms if long-term cannabinoids are ceased, remain poorly understood. Short-term clinical

trials such as those included in this review are often of insufficient power and duration to detect potential harms and AEs associated with long-term cannabis use, such as elevated risk of psychosis and substance dependence.[32,45] It is crucial that these long-term outcomes identified in the epidemiological literature are considered alongside evidence of efficacy from clinical trials when determining overall suitability of cannabinoids as medicines for CNCP. Fourth, cannabinoid dose was often poorly recorded. Often, only a maximum recommended dose was reported and data on participants' actual cannabinoid consumption were seldom recorded, so it is difficult to make strong recommendations on doses that are maximally effective and safe. Fifth, by far, the greatest amount of high-quality evidence was for nabiximols, resulting in small numbers of studies (and in some cases, single study) in some analyses for other types and formulations of cannabinoids (eg, ajulemic acid), meaning that we are be less confident about their efficacy. Sixth, although almost all studies reported data on change in pain intensity, very few reported outcomes for 30% and 50% reduction in pain. Given that pain was a secondary outcome in many studies, it is possible that authors did not report these outcomes because they are drawn from the pain-specific IMMPACT guidelines; however, there is also the possibility that study authors chose not to report outcomes for 30% and 50% reduction in pain when the continuous pain intensity outcome indicated no benefit. Although we have made multiple attempts to account for publication bias throughout this review, there remains the possibility that the studies for which 30% and 50% reduction in pain were not reported did not find evidence of effect. If this is the case, NNTBs for these outcomes may be higher than those reported here; however, our overall conclusion that cannabinoids are unlikely to be effective medicines for CNCP will remain unchanged. Finally, to ensure that all the available evidence of cannabinoids as a treatment for CNCP was considered in this review, we included evidence from RCTs and less rigorous observational study designs. This approach allows researchers, clinicians, and policymakers to map current research activity and to identify knowledge gaps. Although observational studies provide some insight into the efficacy of cannabinoids for CNCP, ultimately only data from high-quality RCTs will be used to inform national treatment guidelines. We noted that most of the higher-quality RCT evidence was for neuropathic pain and MS-related pain. There is scant, low-quality evidence on cannabinoids used for fibromyalgia or visceral pain, and very few studies of cannabinoids' use in the most common and burdensome CNCP conditions, namely back/neck problems, migraines, and arthritides. Thus, the conclusions of this review primarily relate to neuropathic or MS-related pain. Several ongoing studies targeting these more common CNCP conditions were identified and will be analysed when results become available.

Most studies used a placebo comparator and added cannabinoids to stable doses of analgesics, nonsteroidal anti-inflammatory drugs, and antispasticity drugs, so the evidence for cannabinoid use in CNCP is largely around cannabinoids as adjuvant medicines. Often, multiple analgesics were used, which varied between groups, and the ways they were used were not consistently reported. Most studies held doses of other analgesic medications constant, although some studies documented changes in breakthrough medication or adjunctive analgesia.

4.1. Limitations of this review

The findings of this review need to be considered in light of several potential limitations. Some of these limitations have already been noted and include the high risk of bias in many studies because of small N and missing information on study design and rigour of controls; most studies also evaluated cannabinoids as adjunct to other analgesic medications. We attempted to assertively minimise these limitations. Many documents were reviewed by a small research team, which might have led to errors in assessing eligible studies. However, internal checks were conducted by members within this team and a process of double and triple checking existed; we also checked all identified reviews to ensure that no studies had been missed that had been reported in any other reviews of evidence. Third, errors may have been made in data interpretation. To reduce such errors, all sources and data extracted were double checked by at least 2 reviewers and conflicts were resolved by third reviewer when necessary.

5. Conclusions

It seems unlikely that cannabinoids are highly effective medicines for CNCP. There is moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. However, NNTBs were high and NNTHs low, with high rates of dropout for AEs, and long-term efficacy and safety is unknown. We also found minimal evidence that cannabinoids are effective in improving other important domains in people with CNCP such as emotional and physical functioning. Cannabinoids are unlikely to be a monotherapy for CNCP. People living with CNCP often have complex comorbidities,[9,70] and multidisciplinary treatment that includes physical and psychological therapy rather than reliance on medicines alone is likely to be most effective.

Conflict of interest statement

G. Campbell, S. Nielsen, M. Farrell, and L. Degenhardt have all been investigators on untied investigator-driven educational grants funded by Reckitt Benckiser. M. Farrell and L. Degenhardt have received an untied educational grant from Mundipharma for post-marketing surveillance studies of a potentially tamper-resistant formulation of controlled-released oxycodone. S. Nielsen, M. Farrell, and L. Degenhardt have been investigators on untied investigator-driven educational grants funded by Indivior. M. Farrell and L. Degenhardt have been investigators on an untied investigator-driven educational grant funded by Seqirus. The remaining authors have no conflict of interest to declare.

Funding was received from the Commonwealth Department of Health, the NSW Government Centre for Medicinal Cannabis Research and Innovation, the Victorian Department of Health and Human Services, and the Queensland Department of Health. E. Stockings, G. Campbell, S. Nielsen, and L. Degenhardt are supported by NHMRC research fellowships (#1104600; #1119992; #1132433; and #1041472). The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund.

Acknowledgements

The authors acknowledge Mary Kumvaj who assisted in the development of the search strategy.
Author contributions: L. Degenhardt and M. Farrell conceived the Review. E. Stockings, G. Campbell, S. Nielsen, D. Zagic, R. Rahman, and M. Weier did the systematic search, selected

papers, and extracted data. E. Stockings conducted statistical analyses. G. Campbell, L. Degenhardt, and W.D. Hall drafted the manuscript with critical revisions from all authors. B. Murnion provided clinical important intellectual content. All authors reviewed the paper before submission.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A592.

Supplemental video content

Video content associated with this article can be found online at http://links.lww.com/PAIN/A593.

Article history:
Received 7 December 2017
Received in revised form 22 April 2018
Accepted 1 May 2018
Available online 25 May 2018

References

[1] Abrams DI, Jay C, Shade S, Vizoso H, Reda H, Press S, Kelly M, Rowbotham M, Petersen K. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68:515–21.
[2] Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, Abrams DI, Prasad H, Wilsey B, Indyk D, Johnson M, Sacks HS. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain 2015;16:1221–32.
[3] Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain Physician 2017;20:E755–96.
[4] Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, Nunn A, Cano MG, MacManus D, Miller D, Mallik S, Zajicek J. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess 2015;19:vii–viii, xxv–xxxi, 1–187.
[5] Berman JS. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. 2012. NCT01606176, Vol. 2017, Clinicaltrials.gov.
[6] Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. PAIN 2004;112: 299–306.
[7] Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract 2011;11:353–68.
[8] Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. 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.
[9] Campbell G, Nielsen S, Bruno R, Lintzeris N, Cohen M, Hall W, Larance B, Mattick RP, Degenhardt L. The pain and opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. PAIN 2015;156:231–42.
[10] Carroll CB, Bain PG, Teare L, Liu X, Joint C, Wroath C, Parkin SG, Fox P, Wright D, Hobart J, Zajicek JP. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. Neurology 2004; 63:1245–50.
[11] Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. BMC Med Res Methodol 2002;2:1.
[12] Chung SA, Hossain NK, Blackman AS, Shapiro CM. Can the cannabinoid nabilone help with pain and sleep in fibromyalgia patients? Sleep 2009;32:A325–6.
[13] Deleted in proof.
[14] Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, Notcutt W, O'leary C, Ratcliffe S, Nováková I. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res 2010;32:451–9.
[15] Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Can Med Assoc J 2012;184: 1143–50.
[16] Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. II: binary outcomes. Stat Med 2002;21: 2145–59.
[17] Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III: the issue of carry-over. Stat Med 2002;21: 2161–73.
[18] de Vries M, Van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, Van Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. Br J Clin Pharmacol 2016;81:525–37.
[19] de Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, van Goor H. 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.e4.
[20] Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. BMJ 2013;346:f2304.
[21] Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, Hall WD. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend 2015;147:144–50.
[22] Deeks J, Higgins J, Altman D, Cochrane Statistical Methods Group. Chapter 9: analysing data and undertaking meta-analysis. In: Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions 510 (updated March 2011). London, United Kingdom: The Cochrane Collaboration, 2011.
[23] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[24] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
[25] Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol 2002;31:140–9.
[26] Ellis RJ, Toperoff W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672–80.
[27] Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, Sharma S, Kolahdooz F, Straube S. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;10: CD012509.
[28] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol 2015;14:162–73.
[29] Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. 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.
[30] GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211–59.
[31] Hagenbach U, Luz S, Ghafoor N, Berger J, Grotenhermen F, Brenneisen R, Mäder M. The treatment of spasticity with [Delta] 9-tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord 2007;45:551.
[32] Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383–91.
[33] Harbord R, Harris R, Sterne J. Updated tests for small-study effects in meta-analyses. Stata J 2009;9:197–210.

[34] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS pain), Numeric Rating Scale for Pain (NRS pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63(suppl 11):S240–52.
[35] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. London, United Kingdom: 2011.
[36] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Vol. 4. London, United Kingdom: John Wiley & Sons, 2011.
[37] Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejcko J, Taylor L, Lauder H, Serpell M. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. J Neurol 2015;262:27–40.
[38] Johnston BC, Patrick DL, Thorlund K, Busse JW, da Costa BR, Schünemann HJ, Guyatt GH. Patient-reported outcomes in meta-analyses—Part 2: methods for improving interpretability for decision-makers. Health Qual Life Outcomes 2013;11:211.
[39] Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. J Am Med Assoc 2003;290:1757–62.
[40] Langford R, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. 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.
[41] Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med 2003; 10:1128–30.
[42] Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage 2014;47:166–73.
[43] Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci 1990;240:1–4.
[44] McAlister FA. The "number needed to treat" turns 20—and continues to be used and misused. CMAJ 2008;179:549–53.
[45] Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370:319–28.
[46] Mücke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018;3:Cd012182.
[47] Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain 2008;9:254–64.
[48] National Academies of Sciences Engineering and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.
[49] NCT00710424 (GW Pharmaceuticals). A study of Sativex® for pain relief due to diabetic neuropathy. 2008. NCT00710424, Vol. 2017, Clinicaltrials.gov.
[50] NCT01606176 (GW Pharmaceuticals). A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. 2012. NCT01606176, Vol. 2017, Clinicaltrials.gov.
[51] NCT01606202 (GW Pharmaceuticals). A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. 2012. NCT01606202, Vol. 2017, Clinicaltrials.gov.
[52] Notcutt W. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. 2012. NCT01606202, Vol. 2017, Clinicaltrials.gov.
[53] Notcutt W, Phillips C, Hughes J, Lacoux P, Vijayakulasingam V, Baldock L. A retrospective description of the use of nabilone in UK clinical practice—extension study (conference poster). Mult Scler 2014;468.
[54] Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P. 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.
[55] Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Kanasagara D. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med 2017;167: 319–31.
[56] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. PAIN 2007; 133:210–20.
[57] Nyaga VN, Arbyn M, Aerts M. Metaprop: a stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39.
[58] Ostelo RWJG, de Vet HCW. Clinically important outcomes in low back pain. Best Pract Res Clin Rheumatol 2005;19:593–607.
[59] Palmieri B, Laurino C, Vadala M. Short-term efficacy of CBD-enriched hemp oil in girls with dysautonomic syndrome after human papillomavirus vaccination. Isr Med Assoc J 2017;19:79–84.
[60] Petzke F, Enax-Krumova EK, Hauser W. Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: a systematic review of randomized controlled studies (article in German). Schmerz 2016;30: 62–88.
[61] Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain 2012;13:677–84.
[62] Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial. Wiener Klinische Wochenschrift 2006;118:327–35.
[63] Platt L, Reed J, Minozzi S, Vickerman P, Hagan H, French C, Jordan A, Degenhardt L, Hope V, Hutchinson S. Effectiveness of needle/syringe programmes and opiate substitution therapy in preventing HCV transmission among people who inject drugs. Cochrane Database of Systematic Reviews 2016;1:1–13. CD012021.
[64] Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil 2010;89:840–8.
[65] Riva N, Mora G, Soraru G, Lunetta C, Falzone Y, Marinou K, Maestri E, Fazio R, Comola M, Comi G. The canals study: a randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacyon spasticity symptoms of a cannabis sativa extract in motor neuron disease patients. Amyotroph Lateral Scler Frontotemporal Degener 2016;17:44.
[66] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812–19.
[67] Rudich Z, Stinson J, Jeavons M, Brown SC. Treatment of chronic intractable neuropathic pain with dronabinol: case report of two adolescents. Pain Res Manag 2003;8:221–4.
[68] Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. Eur Neurol 2017;78:320–9.
[69] Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Curr Med Res Opin 2006; 22:1269–76.
[70] Scott KM, Lim C, Al-Hamzawi A, Alonso J, Bruffaerts R, Caldas-de-Almeida JM, Florescu S, de Girolamo G, Hu C, de Jonge P, Kawakami N, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, O'Neill S, Piazza M, Posada-Villa J, Torres Y, Kessler RC. Association of mental disorders with subsequent chronic physical conditions: world mental health surveys from 17 countries. JAMA Psychiatry 2016;73:150–8.
[71] Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. 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.
[72] Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E. 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.
[73] Shah A, Craner J, Cunningham JL. Medical cannabis use among patients with chronic pain in an interdisciplinary pain rehabilitation program: characterization and treatment outcomes. J Subst Abuse Treat 2017;77:95–100.
[74] Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008;9:164–73.
[75] StataCorp. Stata Statistical Software: Release 15, Vol. 15.0. College Station: StataCorp LLC, 2017.
[76] Sterne J, Higgins J, Reeves B. Extending the risk of bias tool to allow for assessment of non-randomised studies, cluster-randomised trials and cross-over trials: a Cochrane methods innovation fund project (Workshop). *Proceedings of the Book Extending the Risk of Bias Tool*

to Allow for Assessment of Non-Randomised Studies, Cluster-Randomised Trials and Cross-Over Trials: A Cochrane Methods Innovation Fund Project (Workshop). In: Better Knowledge for Better Health | Un meilleur savoir pour une meilleure santé. Abstracts of the 21st Cochrane Colloquium; 2013 19-23 Sep; Québec City, Canada. John Wiley & Sons, 2013. p. 203–4.

[77] Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004;329:253.

[78] Tesfaye SA. Study of Sativex® for pain relief due to diabetic neuropathy. 2008. NCT00710424, Vol. 2017, Clinicaltrials.gov.

[79] The Nordic Cochrane Centre. Review Manager (RevMan). Copenhagen, Denmark: The Cochrane Collabration, 2014.

[80] Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestard J, Korngut L. 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.

[81] Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, Galloway K, Namaka M. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med 2015;16:149–59.

[82] Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. PAIN 2003; 106:337–45.

[83] van Amerongen G, Kanhai K, Baakman AC, Heuberger J, Klaassen E, Beumer TL, Strijers RLM, Killestein J, van Gerven J, Cohen A, Groeneveld GJ. Effects on spasticity and neuropathic pain of an oral formulation of delta9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther 2017 Feb 9. pii: S0149-2918(17)30054-1. doi: 10.1016/j.clinthera.2017.01.016 [epub ahead of print].

[84] Veritas Health Innovation. Covidence systematic review software. Melbourne. Available at: www.covidence.org. Accessed 2 July 2018.

[85] Vermersch P, Trojano M. Tetrahydrocannabinol: cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice. Eur Neurol 2016;76:216–26.

[86] Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler J 2004;10:434–41.

[87] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms—cross over study. Clin Rehabil 2003;17:21–9.

[88] Walitt B, Klose P, Fitzcharles MA, Phillips T, Hauser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev 2016;7:Cd011694.

[89] Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015;16: 616–27.

[90] Ware MA, Fitzcharles M-A, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 2010;110:604–10.

[91] Ware MA, Wang T, Shapiro S, Collet JP; Team Cs. Cannabis for the management of pain: assessment of safety study (COMPASS). J Am Pain Soc 2015;16:1233–42.

[92] Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Can Med Assoc J 2010;182: E694–701.

[93] Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015;313:2456–73.

[94] Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14:136–48.

[95] Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9:506–21.

[96] Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain 2016;17:982–1000.

[97] Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, Schelosky LD. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain. J Neurol 2006;253:1337–41.

[98] Wong BS, Camilleri M, Busciglio I, Carlson P, Szarka LA, Burton D, Zinsmeister AR. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology 2011;141:1638–47. e1637.

[99] Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003;362:1517–26.

[100] Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, Group MR. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry 2012;83:1125–32.