Systematic Review and Meta-Analysis

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Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

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Abstract

Cannabinoids, cannabis, and cannabis-based medicines (CBMs) are increasingly used to manage pain, with limited understanding of their efficacy and safety. We summarised efficacy and adverse events (AEs) of these types of drugs for treating pain using randomised controlled trials: in people of any age, with any type of pain, and for any treatment duration. Primary outcomes were 30% and 50% reduction in pain intensity, and AEs. We assessed risk of bias of included studies, and the overall quality of evidence using GRADE. Studies of <7 and >7 days treatment duration were analysed separately. We included 36 studies (7217 participants) delivering cannabinoids (8 studies), cannabis (6 studies), and CBM (22 studies); all had high and/or uncertain risk of bias. Evidence of benefit was found for cannabis <7 days (risk difference 0.33, 95% confidence interval 0.20-0.46; 2 trials, 231 patients, very low-quality evidence) and nabiximols >7 days (risk difference 0.06, 95% confidence interval 0.01-0.12; 6 trials, 1484 patients, very low-quality evidence). No other beneficial effects were found for other types of cannabinoids, cannabis, or CBM in our primary analyses; 81% of subgroup analyses were negative. Cannabis, nabiximols, and delta-9-tetrahydrocannabinol had more AEs than control. Studies in this field have unclear or high risk of bias, and outcomes had GRADE rating of low- or very low-quality evidence. We have little confidence in the estimates of effect. The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain.

Keywords: Cannabis, Cannabis-based medicine, Cannabinoids, Systematic review, Meta-analysis, Pain, Chronic pain

1. Introduction

Pain is a common symptom of a wide variety of common conditions, and the primary reason most patients seek health care.[41] Globally, tension type headache is the primary cause of morbidity, with musculoskeletal and neuropathic pain also common.[58] The incidence of chronic pain is routinely estimated to be between 11% and 40% of the population, with as many as 10% reporting high impact pain.[9,19] Chronic pain has a larger impact on quality of life than other common chronic conditions,[71] and there is a graded increase in mortality as pain severity increases in older adults, especially for patients who report walking disability.[66,67]

Pharmacological treatments can provide considerable improvements, including reduced pain intensity and increased function. However, this benefit is limited to a minority of patients,[45] or those reporting acute pain after surgery and cancer

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pain.[46] These findings all relate to adult data. For children and adolescents, there are little data of any kind to guide practice.[14,15]

Cannabis plant material typically contains over 450 different compounds, with over 100 classified as phytocannabinoids. The 2 phytocannabinoids that have been most studied to date in the context of medical research are delta 9-tetrahydrocannabinol (THC, the main psychoactive constituent) and cannabidiol (CBD). A large body of preclinical data provides evidence for antinociceptive effects of cannabinoids and modulators of the body's own endogenous cannabinoids (endocannabinoids).[55,72,80] The analgesic effects of THC are mediated primarily through agonism of cannabinoid$_1$ (CB_1) and cannabinoid$_2$ (CB_2) receptors, with the former being chiefly responsible for its psychoactive effects. By contrast, CBD does not activate CB_1 or CB_2 receptors and seems to have a complex pharmacology with activity at a number of different targets which include, but are not limited to: 5-HT_{1A} receptor agonism, negative allosteric modulation of CB_1, GPR55 antagonism, TRPV1 activation, PPARγ activation, and reuptake inhibition [eg, anandamide and adenosine]).[7,31,36,56,60,61,74] **Table 1** (adapted from Hauser et al.[28]) provides a summary of current terminology, definitions, and typical products.

There is considerable research interest in the use of cannabinoids, medicinal cannabis, and cannabis-based medicines (CBMs), including for pain. In our recent overview review, we found 57 reviews of which 49 were very low or low quality. There is a need for a high-quality systematic review summarising the evidence.

In 2018, the International Association for Study of Pain (IASP) established a Presidential Task Force on Cannabis and Cannabinoid Analgesia to investigate the use of cannabis and cannabinoid-based medicinal products for pain management. This review is part of the Task Force and aimed to provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and CBM in clinical acute and chronic pain management, across the lifespan. We used randomized trials because they typically provide the least biased estimate for treatment efficacy. In this review, we (1) provide estimates of the efficacy and adverse events from trial data, and (2) provide an assessment of the risk of bias and quality of evidence.

2. Methods

2.1. Protocol registration

We published the protocol for this systematic review[20] and also registered it on Prospero (ID: CRD42019124714). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[42] The aim, rationale, and methods are identical to those set out in the protocol. Where we deviated from the protocol, we have noted this. This review was conducted alongside an overview review[47] and as part of the IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia.

Table 1

Terminology and Definitions (Adapted from Soliman et al., 2019[71], after modification from Hauser et al., 2018[28]).

Term	Definition	Examples/typical products
(Herbal) Cannabis	The whole plant or parts or material from the plant (eg, flowers, buds, resin, leaves)	*Cannabis sativa*, hashish
Medicinal cannabis	The term "medicinal cannabis" (or "medical cannabis/marijuana") is used for cannabis plants, plant material, or full plant extracts used for medical purposes.	Bedrocan, Bedrobinol, Tilray 10THC/10CBD
Cannabinoids	Cannabinoids are biologically active constituents of cannabis, or synthetic compounds, usually having affinity for and activity at cannabinoid receptors.	THC, CBD, CP55940, WIN55212-2, HU210, nabilone
Phytocannabinoid	A cannabinoid found in cannabis plants or purified/extracted from plant material	THC, CBD
Endocannabinoid	An endogenous ligand found in the body of humans and other animals and which has affinity for, and activity at, cannabinoid receptors	Anandamide, 2-AG
Cannabinoid receptor antagonists and negative allosteric modulators	Directly block cannabinoid receptors or reduce signalling indirectly via impeding action of endogenous ligand through actions at a distinct site	Rimonabant (SR141716A), AM251, SR144528, AM630
Modulators that increase or enhance endocannabinoid system activity	In addition to individual phytocannabinoids, cannabis-derived or cannabis-based medicines, and cannabis extracts, other pharmacological approaches under development for manipulation of the endocannabinoid system include selective synthetic cannabinoid receptor agonists, inhibitors of the catabolism (eg, fatty acid amide hydrolase [FAAH] inhibitors), transport (eg, FABP inhibitors) or reuptake of endocannabinoids, or positive allosteric modulators of cannabinoid receptor signalling.	PF-04457845, URB597, URB937, AM404, VDM11, URB602, JZL184, ZCZ011, GAT211
Cannabis-based (or cannabis-derived) medicines	Medicinal cannabis extracts with regulatory approval for marketing as a therapeutic with defined and standardized THC and/or CBD content.	Nabiximols (Sativex), dronabinol, marinol, Epidiolex

CBD, cannabidiol; FABP, fatty acid binding protein; THC, Δ9-tetrahydrocannabinol; 2-AG, 2-arachidonoyl glycerol.

2.2. Type of participants

We included people with acute or chronic pain. Chronic pain is defined as continuous or recurrent pain lasting for longer than 3 months. Acute or chronic pain includes, but was not limited to, the following conditions: abdominal pain, cancer pain, headache, migraine, acute or chronic neuropathic pain, acute or chronic musculoskeletal pain, pelvic pain, menstrual pain, acute postoperative pain, or any other form of pain. We included people with pain across the lifespan (including children). However, we excluded trials of people undergoing experimental pain procedures. We only included trials that retained 30 participants/arm or more at posttreatment. Trials that include smaller sample sizes are more likely to produce larger effects.[10,73] However, for transparency, we have included a discussion of smaller trials in appendix 4, available at http://links.lww.com/PAIN/B48.

2.3. Types of interventions and comparators

We included any type of cannabinoid product, natural or synthetic, delivered by any route of administration. We included any control, including placebo or active pain therapy, pharmacological or nonpharmacological. Trials that delivered cannabinoids, cannabis, or CBM in addition to other drugs were also included. We only included trials that had the intention of decreasing self-reported pain intensity in participants.

2.4. Types of outcomes

We extracted the following primary and secondary outcomes:

2.4.1. Primary outcomes

(1) The proportion of people with at least 30% pain intensity reduction/moderate improvement defined by IMMPACT;[13]
(2) The proportion of people with at least 50% pain intensity reduction/substantial improvement defined by IMMPACT.[13]

2.4.2. Secondary outcomes

(1) Continuous assessments of pain intensity (eg, using a numerical rating scale or visual analogue scale);
(2) The proportion of people who experienced a decrease in pain from moderate/severe to mild;
(3) Disability or physical functioning;
(4) Emotional functioning (eg, anxiety and depression);
(5) Carer Global Impression of Change;
(6) Quality of life as defined by validated scales;
(7) The number of adverse events (AEs). Adverse events will include measures of harm, including withdrawal due to serious AEs, withdrawal because of AEs, patients reporting any AE, and particular AEs (especially central nervous system and cardiovascular AEs). Following the PRISMA Harms Checklist, we will describe how AEs were addressed, how they were reported, and over what period the harm was experienced;[83]
(8) Requirement for rescue analgesia;
(9) Sleep duration and quality;
(10) Onset and duration of analgesic effects (when relevant in acute pain trials).

2.5. Search method and study selection

We searched the literature using a staged approach. (1) We searched PubMed, EMBASE, and CENTRAL to April 2019 (see Appendix 1 for search strategies, available at http://links.lww.com/PAIN/B48). We conducted a targeted search for RCTs in this area in January 2020 for any new studies. Two authors independently sifted the titles and abstracts identified in the database search. A third author resolved any disagreements. We did not restrict the searches on language or date. (2) We searched online trial registry databases including clinicaltrials.gov, EudracT. (3) We searched the trials of systematic reviews included in the overview review.[47] (4) We conducted reference and citation searches of included trials to search for further trials.

We included any peer-reviewed publication or online trial registration that investigated the therapeutic effects of any cannabinoid preparation, given by any route of administration, for relief of pain, compared with placebo or a different active treatment. We did not include trials based on the measures they reported. We did not seek other types of gray literature (eg, unpublished dissertations) or conference abstracts.

2.6. Data extraction

Two authors independently extracted data from included trials. A third author resolved disagreements. We extracted the following data from each study:
(1) Study characteristics, eg, design, participants enrolled, age, sex, pain condition, and inclusion/exclusion criteria.
(2) Intervention and comparator characteristics, eg, type of cannabinoid, dose, route of administration, comparator.
(3) Outcomes—we extracted any outcomes listed in the primary and secondary outcomes of this review. We extracted outcomes at short-term (between up to 7 days postadministration) and long-term (greater than or equal to 7 days postadministration).

2.7. Risk of bias

Two authors independently assessed the risk of bias of included studies using the Cochrane risk of bias tool[30] and a third author resolved disagreements. We assessed the following risk of bias categories, making judgements using the following criteria (please note that this section uses suggested wording from the Cochrane Pain, Palliative, and Supportive Care Review Group template, which is used in a number of Cochrane reviews including, but not limited to[44,76] and is unaltered from the original).
(1) Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, eg, random number table; computer random number generator); unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as "low" or "high" risk of bias). Studies using a nonrandom process (eg, odd or even date of birth; hospital or clinic record number) were excluded.
(2) Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (eg, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as "low" or "high" risk of bias). Studies that do not conceal allocation (eg, open list) were excluded.

(3) Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (no blinding or incomplete blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding, or blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken); unclear risk of bias (insufficient detail about the method of blinding to be able to judge the generation as "low" or "high" risk of bias, or the study does not address this outcome), or high risk of bias (no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding, or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding).
(4) Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (no blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding, or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken); unclear risk of bias (insufficient detail about the method of blinding to be able to judge the generation as "low" or "high" risk of bias, or the study does not address this); high risk of bias (no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding, or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding).
(5) Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; missing data have been imputed using "baseline observation carried forward" analysis); unclear risk of bias (insufficient reporting of attrition/exclusions to permit a judgement of "low risk" or "high risk" (eg, number randomised not stated, no reasons for missing data provided, or the study did not address this outcome); high risk of bias (reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; "as-treated" analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation).
(6) Selective reporting (checking for reporting bias). We assessed reporting biases due to selective outcome reporting. We judged studies as: low risk of bias (the study protocol is available and all of the study's prespecified [primary and secondary] outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified [convincing text of this nature may be uncommon]); unclear risk of bias (insufficient information available to permit a judgement of "low risk" or "high risk"); high risk of bias (not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data [eg, subscales] that were not prespecified; one or more reported primary outcomes were not prespecified [unless clear justification for their reporting is provided, such as an unexpected adverse effect]; one or more outcomes of interest in the review have been reported incompletely so that they cannot be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study).
(7) Size (checking for possible biases confounded by small size). We assessed size of study as low risk of bias (>200 participants/arm); unclear risk of bias (50-199 participants/arm); or high risk of bias (<50 participants/arm).

2.8. Quality of the evidence

We assessed the quality of the evidence using GRADE (please note that this section uses suggested wording from the Cochrane Pain, Palliative, and Supportive Care review group template, which are used in a number of Cochrane reviews (including, but not limited to[44,76] and is unaltered from the original.). Two review authors rated the quality of each outcome. The GRADE approach uses 5 considerations (study limitations, unexplained heterogeneity or inconsistency, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:
(1) High: we are very confident that the true effect lies close to that of the estimate of the effect;
(2) Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
(3) Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
(4) Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Factors that may decrease the quality level of a body of evidence are:
(1) Limitations in the design and implementation of available studies suggesting high likelihood of bias;
(2) Indirectness of evidence (indirect population, intervention, control, outcomes);
(3) Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
(4) Imprecision of results (wide confidence intervals [CIs]);
(5) High probability of publication bias.

We decreased the grade rating by 1 (−1) level (from high to moderate quality of evidence), 2 (−2) levels (to low-quality evidence), or 3 (−3) levels (to very low-quality of evidence). Outcomes can be downgraded a maximum of 3 levels using the following criteria:
1, Serious (−1) or very serious (−2) study limitations.
2, Some (−1) or considerable (−2) inconsistency of results.
3, Some (−1) or considerable (−2) uncertainty about directness.
4, Some (−1) or considerable (−2) imprecision.
5, Some (−1) or considerable (−2) probability of reporting bias.

There may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines.[25] Examples might be where there are so few participants that the results are highly susceptible to the random

play of chance, or if studies use last observation carried forward imputation in circumstances where there are substantial differences in AE withdrawals. In circumstances such as this, there would be little confidence in the result, which would be downgraded 3 levels, to very low quality. In circumstances where there are no data reported, we reported the level of evidence as very low quality.[24]

2.9. "Summary of findings" tables

We planned to present 2 main "summary of findings" tables: cannabis vs control, and CBM (to include individual cannabinoids) vs control. We planned to include the following 7 outcomes: 50% pain reduction, 30% pain reduction, AEs, serious AEs, physical functioning, emotional functioning, and sleep. We rated the quality of evidence for all analyses.

2.10. Data synthesis

We combined data in meta-analyses where sufficient data were available using Revman 5.0. We used MDs for continuous outcomes, and risk difference (RD) for dichotomous outcomes. We calculated number needed to treat to benefit (NNTB) where we were able. Heterogeneity was interpreted following the Cochrane Handbook.[30] Adverse events were entered into meta-analyses and calculated using RDs and 95% CIs. Where possible, we described any assessment of possible causality of AEs.

We conducted comparisons of cannabis vs control, and CBM (including individual cannabinoids) vs control, for each of our named outcomes to determine efficacy. We conducted 4 primary analyses, which included all trials, conducted with a subgroup analysis by drug type, at 2 time-points:

(1) Cannabis vs control at short-term follow-up (up to 7 days treatment duration)
(2) Cannabis vs control at long-term follow-up (greater than or equal to 7 days treatment duration)
(3) Cannabis-based medicine vs control at short-term follow-up (up to 7 days treatment duration)
(4) Cannabis-based medicine vs control at long-term follow-up (greater than or equal to 7 days treatment duration).

We planned to conduct sensitivity analyses where appropriate to investigate the impact of risk of bias and study quality.

2.10.1. Subgroup analyses

In addition, where enough data were available, we conducted the following subgroup analyses at 2 time-points outlined above:

(1) Age of participants (2-10 years, 11-17 years, 18-64 years, over 65 years);
(2) Type of comparator;
(3) Route of administration;
(4) Dose of treatment;
(5) Type of pain experienced (acute, neuropathic pain, fibromyalgia, musculoskeletal pain, headache/migraine, etc.).
(6) Cannabis or CBM administered adjunctively vs nonadjunctively to other medicines.

3. Results

We found 8608 abstracts in the database search and 130 abstracts from other searches. After duplicates were removed, we sifted 7080 abstracts (**Fig. 1**). We pulled 165 full texts and subsequently excluded 129 full texts, with 36 trials meeting our inclusion criteria.

Of the 129 excluded studies, we excluded 39 studies that included fewer than 30 participants posttreatment, 27 studies that did not include people with a pain condition, 24 studies that did not assess pain as an outcome, 21 conference abstracts, 2 follow-up studies that were single arm, and one experimental pain study (see Appendix 2, available at http://links.lww.com/PAIN/B48). Fifteen trials are awaiting classification; of these, 3 are completed, 5 are not yet recruiting, 3 are recruiting, one is ongoing, one is unknown, and 2 prematurely ended (no results) (see Appendix 3, available at http://links.lww.com/PAIN/B48).

Appendix 4 describes the 39 excluded studies due to small size alone, available at http://links.lww.com/PAIN/B48.

3.1. Included studies

The 36 completed RCTs meeting our inclusion criteria included 4 trial registrations without associated journal manuscripts. Across all studies, 7217 participants were randomized to trial arms and 6149 completed treatment, giving an average of 14.4% attrition (0%-33%). In 34 trials that reported sex, females (n = 3691) outnumbered males (3163). The average age of participants was 51 years (SD = 11). We did not find any trials including children or adolescents <18 years of age.

We found trials that treated people with neuropathic pain (n = 13), cancer (n = 6), acute pain after surgery (n = 4), multiple sclerosis (MS) (n = 10), and one each treated people with chronic prostatitis/chronic pelvic pain, carpal tunnel syndrome, and back pain.

Twenty-three trials had 2 arms, 8 trials had 3 arms, 2 trials had 4 arms, 2 trials had 5 arms, and 1 trial included 6 arms.

Trials delivered a treatment arm of nabiximols (n = 17), cannabis (n = 6), THC (n = 4; varying doses), palmitoylethanolamide (PEA; n = 3), fatty acid amide hydrolase (FAAH) inhibitors (n = 2; ASP3652, ASP8477), dronabinol (n = 2), nabilone (n = 2), cannabinoid receptor agonist (n = 2; AZD1940, GW842166), and THC congener (n = 1; benzopyran peridine). A summary of trial characteristics is shown in **Table 2**. A more extensive description can be found in Appendix 9 and 10, available at http://links.lww.com/PAIN/B49.

Thirty trials used only a placebo control arm. Two studies used active controls of dihydrocodeine or piritramide. Four trials delivered naproxen, ibuprofen, or codeine in addition to placebo. Most studies delivering treatments to participants with chronic pain did so in addition to ongoing analgesics.

3.2. Risk of bias

Risk of bias judgments for each study are shown in **Figures 2 and 3** and described in Appendix 5, available at http://links.lww.com/PAIN/B48.

3.2.1. Random sequence generation

Random sequence generation (checking for possible selection bias). We judged 17 studies to be at low risk of bias for random sequence generation, and we judged the remaining studies as unclear risk of bias because they did not provide a method of randomisation.

3.2.2. Allocation concealment

Allocation concealment (checking for possible selection bias). Eleven studies described a convincing method of allocation concealment and were rated as low risk of bias. The remaining studies did not describe how they concealed allocation and therefore we rated them unclear.

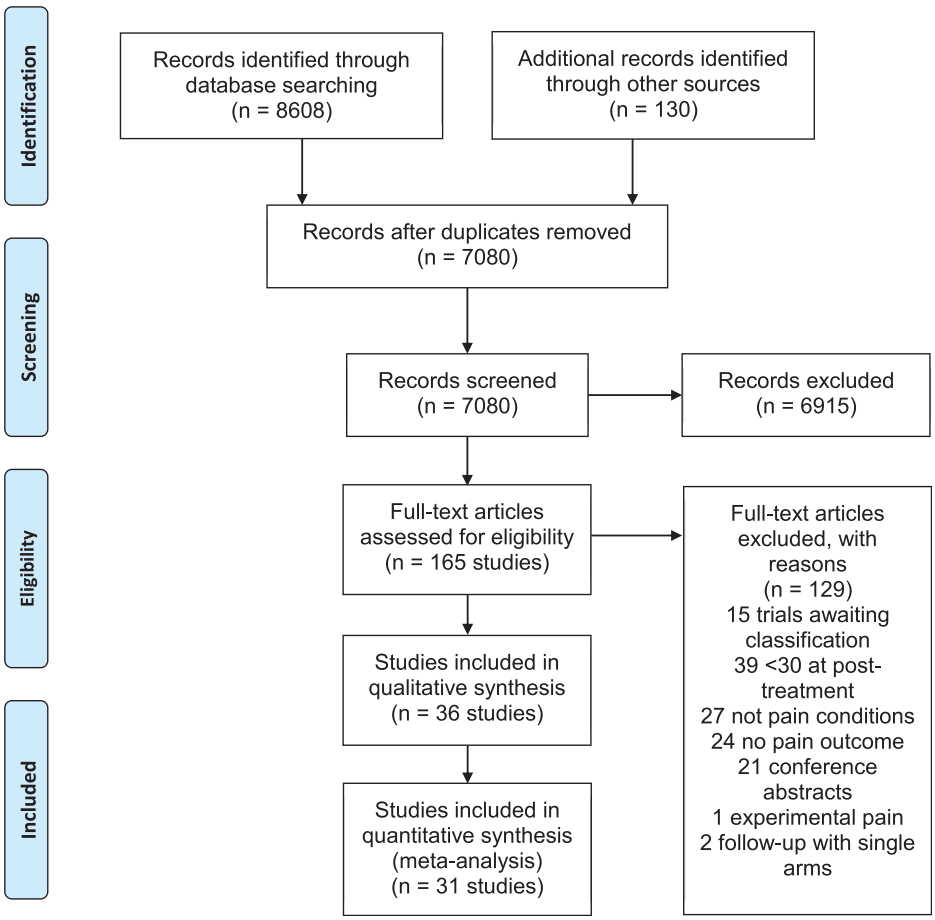

Figure 1. PRISMA flow chart of studies.

3.2.3. Blinding of participants and personnel

Blinding of participants and personnel (checking for possible performance bias). We found 18 studies that provided a method of blinding participants and personnel, which we rated as low risk of bias. The remaining studies did not provide a clear statement of blinding, and therefore we rated these as unclear risk of bias.

3.2.4. Blinding of outcome assessment

Blinding of outcome assessment (checking for possible detection bias). We rated 17 studies as low risk of bias, which stated a clear method of blinding outcome assessors in studies. We rated the remaining studies as unclear because they did not provide a clear method of blinding their outcome assessors.

3.2.5. Incomplete outcome data

Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We rated 10 studies as low risk of bias for incomplete outcome data. These studies either did not report many dropouts during treatment or used baseline observation carried forwards. Twenty studies did not clearly report their data imputation method and therefore we rated these as unclear risks of bias. The remaining 6 studies used last observation carried forwards and therefore, we rated these studies as high risk of bias.

3.2.6. Selective reporting

Selective reporting (checking for reporting bias). We found 12 studies pre-registered a protocol and reported all prespecified outcomes. We found 9 studies did not pre-register the protocol and rated these as unclear risk of bias. We rated 15 studies as high risk of bias; these studies pre-registered their protocol but did not report all outcomes in the trial or included additional outcomes in the trials, or have not published their results in a scientific journal.

3.2.7. Size

We found 2 studies had more than 200 participants/arm and therefore rated these as low risk of bias. A further 14 studies included between 50 and 200 participants/arm and judged these to be unclear risk of bias. We judged the remaining studies as high risk of bias, including fewer than 50 participants/arm.

3.3. Treatment efficacy

We found very few posttreatment mean values and SDs in treatment manuscripts and clinical registries to enter into analyses. When we requested data from authors, few replied. The authors who did respond referred us to the pharmaceutical companies, who referred us to the published article and clinical registry, and did

Table 2

Characteristics of included studies.

Study	Posttreatment N	Trial arms	Cannabis type	Control group	Treatment length (wk)
Acute pain					
Kalliomaki et al.[34]	151	3	Receptor agonist	Naproxen placebo + AZD1940 placebo/ Naproxen 500 mg + AZD1940 placebo	0.14
Levin et al.[38]	334	2	Nabilone	Placebo	0.14
Ostenfeld et al.[54]	121	4	Receptor agonist	Placebo	0.14
Seeling et al.[63]	100	2	THC	Piritramide	0.3
Back pain					
Guida et al.[23]	619	3	PEA "Normast"	Placebo	3
Cancer <7 days					
Jochimsen et al.[32]	35	5	THC congener	Placebo/Codeine	0.14
Noyes et al.[51]	36	5	THC (10 mg, 20 mg)	Placebo/Codeine	0.14
Cancer 2-5 weeks					
Fallon et al.[17] (study 1)	294	2	Nabiximols	Placebo	5
Fallon et al.[17] (study 2 EERW)	165	2	Nabiximols	Placebo	5
Johnson et al.[33]	144	3	Nabiximols; THC	Placebo	2
Lichtman et al.[39]	291	2	Nabiximols	Placebo	5
Portenoy et al.[57]	263	4	Nabiximols	Placebo	5
Carpal tunnel					
Faig-Marti and Martinez-Catassus[16]	61	2	PEA	Placebo	8.5
Multiple sclerosis, >4 weeks					
Langford et al.[35]	297	2	Nabiximols	Placebo	14
Rog et al.[59]	64	2	Nabiximols	Placebo	5
Schimrigk et al.[62]	169	2	Dronabinol	Placebo	16
Multiple sclerosis, progression					
Ball et al.[2]	415	2	Dronabinol	Placebo	144
Multiple sclerosis, spasticity					
Collins, 2010[5]	305	2	Nabiximols	Placebo	14
Corey-Bloom et al.[6]	30	2	Cannabis (with THC)	Placebo	0.4
Leocani et al.[37]	38	2	Nabiximols	Placebo	4
Markova, 2019[40]	96	2	Nabiximols	Placebo	4
Zajicek et al.[82]	224	2	Cannabis	Placebo	15
Zajicek et al.[81]	611	3	Cannabis and THC/CBD	Placebo	12
Neuropathic pain <1 day					
Wilsey et al.[78]	32	3	Cannabis	Placebo	0.14
Wilsey et al.[77]	36	3	Cannabis	Placebo	0.14
Wilsey et al.[79]	42	3	Cannabis	Placebo	0.14
Neuropathic pain <4 weeks					
Berman et al.[3]	45	3	CBD+THC (1:1) and THC	Placebo	2
NCT01606176[48]	63	2	Nabiximols	Placebo	3
Neuropathic pain >4 week					
Andresen et al.[1]	63	2	PEA	Placebo	12
Bradford et al.[4]	63	2	FAAH	Placebo	6
EUCTR2004-002530-20[26]	230	2	Nabiximols	Placebo	14
Frank et al.[21]	64	2	Nabilone	30 mg dihydrocodeine	14
NCT00710424[27]	230	2	Nabiximols	Placebo	14
NCT01606202[49]	106	2	Nabiximols	Placebo	7
Nurmikko et al.[53]	105	2	Nabiximols	Placebo	5
Serpell et al.[64]	173	2	Nabiximols	Placebo	14
Pelvic pain					
Wagenlehner et al.[75]	199	6	FAAH	Placebo	12

EERW, enriched enrollment with randomised withdrawal; FAAH, fatty acid amide hydrolase.

not provide additional data not listed in either place. Most extractable data reported mean change from baseline.

We were unable to conduct the intended subgroup analysis due to lack of variability in the included studies. We also did not conduct sensitivity analyses by risk of bias because most studies were either unclear or high risk of bias. Therefore, we included subgroup analyses of drug type in the primary comparisons, and also by pain condition.

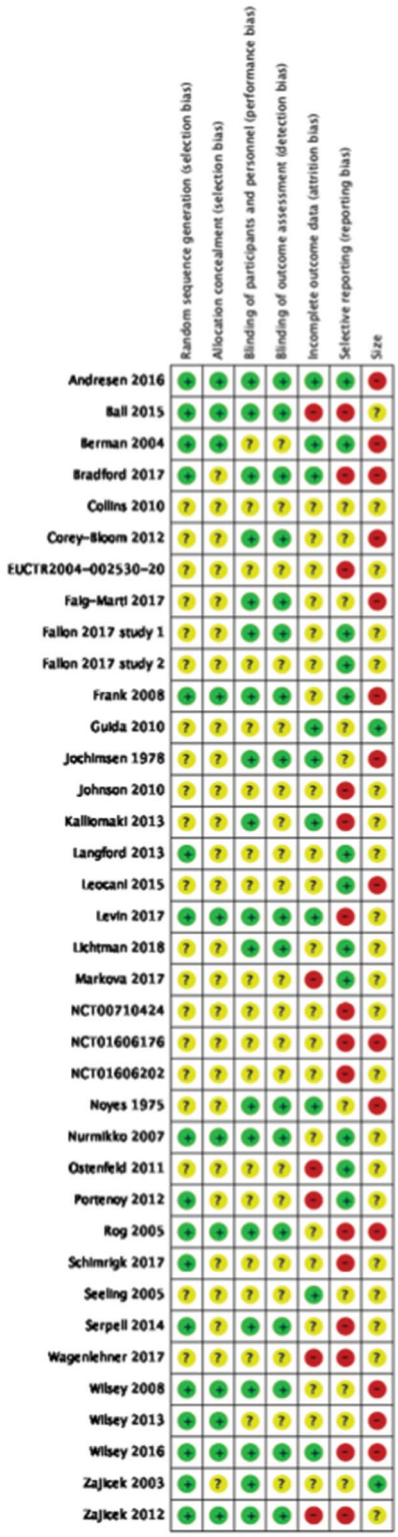

Figure 2. Risk of bias.

We present efficacy outcomes of 30% and 50% reduction in pain intensity, and posttreatment mean values and SDs. Due to the lack of transparency caused by the inaccessibility of mean values and SD data, we decided after protocol to also extract change from baseline mean values and SD. Although this is selective reporting from the primary investigator, our reporting of them provides greater transparency. We report the change from baseline scores for pain below, and change from baseline mean values for secondary outcomes are fully described with forest plots in Appendices 6 and 7, available at http://links.lww.com/PAIN/B48.

We report AEs for cannabis and individual CBM, but do not report AEs by treatment length.

We planned to present 2 main "summary of findings" tables: cannabis vs control, and CBM (to include individual cannabinoids) vs control. However, due to the lack of data for cannabis and most CBM, we only present one summary of findings table for nabiximols (**Table 3**).

3.3.1. Cannabis vs control at short-term follow-up (up to 7 days treatment duration)

Three trials by one author group evaluated the effects of inhaled or vaporised cannabis on chronic neuropathic pain in single-dose experiments lasting one day or less.[77–79] The studies were all 3-arm trials, comparing different doses of THC content to placebo. One further study conducted a single-dose crossover trial including cannabis and placebo in participants with MS.[6] Only one trial included participants with a minimum pain intensity score.[79]

3.3.1.1. Pain

Two trials (231 patients) reported a beneficial effect of cannabis at reducing pain intensity by at least 30% (RD 0.33, 95% CIs 0.20 to 0.46; very low-quality, Analysis 1.1).[77,79] An earlier study by the same group that met inclusion also indicated short-term antinociceptive effects of inhaled cannabis.[78] This would be equivalent to an NNTB of 3; the number of patients in nil effect trials required to reduce the effect to a clinically irrelevant NNTB of 10 would be 773, and to an NNTB of 20 would be 1876.

These 2 studies showed a short-term analgesic effect for inhaled cannabis after single doses. The size of effect (33% more patients with at least 30% pain intensity reduction) was of potential clinical significance.

One study reported continuous pain intensity after treatment and so could not be combined in an analysis.[6] There was no difference between treatment and control for pain intensity.

3.3.1.2. Secondary outcomes

One study presented extractable data for emotional functioning.[6] However, there was no difference between groups after treatment. Despite other outcomes assessed, we could not extract any data from the trials or clinicaltrial.gov registration.

We downgraded GRADE ratings on all outcomes for this comparison to very low due to the small number of participants contributing to analyses, meaning we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

3.3.2. Cannabis vs control at long-term follow-up (greater than or equal to 7 days treatment duration)

Two studies by one author group delivered cannabis treatment compared to placebo control over a 12- to 15-week treatment period.[81,82] Oral capsules were delivered to participants with MS, and neither study defined a minimum pain intensity as part of the inclusion criteria. We could not combine any data and therefore no meta-analyses are presented.

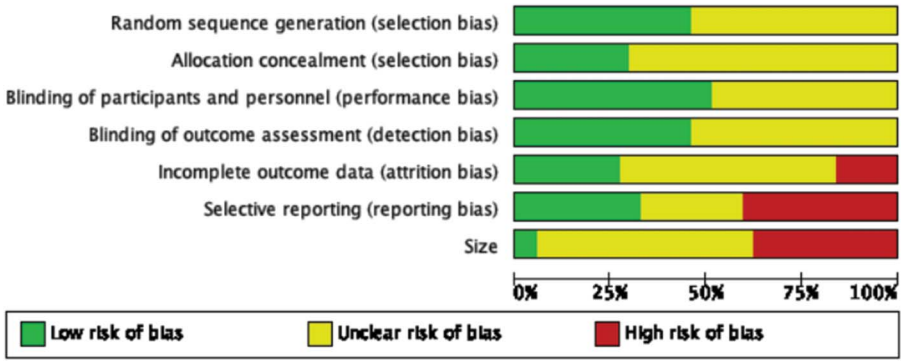

Figure 3. Risk of bias summary.

3.3.2.1. Pain

One study with 174 participants reported 30% reduction in pain intensity and showed a proportion of the treatment group with high baseline pain reported significantly higher reduction in pain compared to placebo[82] (Analysis 2.1). However, when reporting mean pain intensity of the whole sample after treatment, no significant effect was reported. A separate study by the same author group described a greater proportion of patients with undefined "improvement" in pain for oral cannabis extract over 15 weeks, although this is difficult to interpret without understanding how the authors defined "improvement."[81]

3.3.2.2. Secondary outcomes

One study reported mean sleep after treatment and found no difference between groups.[82] No other outcomes were reported.

We downgraded all outcomes for this comparison to very low due to the small number of participants contributing to analyses.

3.3.3. Cannabis-based medicine vs control at short-term follow-up (up to 7 days treatment duration)

Four trials studied the effects of single-dose cannabinoids on acute postoperative pain[34,38,54,63] and 2 on cancer pain[32,51] over the short term. A number of cannabinoids were delivered including a THC congener benzopyran peridine,[32] a cannabinoid receptor agonist AZD1940[34] and GW842166,[54] nabilone (a synthetic THC analog[38]), and 2 studies delivering different doses of THC (5-20 mg;[51,63]). We analysed these studies together because there were too few data to analyse by CBM or cannabinoid type.

3.3.3.1. Pain

One study including 105 participants with cancer reported 30% pain reduction[32] and 2 studies including 207 participants with cancer reported 50% pain reduction.[32,51] Those studies delivered a THC congener or THC, respectively. Neither analysis showed differences between cannabinoid and placebo (30% pain reduction: RR 0.11, 95% CI −0.09 to 0.32, very low-quality, Analysis 3.1; 50% pain reduction: RR 0.07, 95% CI −0.29 to 0.43, very low-quality; Analysis 3.2). No trials of acute postoperative pain could be entered into analyses.

We were unable to combine any other data for other outcomes across these studies. One three-arm study showed no difference between AZD1904 and placebo, but participants receiving naproxen reported a significantly lower pain intensity compared to placebo after the operation.[34] A second study also failed to show any difference between GW842166 and placebo, and ibuprofen was superior to both at reducing pain intensity.[54] Oral THC and nabilone were also without effect.[38,63]

In conclusion, we found no analgesic effect for CBM in acute or cancer pain when treatment was delivered up to 7 days.

3.3.3.2. Secondary outcomes

One study assessed mood and found no difference between groups on anxiety after treatment.[34]

Rescue medications were assessed in 2 acute pain studies.[34,54] One study found that participants in the treatment group requested rescue medication later compared to placebo, but earlier compared to ibuprofen.[54] There was no difference between participants in the AZD1940 and placebo group requesting rescue medications.[34] However, people taking naproxen requested significantly fewer rescue medications compared to the other 2 groups.[34]

We could not extract data for other outcomes. We downgraded all outcomes for this comparison to very low due to the small number of participants contributing to analyses, meaning we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

3.3.4. Cannabis-based medicine vs control at long-term follow-up (greater than or equal to 7 days treatment duration)

We could combine data for nabiximols, THC, PEA and FAAH. Due to single studies delivering other types of cannabinoids, we did not combine data. Studies that did not include a minimum pain intensity are not included in these analyses. See **Table 3** for quality of evidence summary of findings.

3.3.4.1. Nabiximols

We could extract data from 12 studies.[3,17,27,33,35,39,48,49,53,57,59,64]

3.3.4.1.1. Pain

Six trials (1484 patients) have reported results for at least 30% pain relief compared with placebo in any pain condition.[33,35,53,57,59,64] The combined effect was a small beneficial effect (RD 0.06, 95% CI 0.01 to 0.12, very low-quality evidence, Analysis 4.1.1). This would be equivalent to an NNTB of 17; the number of patients in nil effect trials required to reduce the effect to a clinically irrelevant NNTB of 20 would be 262. We downgraded this outcome twice for limitations in the design and implementation of available studies and once for indirectness of evidence.

Two trials (464 participants) have reported results for at least 50% pain relief, showing no difference from placebo (RD 0.07, 95% CI −0.04 to 0.17; very low-quality of evidence, Analysis

Table 3

Summary of findings for nabiximols (>7 days).

Nabiximols compared with control for people with pain						
Patient or population: people with pain **Settings: any setting** **Intervention: Nabiximols >7 days** **Comparison: control**						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Any control	**Nabiximols**				
30% reduction in pain intensity	308 per 1000	346 per 1000	RD 0.06 (0.01 to 0.12)	1484 participants (6 studies)	⊕⊖⊖⊖ very low†‡	
50% reduction in pain intensity	236 per 1000	273 per 1000	RD 0.07 (−0.04 to 0.17)	464 participants (2 studies)	⊕⊖⊖⊖ very low§	
Pain intensity change scores Higher scores indicate greater decreases in pain intensity		The mean change in pain intensity in the intervention groups was 0.34 lower (0.54 lower to 0.14 lower)		2497 participants (12 studies)	⊕⊖⊖⊖ very low†‖	All studies used 0-10 NRS/VAS for pain intensity.
Physical functioning (change scores) Higher scores indicate better physical functioning		The mean change in physical functioning in the intervention groups was 2.84 lower (5.21 lower to 0.47 lower)		364 participants (4 studies)	⊕⊖⊖⊖ very low§	3 trials used the pain Disability Index and 1 used the Expanded Disability Status scale
Emotional functioning (change scores) Higher scores indicate better emotional functioning		The mean change in emotional functioning in the intervention groups was 0.38 higher (0.74 lower to 1.50 higher)		561 participants (4 studies)	⊕⊕⊖⊖ low¶#	Trials used the Short Form-36, General Health Questionnaire, Montgomery–Asberg Depression rating scale, and Hospital Anxiety Depression scale.
Sleep quality (change scores) Higher scores indicate better sleep quality		The mean change in sleep quality in the intervention groups was 0.36 lower (0.57 lower to 0.14 lower)		2758 participants (13 studies)	⊕⊖⊖⊖ very low†‖	Most studies used a 0-10 NRS for sleep quality/disruption.
Participants with any adverse event	578 per 1000	705 per 1000	RD 0.13 (0.08 to 0.19)	2551 participants (12 studies)	⊕⊕⊖⊖ low†	

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

* The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

† Downgraded twice for limitations in the design and implementation of available studies.

‡ Downgraded once for indirectness of evidence.

§ Downgraded to very low due to small number of participants that could be entered into the analysis.

‖ Downgraded once for unexplained heterogeneity.

¶ Downgraded once for limitations in the design and implementation of available studies.

Downgraded once for imprecision.

CI, confidence interval; RD, risk difference.

4.2.1).[35,53] We downgraded this outcome due to small number of participants contributing to the analyses.

Only one study reported posttreatment mean values and SDs, and therefore we analysed mean change to be comprehensive.[59] Twelve studies (2497 patients) reported mean pain change, showing a small benefit (mean difference [MD] −0.34, 95% CI −0.54 to −0.14; very low-quality of evidence, Analysis 4.3.1).[3,17,27,33,35,39,48,49,53,57,59,64] We downgraded this outcome twice for limitations in the design and implementation of available studies and once for unexplained heterogeneity (50%).

3.3.4.1.2. Secondary outcomes

No studies reported posttreatment mean values and SDs for the secondary outcomes with the exception of quality of life. In one study, no differences between groups were found for quality of life outcomes.[33] Change score analyses were conducted for physical functioning, emotional functioning, sleep, and quality of life; no difference between groups was found with the exception of a significant improvement in sleep quality, favouring nabiximols. NCT01606176 reported a significant difference between the number of days using rescue analgesia, favouring the treatment group,[48] but 6 other trials reporting change scores found no difference between groups.

3.3.4.2. THC

3.3.4.2.1. Pain

We could include 2 trials (528 participants) in an analysis for at least 30% pain relief compared with placebo in any pain condition.[2,33] There was no beneficial effect (RD −0.02, 95% CI −0.09 to 0.05; very low-quality of evidence, Analysis 4.1.2). We downgraded this outcome to very low due to limitations in the design and implementation of available studies and

indirectness of evidence. We did find any studies that reported 50% reduction of pain intensity.

One study reported posttreatment mean values and SDs so we could not analyse data (no differences reported between groups).[38] For comprehension, we also analysed mean change and found that 4 studies (795 patients) have reported no beneficial effect of THC compared to control (MD −0.15, 95% CI -−0.48 to 0.17; very low-quality, Analysis 4.3.2).[2,3,33,62] We downgraded twice for limitations in the design and implementation of available studies and once for selective reporting biases.

3.3.4.2.2. Secondary outcomes

Two studies reported no difference in sleep quality between groups. No data could be extracted to assess other outcomes.

3.3.4.3. PEA

3.3.4.3.1. Pain

Two trials (744 patients) have reported results for at least 30% pain relief compared with placebo in any pain condition. The combined effect showed no benefit of PEA compared to placebo (RD 0.21, 95% CI −0.37 to 0.80; very low-quality Analysis 4.1.3).[1,23] We downgraded once for limitations in the design and implementation and twice for heterogeneity (98%). Two trials (704 patients) have reported results for at least 50% pain relief, with no beneficial effect of PEA compared to placebo (RD 0.17, 95% CI −0.23 to 0.57, very low-quality evidence, Analysis 4.2.3).[1,23] We downgraded both outcomes once for limitations in the design and implementation and twice for heterogeneity (>95%).

One study (78 participants) assessed posttreatment mean values and SDs and did not find a beneficial effect of PEA compared to control.[16] Two studies (697 patients) reported mean pain change, showing no benefit (MD −0.95, 95% CI −3.14 to 1.25, very low-quality, Analysis 4.3.3).[16,23] We downgraded once for limitations in the design and implementation twice for imprecision.

3.3.4.3.2. Secondary outcomes

No other meta-analyses could be conducted. One study reported no differences between groups on physical functioning, emotional functioning, sleep, and quality of life.[1]

3.3.4.4. Fatty acid amide hydrolase inhibitors

3.3.4.4.1. Pain

No studies reported 30% or 50% reduction of pain intensity. One study delivered FAAH inhibitor ASP3652 and reported posttreatment mean and SDs but no effect was found.[75] The same study (86 participants) reported mean change from baseline, and similarly, no beneficial effect was found between groups.[75] We downgraded both outcomes to very low due to small number of participants contributing to the analysis.

3.3.4.4.2. Secondary outcomes

No data were extractable for the remaining outcomes.

No other CBM reported results in more than 2 studies.

3.3.5. Adverse events

The following analyses included all studies delivering cannabis or relevant CBM regardless of treatment length.

3.3.5.1. Cannabis

3.3.5.1.1. Participants with adverse events

Two studies, (750 participants) reported participants with any AEs and reported no difference between groups (RD 0.08, 95% CI −0.10 to 0.25, very low-quality, Analysis 5.1.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (<95%). One study reported if participants experienced treatment-related AEs and found a significantly higher number of people receiving cannabis reported AEs compared to those in the control group.[82]

3.3.5.1.2. Participants with serious adverse events

Three studies (690 participants) reported no difference between groups on the number of people with serious AEs (SAEs) overall (RD −0.05, 95% CI −0.16 to 0.07, very low-quality, Analysis 5.3.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (>75%). One study (120 participants) reported treatment-related SAEs and also found no difference between groups.

3.3.5.1.3. Withdrawals

Two studies (605 participants) reported all causes of withdrawal, but no difference between groups was found (RD 0.05, 95% CI −0.03 to 0.13, very low-quality, Analysis 5.5.1). We downgraded this outcome once for limitations in the design and implementation, once for indirectness, and once for heterogeneity (>50%). Two studies also reported withdrawals due to AEs in 605 participants, and no differences was found between groups (RD 0.08, 95% CI −0.08 to 0.25, very low-quality, Analysis 5.6.1). We downgraded this outcome once for limitations in the design and implementation and twice for heterogeneity (<95%). Just one study reported withdrawal due to lack of efficacy, and similarly no difference between groups was reported. No studies reported withdrawals due to SAEs.

3.3.5.2. Nabiximols

3.3.5.2.1. Participants with adverse events

Twelve studies (2551 participants) reported participants in the treatment group were more likely to have an AE compared to control (RD 0.13, 95% CI 0.08 to 0.19, low-quality evidence, Analysis 5.1.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. Similarly, participants in the nabiximols group were significantly more likely to report a treatment-related AE compared to control (RD 0.19, 95% CI 0.10 to 0.27, very low-quality, Analysis 5.2.2). We downgraded this outcome twice for limitations in the design and implementation of included studies and once for heterogeneity (>50%).

3.3.5.2.2. Participants with serious adverse events

When investigating SAEs, we found no group differences in 11 studies (2108 participants; RD 0.02, 95% CI −0.00 to 0.04, low quality, Analysis 5.3.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. Similarly, in 5 studies with 1418 participants, no difference was found for treatment-related SAEs (RD 0.01, 95% CI −0.02 to 0.04, very low-quality, Analysis 5.4.2). We downgraded this outcome twice for limitations in the design and implementation of included studies and once for heterogeneity (>50%).

3.3.5.2.3. Withdrawals

Eleven studies (2489 participants) reported all causes of withdrawals and no difference was found between groups (RD 0.03, 95% CI −

0.01 to 0.07, low-quality evidence, Analysis 5.5.2). We downgraded this outcome twice for limitations in the design and implementation of included studies. However, significantly more people withdrew from the treatment group due to AEs compared to control (12 studies, 2601 participants, RD 0.04, 95% CI 0.01 to 0.06, very low-quality, Analysis 5.6.2). We downgraded twice for limitations in the design and implementation of included studies and once for unexplained heterogeneity (>50%). When investigating withdrawals due to lack of efficacy (9 studies, 2001 participants) and due to SAE (5 studies, 729 participants), we did not find differences between groups (RD −0.01, 95% CI −0.02 to 0.00, Analysis 5.7.2; RD 0.00, 95% CI −0.01 to 0.02, Analysis, 5.8.1, respectively). We rated both as low-quality evidence. We downgraded the former twice for limitations in the design and implementation of included studies and the latter once for limitations in the design and implementation of included studies and once for indirectness.

3.3.5.3. THC

3.3.5.3.1. Participants with adverse events

We found participants in the THC arm reported more AEs compared to the control arm in 4 studies with 1168 participants (RD 0.15, 95% CI 0.05 to 0.24, very low-quality, Analysis 5.1.3). We downgraded this outcome once for unexplained heterogeneity (>50%) and twice for selective reporting biases. Only one study with 240 participants reported treatment-related AEs, which were significantly higher in the treatment compared to control group.

3.3.5.3.2. Participants with serious adverse events

Five studies reported SAEs (1012 participants) and one study reported treatment-related SAEs (240 participants). We found both analyses showed no difference between treatment and control groups (RD 0.00, 95% CI −0.02 to 0.02, low-quality, Analysis 5.3.3; RD 0.01, 95% CI −0.01 to 0.03, very low-quality, Analysis 5.4.3, respectively). We downgraded the former once for limitations in the design and implementation of included studies and once for selective reporting bias, and the latter to very low due to the small number of participants able to be included in the analysis.

3.3.5.3.3. Withdrawals

We found 6 studies (1357 participants) reported all causes of withdrawals, and no difference between groups was found (RD 0.01, 95% CI −0.06 to 0.08, very low-quality, Analysis 5.5.3). We downgraded once for limitations in the design and implementation of included studies and twice for heterogeneity. We found no differences between groups when investigating withdrawals due to AEs (7 studies, 1428 participants, RD 0.02, 95% CI −0.01 to 0.05, very low-quality, Analysis 5.6.3), SAEs (4 studies, 979 participants, RD 0.00, 95% CI −0.01 to 0.01, low-quality, Analysis 5.8.2), or lack of efficacy (3 studies, 675 participants, RD 0.00, 95% CI −0.01 to 0.01, very low-quality, Analysis 5.7.3).

We downgraded withdrawals due to AEs twice for heterogeneity and once for selective reporting bias. We downgraded withdrawals due to SAEs once for indirectness and once for selective reporting bias. We downgraded withdrawals due to lack of efficacy once for limitations in the design and implementation of included studies, once for heterogeneity, and once for selective reporting bias.

3.3.5.4. PEA

3.3.5.4.1. Participants with adverse events

We analysed 3 studies (770 participants) that reported any AE and found no differences between groups (RD 0.03, 95% CI −0.07 to 0.14, very low-quality, Analysis 5.1.4). We downgraded once for or limitations in the design and implementation of included studies and twice for heterogeneity. No studies reported treatment-related AEs.

3.3.5.4.2. Participants with serious adverse events

We analysed 3 studies (770 participants) that reported SAEs and treatment-related SAEs and found no differences between groups for either outcomes (RD 0.02, 95% CI −0.05 to 0.08, very low-quality, Analysis 5.3.4; RD 0.00, 95% CI −0.01 to 0.01, low quality, Analysis 5.4.4). We downgraded the former outcome once for limitations in the design and implementation of included studies and twice for heterogeneity and the latter outcome once for limitations in the design and implementation of included studies and once for indirectness.

3.3.5.4.3. Withdrawals

We analysed 3 studies (770 participants) that presented data for withdrawals and found no differences between groups (RD −0.03, 95% CI −0.07 to 0.01, low-quality evidence, Analysis 5.5.4). We downgraded this outcome once for limitations in the design and implementation of included studies and once for indirectness.

We could not run a meta-analysis for withdrawals due to AEs or SAEs because only one study with 73 participants reported these data. This study indicated no differences between groups. No study reported withdrawal due to lack of efficacy.

3.3.5.5. Fatty acid amide hydrolase inhibitors

3.3.5.5.1. Participants with adverse events

A single study (238 participants) could be included when assessing participants with AEs and treatment-related AEs, and there was no difference between groups in either analysis. A second EERW study reported AEs but we did not combine data due to the different study types.[4]

3.3.5.5.2. Participants with serious adverse events

One EERW study reported one SAE in each group and no SAEs in either group relating to treatment.[4] A further study reported no differences for participants experiencing treatment-related SAEs.[75] The data were not combined in an analysis due to different study designs.

3.3.5.5.3. Withdrawals

We found 2 studies with different study designs report on withdrawals, but we did not combine the data. No differences were found for all causes of withdrawals. One study reported withdrawals due to AEs and found more people withdrew in the treatment compared to the control group. We could not extract any data for other withdrawal outcomes.

3.3.5.6. Cannabinoid receptor agonists

3.3.5.6.1. Participants with adverse events

One study (123 participants) reported any AEs and indicated no differences between groups. No studies reported AEs related to treatment.

3.3.5.6.2. Participants with serious adverse events

We found 2 studies (274 participants) that reported any participants with an SAE. The analysis did not show any differences between groups (RD −0.04, 95% CI −0.22 to 0.15, very low-

quality, Analysis 6.3.4). We downgraded this outcome to very low due to small number of participants that could be included in the analysis. No studies reported treatment-related SAEs.

3.3.5.6.3. Withdrawals

We found 2 studies (274 participants) that reported all causes of withdrawal, withdrawals due to AEs, and withdrawals due to SAEs. For all analyses, no differences could be found between groups (RD 0.01, 95% −0.02 to 0.04, Analysis 5.5.6; RD 0.00, 95% CI −0.02 to 0.02, Analysis 5.6.6; RD 0.00, 95% CI −0.02 to 0.02, Analysis 6.8.6 respectively). We rated all 3 outcomes as very low-quality evidence due to the small number of participants that could be included in the analysis. One study reported withdrawals due to lack of efficacy and did not indicate any difference between groups.

3.3.6. Subgroup analyses

We analysed studies by pain condition type, irrespective of drug, dose, or route of administration; **Figure 4** shows results for 30% pain intensity reduction, **Figure 5** shows 50% pain intensity reduction, and **Figure 6** shows MD (on a 0-10 scale). A description and forest plot relating to secondary outcomes can be found in Appendix 8, available at http://links.lww.com/PAIN/B48.

3.3.6.1. Acute pain

Four trials studied the effects of single-dose cannabinoids on acute pain over the short term, 3 on postoperative pain,[34,54,63] and one studied postoperative nausea and vomiting.[38] We did not find any other acute pain studies, and no data from these studies could be combined into a meta-analysis. See section 3.3.3 for a description of the results.

3.3.6.2. Cancer pain

Two trials studied the effects of THC congener or THC for cancer pain over 6 hours.[32,51] Five trials (4 studies) studied the effects of cannabinoids on cancer pain over 2 to 5 weeks, all using nabiximols. Four studies delivered nabiximols,[17,33,39,57] one study also delivered THC alone.[33] Five of these studies had a minimum pain intensity of 4/10, so should have had sufficient sensitivity to detect a difference.

3.3.6.2.1. Pain

Pain outcomes for the 2 trials delivering treatment over 6 hours to participants with cancer pain are described in section 3.3.3.

Two trials delivering treatment 2 to 5 weeks[33,57] (477 participants) reported at least 30% pain relief; however, no benefit of cannabinoids were identified for reducing pain compared to placebo (RD 0.09, 95% CI −0.06 to 0.23, very low-quality, Analysis 6.1.2). We rated this outcome as very low-quality evidence due to the small number of participants that could be included in the analysis. No studies reported 50% pain reduction or pain intensity post-treatment.

Instead, 4 studies reported mean change from baseline (1259 participants) and findings showed no benefit of nabiximols compared to placebo (MD on a 0-10 scale −0.22, 95% CI −0.49 to 0.06, very low-quality Analysis 6.3.1;[17,33,39,57]). We downgraded twice for limitations in the design and implementation of included studies and once for unexplained heterogeneity (>50%).

The second study from Fallon et al.[17] was an enriched enrolment randomised withdrawal study that found no difference between nabiximols and placebo.

3.3.6.2.2. Secondary outcomes

No data could be combined in an analysis for remaining outcomes. Change from baseline was reported for emotional functioning, sleep, and quality of life but no differences were found in favour of CBM, and declines in cognitive functioning and nausea were reported in 2 studies in the treatment groups.

These findings show no analgesic effect for CBM in cancer pain.

3.3.6.3. Neuropathic pain, less than 1-day cannabinoid treatment duration

The results for 3 trials[77–79] evaluated the effects of inhaled or vaporised cannabis (THC) on chronic neuropathic pain in single-dose experiments lasting 1 day or less and are described in 3.3.1.

3.3.6.4. Neuropathic pain studies less than 4 weeks' treatment duration

Two studies delivered nabiximols to participants with neuropathic pain lasting 1 day to 4 weeks but did not provide data for our primary analyses.[3,48] Both studies had a minimum pain intensity of 4/10 and should have sufficient sensitivity to detect a difference.

One study conducted a three-way crossover of nabiximols, THC, and placebo, with pain measured over the last week of a 2-week treatment phase in 48 patients with brachial plexus avulsion.[3] There was a small but statistically significant reduction in mean pain score compared with placebo, with an implied 10% more patients achieving at least 30% pain intensity reduction. NCT01606176[48] was a 3-week trial of nabiximols in 70 patients with chronic refractory pain of neurological origin.[48] Both studies presented change scores and a difference between groups was found (MD −0.55, 95% CI −0.93 to −0.17, very low-quality, Analysis 6.3.2). We downgraded to very low-quality due to the small number of participants in the analysis.

No convincing analgesic effect was found for CBM in neuropathic pain in studies less than 4 weeks' duration.

3.3.6.4.1. Secondary outcomes

No data could be combined in an analysis for remaining outcomes. NCT01606176 reported a significant difference between the number of days using rescue analgesia, favouring the treatment group.[48] Change data did not show any notable differences between groups.

3.3.6.5. Neuropathic pain studies; more than 4 weeks' cannabinoid treatment duration

Eight studies lasting longer than 5 to 15 weeks evaluated the effects of CBM in neuropathic pain (neuropathic pain in MS is handled separately). Of the 8 studies, 5 delivered nabiximols, and one each delivered nabilone, PEA, or an FAAH-1 inhibitor. All studies had a minimum pain intensity of 4/10 and therefore should have sufficient sensitivity to detect a difference.

3.3.6.5.1. Pain

Four trials (736 participants) reported 30% pain reduction after treatment. We found no difference between treatment and placebo groups (RD 0.03, 95% CI −0.07 to 0.12, low-quality, Analysis 6.1.5).[1,27,53,64] We downgraded once for limitations in the design and implementation of included studies and once for unexplained heterogeneity. Similarly, in 2 trials (193 participants) that reported 50% reduction in pain intensity, we found no difference between treatment and control groups (RD 0.05, 95%

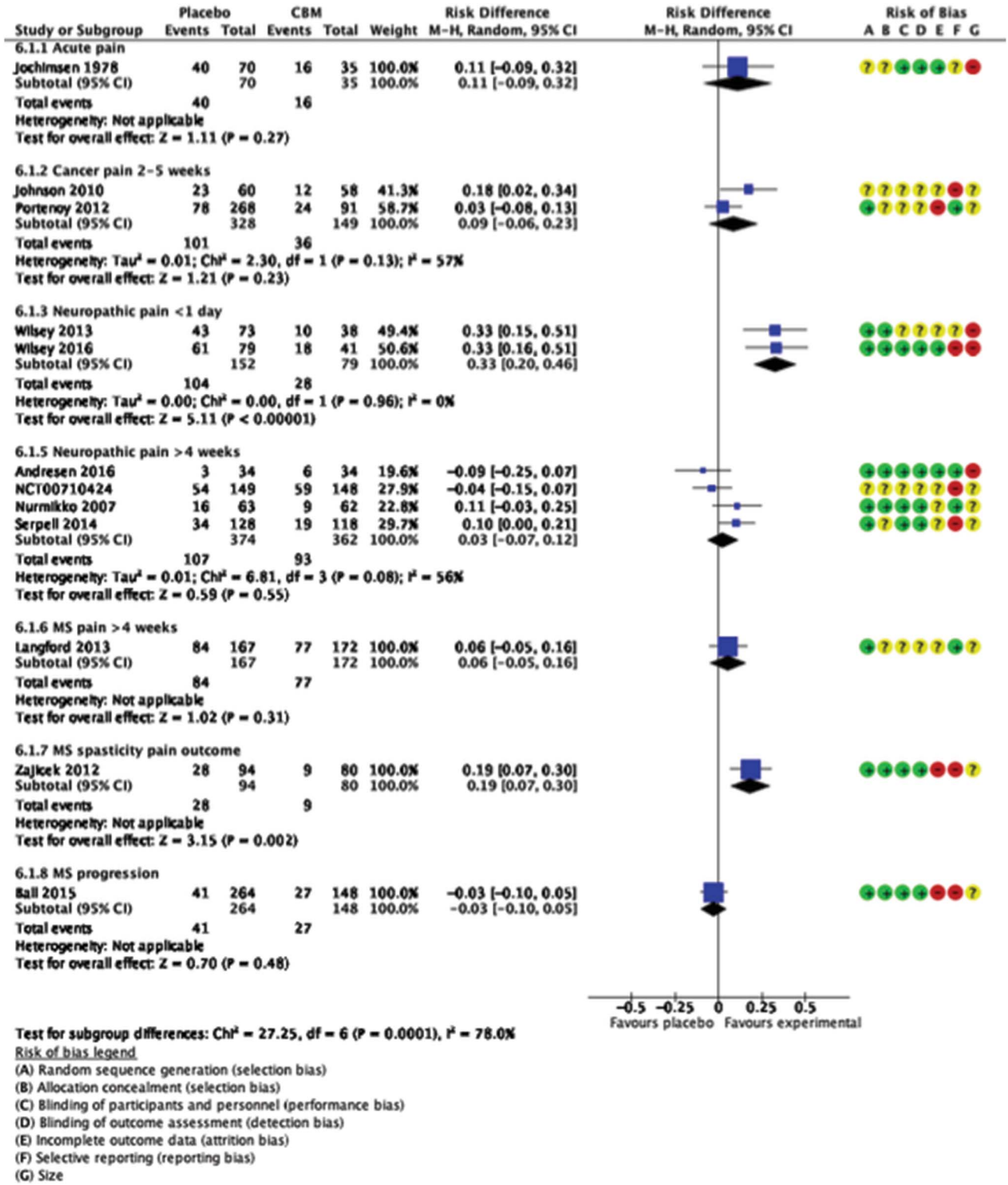

Figure 4. Analysis 6.1. Thirty percent reduction in pain intensity.

CI −0.11 to 0.21, very low-quality, Analysis 5.2.5).[1,53] We downgraded this outcome to very low due to the small number of participants contributing to the analysis.

Only one study reported end of treatment mean values and SDs for pain intensity and showed no difference between groups.[1] Therefore, for comprehension, we extracted mean change data from baseline, reported by 5 studies (768 patients). We found no significant change in pain between treatment groups (MD −0.31, 95% CI −0.65 to 0.03, low-quality, Analysis 6.3.3).[1,27,49,53,64] We downgraded this outcome once for limitations in the design and implementation of included studies and once for selective reporting bias.

Two studies did not provide data for analysis. One study compared nabilone with dihydrocodeine in 96 patients with

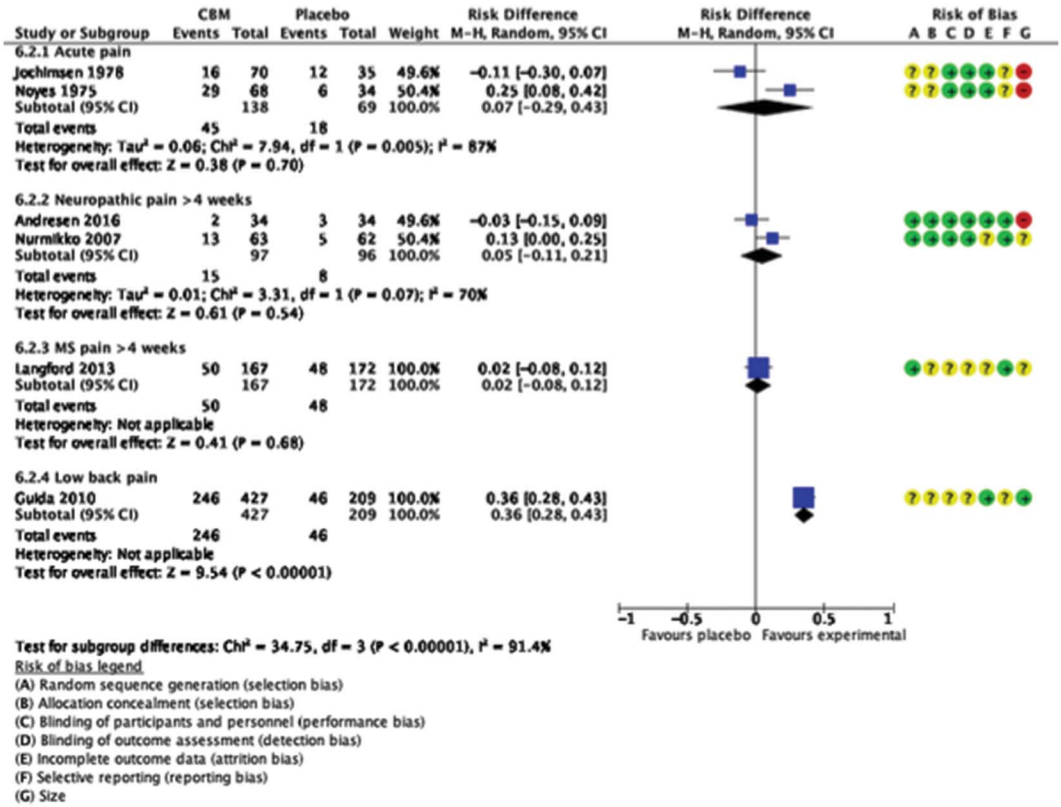

Figure 5. Analysis 6.2. Fifty percent reduction in pain intensity.

chronic neuropathic pain in a crossover study and found dihydrocodeine to be significantly better.[21] A separate study reported no difference in reduction of pain between groups.[26]

A further study used an enriched enrolment randomised withdrawal design lasting longer than 4 weeks in total, and with a 3-week randomised withdrawal phase.[4] Due to the different study design, we describe these findings separately. The authors compared FAAH inhibitor with placebo. Of the 132 patients with peripheral neuropathic pain entering the initial phase, 71 entered the randomised withdrawal phase; there was no difference between active drug and placebo.

No convincing analgesic effect was found for CBM in neuropathic pain in studies longer than 4 weeks.

3.3.6.5.2. Secondary outcomes

No other meta-analyses could be conducted. One study reported no differences between groups on physical functioning, emotional functioning, sleep, and quality of life.[1] The same study reported a significantly larger number of participants in the PEA groups consumed rescue analgesia compared to the control group.[1] However, change analyses from 4 studies showed better sleep in participants in the treatment group compared to control, but no other analyses could be conducted.

3.3.6.6. Multiple sclerosis-related chronic pain: cannabis-based medicine studies longer than 4 weeks

Three studies lasting 5 to 14 weeks examined the effects of CBM, specifically for chronic pain associated with MS.[35,59,62] Two studies had a minimum pain on entry of 40% of maximum, and all had mean initial pain scores of 65% of maximum or greater, so should have had sufficient sensitivity to detect a difference. Two used nabiximols, and one dronabinol and all compared to placebo control.

3.3.6.6.1. Pain

One study studied 339 patients taking nabiximols or placebo for 14 weeks, and provided the proportions achieving at least 30% and 50% pain intensity reduction; neither showed a benefit of nabiximols compared to placebo (Analysis 5.1.6 and 5.2.6).[35]

One study reported end of treatment mean values and SDs and showed a significant reduction in pain intensity for the treatment compared to control.[59] All 3 studies (613 patients) provided mean change in pain scores, and we found no difference between CBM and placebo (MD −0.41, 95% CI −1.02 to 0.19, very low-quality, Analysis 6.3.4).[35,59,62] We downgraded once due to unexplained heterogeneity and twice for selective reporting bias.

No convincing analgesic effect was found for CBM in neuropathic pain associated with MS in studies longer than 4 weeks.

3.3.6.6.2. Secondary outcomes

No data could be extracted for the remaining outcomes.

3.3.6.7. Multiple sclerosis studies principally examining CBM for spasticity

Six studies lasting less than 1 day to 15 weeks examined the effects of CBM in MS and reported some pain measures. None had a minimum pain requirement at baseline, and 2 reported initial pain at baseline (15% and 55% of maximum.[6,40] Three delivered nabiximols[5,37,40] and 3 delivered cannabis extract (all with THC;[6,81,82]). All studies compared to placebo control.

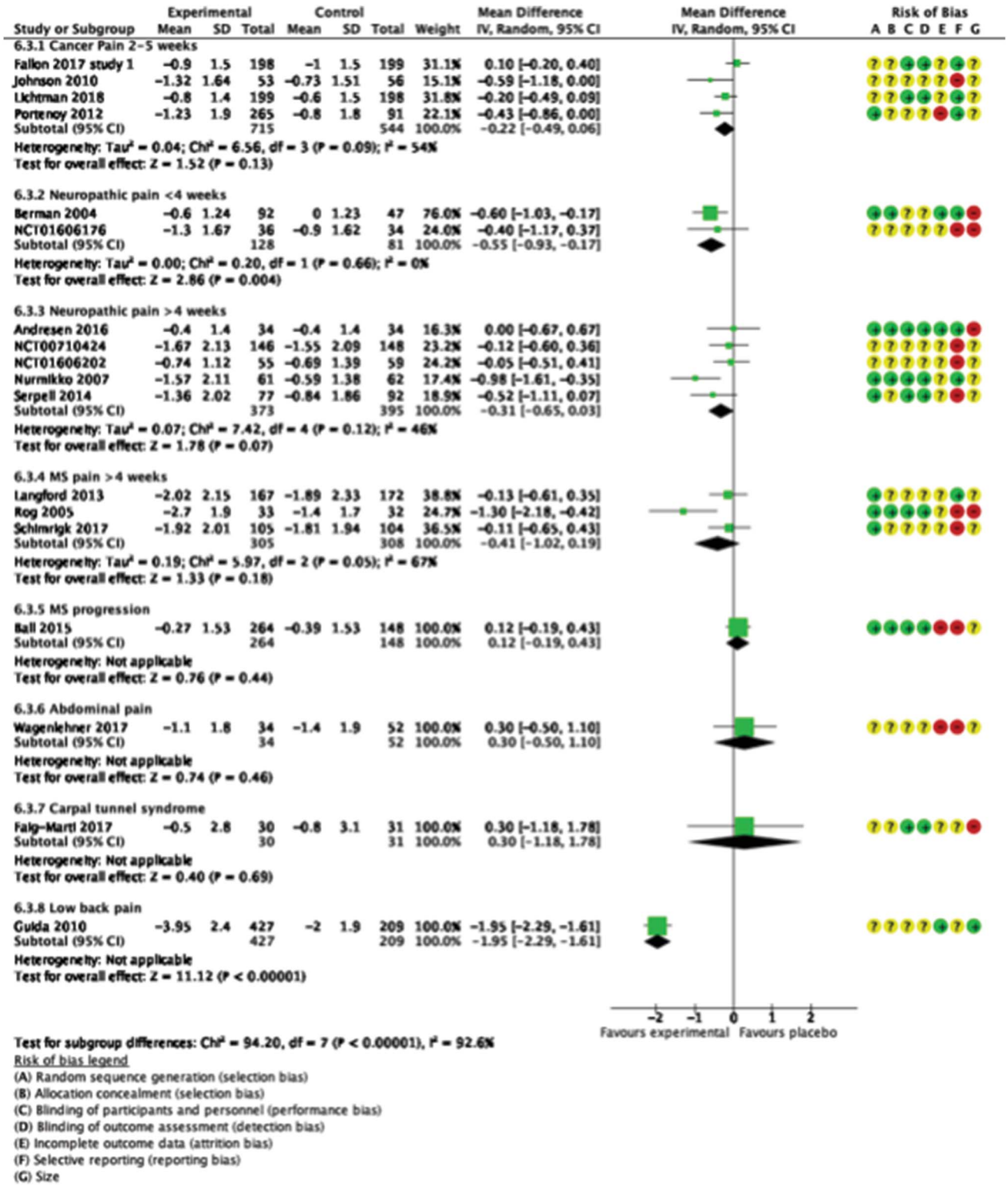

Figure 6. Analysis 6.3. Mean change for pain intensity (0-10 rating scale).

3.3.6.7.1. Pain

One study with 174 participants reported 30% reduction in pain intensity and showed the treatment group reported significantly higher reduction in pain compared to placebo (Analysis 6.1.7).[82] Another study reported that 76% (n = 37) of patients with a ≥30% spasticity response also reported ≥30% reduction in pain intensity (but did not provide numbers for the placebo group).[5] A third study described a greater proportion of patients with undefined "improvement" in pain for oral cannabis extract over 15 weeks, although this is difficult to interpret without understanding how the authors defined "improvement."[81]

When extracting mean pain intensity after treatment, 2 studies with 337 participants[6,82] reported no significant difference between groups.

One study found no difference between nabiximols and placebo for pain in a four-week crossover study.[37] A further study reported results of an enriched enrolment study in 107 patients over 12 weeks; mean pain was significantly lower with nabiximols than placebo.[40]

There is some evidence that CBM used to treat spasticity in MS also reduces pain, and there is a possibility that the 2 effects are linked.

3.3.6.7.2. Disability

In an enriched enrolment trial, no difference was found between groups for activities of daily living.[40]

3.3.6.7.3. Emotional functioning

One study used the Brief Symptom Inventory and found no difference between groups post-treatment.[6] Another study also reported the SF-36 and reported no significant differences between groups on the mental health subscale at the end of treatment.[40]

3.3.6.7.4. Secondary outcomes

No other meta-analyses could be conducted.

3.3.6.8. Multiple sclerosis progression

A single study evaluated the effects of THC on slowing progression in 363 MS patients over 3 years.[2]

3.3.6.8.1. Pain

There was no significant difference in mean pain/discomfort measured by the Multiple Sclerosis Spasticity Scale-88 at any time during the study, or in the proportion feeling significantly better at the end of the study. No other outcomes were assessed.

3.3.6.8.2. Physical functioning

The study also reported the SF-36 "physical health" subscale but no differences were reported between groups throughout the study.

3.3.6.8.3. Secondary outcomes

No other meta-analyses could be conducted.

3.3.6.9. Pelvic pain

A single study examined the effects of a FAAH inhibitor to placebo on 226 participants with chronic prostatitis or pelvic pain over 12 weeks.[75] There were no minimum inclusion criteria regarding minimum reported pain intensity.

3.3.6.9.1. Pain

One study reported no significant differences between ASP3652 and placebo on pain intensity.[75]

3.3.6.9.2. Quality of life

Similarly, no differences between treatment and control were reported for quality of life outcomes.[75]

3.3.6.9.3. Secondary outcomes

No other meta-analyses could be conducted.

3.3.6.10. Carpal tunnel syndrome

A single study examined the effects of oral PEA to placebo in 61 patients with carpal tunnel syndrome over 8 weeks.[16] There were no minimum inclusion criteria regarding minimum reported pain intensity.

3.3.6.10.1. Pain

There was no significant difference between PEA and placebo.

3.3.6.10.2. Physical functioning

There was no significant difference between PEA and placebo.

3.3.6.10.3. Secondary outcomes

No other meta-analyses could be conducted.

3.3.6.11. Low back pain

A single study examined the effects of oral PEA 300 mg or 600 mg in 676 patients with low back pain-sciatica, defined as "lumbosciatic algias" over 3 weeks,[23] with additional analyses[8]. Participants had to report a minimum pain intensity of 5/10 or equivalent to be included in the study.

3.3.6.11.1. Pain intensity

This study reported 50% reduction in pain intensity showing considerable benefit over placebo (Analyses 6.3.8).[23] The proportion with at least 50% pain intensity reduction with placebo was 22%, and with PEA was 58%; there was an obvious dose response, with much larger benefit with 600 mg daily. There was also a much greater reduction in average pain score with PEA (both doses combined) than placebo, again with a greater effect with 600 mg. We rated both outcomes as very low-quality because they only included one study, and had limitations in the design and implementation of available studies.

This is a significant result in a large number of patients.

3.3.6.11.2. Physical functioning

Physical functioning was also increased in those participants in the treatment group compared to the control group. The authors found 63% of participants improved their physical functioning score in the treatment group compared to 22% in the control group.[23]

3.3.6.11.3. Secondary outcomes

No other meta-analyses could be conducted.

3.3.7. Potential impact of exclusion of small studies

Thirty-nine studies (794 patients given cannabinoids, cannabis, or CBM, mean 20 per trial, median 21 per trial) were excluded because of small size, potentially adding 108% additional trials but only 13% additional patients completing trials. Appendix 4 provides an analysis and details of the small excluded studies, available at http://links.lww.com/PAIN/B48. These studies involved 12 different types of cannabis, cannabinoid, or CBM in 18 different pain conditions, mostly (22/39) crossover studies. The majority (69%) used the oral route of administration, with 5 sublingual, 3 smoked, 2 inhaled, and 2 intramuscular injections. Eleven were single-dose studies with duration less than 1 day and a further 10 lasted 1 to 14 days. There was variable reporting of outcomes.

Of the 39 trials, 22 claimed no effect of cannabis, cannabinoid, or CBM, whereas 17 claimed some statistical benefit. Because of the small numbers potentially added to any analyses and very considerable clinical heterogeneity, the results of the main analyses in this review could not materially be altered by adding the small studies.

4. Discussion

This review of RCTs forms part of a wider programme of work requested by the International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia. We aimed to summarise the evidence of cannabinoids, cannabis, and CBM for people with pain, examining the efficacy and AEs reported in trials. We found 36 trials, with 7217 participants randomized to treatment that ranged from a day to 3 years (most studies had a treatment length shorter than 14 weeks). Most studies investigated people with neuropathic pain or included people with pain associated with MS, but we also found studies investigating other pain conditions including acute postsurgical pain, cancer pain, back pain, carpal tunnel, and pelvic pain.

No study was rated as low risk of bias across all risk of bias domains; studies were rated as having unclear or high risk of bias in at least one domain, and typically in several domains. Risks of bias, high heterogeneity in some analyses, and the likelihood of selective reporting biases influenced our judgements of the quality of evidence. No outcomes achieved a higher than "low-quality" rating. In fact, we rated most outcomes as very low-quality of evidence, meaning we are very uncertain of the estimates of effect reported.

We analyzed the efficacy of delivering cannabis (as opposed to individual cannabinoids or CBM) to people with pain and found a limited number of studies providing evidence. When assessing the effect of cannabis delivered for <1 week, 2 studies (231 participants) found a beneficial effect for patients undergoing surgery (very low-quality evidence). Only one study reported extractable data for cannabis delivered for >1 week, which indicated a beneficial effect of cannabis compared to control. We did not find any trials delivering cannabis for people with chronic pain that met our inclusion criteria. We found limited evidence for AEs (1-3 studies contributing to each analysis). We found no difference between groups for the AEs analyses with the exception of treatment-related AEs, where people in the cannabis group reported more AEs compared to the control. We found no differences for withdrawals between groups.

We found 6 studies that delivered CBM (including cannabinoids) to people with pain for a treatment duration of <1 week but could only extract data from 2 or fewer when analyzing outcomes. We did not find beneficial effects for reducing any pain intensity outcome.

We found more evidence for CBM, specifically for nabiximols delivered for >1 week treatment duration. Nabiximols showed small beneficial effects for 30% reduction in pain intensity and change in pain intensity scores (both outcomes very low-quality). THC, PEA, and FAAH inhibitors did not show beneficial effects compared to control in our primary analyses. When analyzing our secondary outcomes, we could only combine change score data for nabiximols and THC. Nabiximols showed beneficial effects for improving physical functioning in 4 studies and sleep quality in 13 studies. Nabiximols did not show beneficial effects for emotional functioning or quality of life, and 2 studies delivering THC did not show beneficial effects for sleep quality (data could not be extracted for other secondary outcomes).

We also analyzed studies by pain condition type and found no beneficial effects in favour of cannabinoids, cannabis, or CBM for participants with acute pain, cancer-related pain, MS; we could not combine data for conditions including pelvic pain, carpal tunnel syndrome, or low back pain. We found a small benefit at reducing pain in neuropathic pain (<7 days) in 2 studies (very low-quality), and pain change scores for neuropathic pain (>4 weeks) in 5 studies (low quality) were undermined by the small size of the benefit and the likelihood of residual positive bias in the studies. Benefits of CBM (including the THC studies that did not show an improvement in sleep) were also found for improving sleep quality for neuropathic pain of both less than and more than 4-week treatment duration (both very low-quality), although similar caveats apply.

The current available evidence provides us with no confidence that a defined cannabinoid, cannabis, or CBM product, at a defined dose, using a defined route of administration, reduces pain intensity in any condition, nor do we fully understand the long-term implications of taking cannabinoids, cannabis, and CBM. Evidence is emerging on the negative long-term effects of cannabis, in particular cannabis with high THC content (>10% potency[12]); but data for longer-term use of cannabinoids, cannabis, and CBM in a medicinal context are lacking at present. A separate work package has investigated the adverse effects of cannabis and CBM[22] and there is a distinct underreporting of AEs in this field.[43,68,69] We found AEs to be higher in nabiximols and THC treatment groups compared to control.

As is usual with systematic reviews of clinical trial evidence, we attempted to extract mean values and SDs after treatment. These data are preferable to change scores because successful randomization will result in no group baseline differences and therefore mean values/SDs can be compared at posttreatment to determine the efficacy of a treatment. However, it was not possible to extract mean values and SDs from the included studies, and when we requested data from authors, we received very few responses. Although one author provided partial data, and another fully responded to our request, pharmaceutical companies stated they could not provide posttreatment mean values and SDs. The lack of openness and transparency is against current best practice in science[50] and can lead one to question why data are being withheld. For the comprehensiveness of our review, we analyzed available change score data and found very few beneficial effects of cannabis or CBM.

There are still many missing areas of understanding within the evidence base, due to poorly reported trials and lack of exploration in this area. For example, we could not extract any caregiver global impression of change across the included studies. There were also very few studies reporting on the effect of physical and emotional functioning, although sleep was more consistently reported across studies.

For transparency, we have described studies including <30 participants/arm at post-treatment which were excluded by our protocol (12 cannabinoids, cannabis, and CBM studies, 18 pain conditions, 5 routes of administration, variation in study duration of <1-84 days, and limitations in outcomes reported). The conclusions of the main analyses in this review could not be affected by adding the small studies. A recent systematic review reported larger effect sizes and higher uncertainty in studies with fewer than 30 participants/arm.[73] Higher effect sizes with small size is a recognized problem in systematic reviews, including systematic reviews of pain treatments.[10,18,44,52]

This systematic review should be interpreted alongside the overview review of cannabinoids, cannabis, and CBM.[47] That overview found 57 systematic reviews analyzing cannabis and

CBMs. Those reviews were rated for quality using several indicators; 41 were rated as critically low, 8 as low quality, 6 as moderate, and 2 as high quality. Twenty-five reviews presented positive recommendations in the abstract, 12 reviews had negative recommendations, 7 held equipoise, and 13 state no recommendations for or against cannabinoid, cannabis, or CBMs. We believe that this review addresses the requirements of AMSTAR-2[65] and the critical pain criteria suggested by Moore et al.[47] as far as the available trial reports allow.

4.1. Implications for research

There are many avenues for future research in this field. First, compared with the diversity of cannabinoids assessed preclinically, very few have been investigated in clinical trials in pain, and better understanding of the analgesic effects of different compounds is needed, including both plant-derived and synthetic modulators of the endocannabinoid system. Thus, research on other cannabinoids where we did not identify any studies here, such as cannabidiol, could be explored to determine whether they have any analgesic properties. Second, research should not be restricted to Western, educated, industrialized, rich, democratic countries[29] and in small sample sizes. All studies came from Western, educated, industrialized, rich, democratic countries and only 2 studies in our review included more than 200 participants/arm and were rated as "low risk of bias" for size. Third, coordinated, double-blind, multicenter studies that include people with a minimum pain intensity of 4/10 should be carefully designed and conducted for well-defined pain conditions and at well-defined doses and routes of administration over long treatment periods. Rigorous reporting of these trials is critical to increasing the quality of evidence and confidence in the estimates of effect. Trial sponsors should register protocols, adhere to registered protocols, and make data available for scrutiny. Fourth, studies that investigate pharmacokinetic/pharmacodynamic relationship relationships are essential.

4.2. Implications for practice

Currently, there is no evidence from RCTs to inform the practice of treating chronic pain patients with cannabinoids, cannabis, or CBM to alter pain intensity, disability, emotional distress, or sleep. Although other, lower-quality forms of evidence (eg, nonrandomised trials and case studies) are available analysing the beneficial and harmful effects of cannabis, cannabinoids, and CBM, these should be interpreted with caution because they are highly susceptible to bias and cannot provide a reliable evidence base on which to translate into practice.

In conclusion, the RCT evidence base for using cannabinoids, cannabis, and CBM is of low or very low quality, and we found very few beneficial effects of the drugs or strains that have been tested to date for people with pain. As with any known analgesic, it is unlikely that cannabinoids, cannabis, or CBM will reduce pain for everyone. However, they may work for a small number of people, under the close supervision of specialists. High-quality trials of other cannabinoids or CBM that have not been tested in clinical trials may provide more answers.

4.3. Changes to protocol

We combined 30% reduction in pain intensity and moderate improvement in pain intensity, and 50% reduction in pain intensity and substantial pain improvement in the methods. Both these assessments report the same outcome. We added the risk of bias domain "size" to the review, which was not outlined in the protocol. We chose to do this due to the risk of bias of smaller studies in analyses. For transparency and comprehensiveness, to allow easy access to a summary, we extracted and reported mean change scores in Appendix 6, and we extracted and reported data but did not analyse them from studies with $n < 30$ in Appendix 4, available at http://links.lww.com/PAIN/B48.

Conflict of interest statement

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B48 and http://links.lww.com/PAIN/B49.

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