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Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis

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Background: Chronic neuropathic pain (NP) presents therapeutic challenges. Interest in the use of cannabis-based medications has outpaced the knowledge of its efficacy and safety in treating NP. The objective of this review was to evaluate the effectiveness of cannabis-based medications in individuals with chronic NP.
Methods: Randomized placebo-controlled trials using tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidivarin (CBDV), or synthetic cannabinoids for NP treatment were included. The MEDLINE, Cochrane Library, EMBASE, and Web of Science databases were examined. The primary outcome was the NP intensity. The risk of bias analysis was based on the Cochrane handbook.
Results: The search of databases up to 2/1/2021 yielded 379 records with 17 RCTs included (861 patients with NP). Meta-analysis showed that there was a significant reduction in pain intensity for THC/CBD by −6.624 units ($P < .001$), THC by -8.681 units ($P < .001$), and dronabinol by -6.0 units ($P = .008$) compared to placebo on a 0−100 scale. CBD, CBDV, and CT-3 showed no significant differences. Patients taking THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain ($P = .008$) and 1.422 times more likely to achieve a 50% reduction ($P = .37$) than placebo. Patients receiving THC had a 21% higher improvement in pain intensity ($P = .005$) and were 1.855 times more likely to achieve a 30% reduction in pain than placebo ($P < .001$).
Conclusion: Although THC and THC/CBD interventions provided a significant improvement in pain intensity and were more likely to provide a 30% reduction in pain, the evidence was of moderate-to-low quality. Further research is needed for CBD, dronabinol, CT-3, and CBDV.

Keywords: Cannabidiol; Cannabis; Meta-Analysis; Neuropathic Pain; Systematic Review.

INTRODUCTION

Neuropathic pain (NP) is described by the International Association for the Study of Pain (IASP) as "Pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system" [1]. NP occurs as a result of a pathological maladaptive reaction of the nervous system to damage or injury, and is sometimes described as pain being felt in the absence of afferent nociceptive input or noxious stimuli that are typically interpreted at the cortical level of the brain as pain [2].

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Causes of NP include multiple sclerosis (MS), diabetes, cancer, spinal cord injury, HIV infection, shingles, and stroke, as well as other conditions, such as trigeminal neuralgia (TN), amputation, traumatic or postsurgical nerve injuries, peripheral nerve injury, leprosy, and lumbar or cervical radiculopathies [2,3]. NP impairs the overall quality of life by negatively affecting work performance, influences social relationships, and significantly impacts the healthcare system [4].

NP can be found in many areas of the somatosensory nervous system. It can be acute or chronic, continuous or episodic, and spontaneous or evoked by typically non-painful stimuli. The intensity and pattern can vary between individuals and within individuals [5]. NP can be mediated and maintained by both central and peripheral mechanisms that cause dysfunction in the transmission and processing of neural stimuli within the somatosensory system [5]. Mechanisms implicated in NP include alterations in ion channels, imbalances between excitatory and inhibitory somatosensory signaling, and the variable ways in which pain signals are modified in the central nervous system (CNS) [2]. Central sensitization is an important contributor to persistent pain and allodynia, which is common in chronic NP by altering the sensory reaction produced by normal stimuli, including signals that would normally produce innocuous sensations [6]. The variability of the clinical presentation and symptoms along with the possible involvement of CNS dysfunction have made the treatment of NP a challenge for clinicians. Therefore, it often requires a multimodal and multidisciplinary approach for management [2].

1. Cannabis interventions

Existing evidence suggests that the Cannabis plant has been used by humans for hundreds of years for various purposes, including its therapeutic properties, such as pain relief; appetite stimulation; alleviation of fatigue, anger, and fear; and the treatment of epilepsy [7,8]. In 1970, the Controlled Substances Act made it unlawful to grow and sell hemp and marijuana in the United States (USA), thereby limiting the possibility to explore its properties. Progressive social and political changes in the USA and other countries and the passing of the 2014 Agricultural Act, which differentiated hemp and marijuana's legality, has allowed researchers to investigate the benefits of cannabis and its potential therapeutic use for the management of several medical conditions, including chronic NP [9].

Cannabis is a genus of plants in the Cannabaceae family [10]. Two recognizable species within the cannabis genus are *Cannabis sativa* and *Cannabis indica*, and are known as marijuana [11]. Marijuana and hemp are two strains of *C. sativa*; marijuana is cultivated mainly for its delta 9-tetrahydrocannabinol (delta 9-THC) content, and hemp for its usefulness in the production of industrial products such as clothing, paper, oil, and food [12]. The scientific investigation of *C. sativa* has made significant progress in the past 35 years, as the numerous active ingredients of *C. sativa* strains have been identified, and major breakthroughs have been made concerning the human body's endogenous cannabinoids (CBs) and the endocannabinoid system (ECS) with its regulatory functions in health and disease [13].

The ECS is the pathway by which tetrahydrocannabinol (THC) and other CBs interact in an animal's body. Prior research has shown that CB receptors and ligands are present in the bone, immune system, peripheral nervous system, and CNS [14]. Studies have shown that the ECS has three functions in mammals [15]. The first function affects stress recovery in animals, acting in a feedback loop where endocannabinoid signaling is activated by stress and acts to return nervous, behavioral, and endocrine systems to a homeostatic balance [16]. The second role is thought to regulate the body's energy balance through regulation of food intake, utilization, and storage [17]. The third function involves immune system tasks, whereby endocannabinoid signaling is activated by tissue injury [18] and modulates immune and inflammatory responses [19]. Thus, the ECS is involved in multiple homeostatic and physiological functions, such as antinociception, inflammation, cognition and memory,

nausea and vomiting, endocrine function, and immune system recognition [20].

Cannabis reportedly contains over 450 compounds, with 70 classified as phytocannabinoids. Delta 9-THC is the main active component, with psychoactive (e.g., reduction of anxiety and stress) and pain-relieving properties. Cannabidiol (CBD) is another component of interest. Studies have shown that CBD has a lower affinity for CB receptors and may counteract the undesirable effects of THC on memory, cognition, and mood, but may also have an effect on pain modulation by anti-inflammatory properties [21]. The specific functions of the identified cannabinoids that act as ligands at CB receptors within the nervous system have only been partially elucidated [14]. However, according to data from prior pharmacological studies and research using CB receptor knock-out mice, the mechanisms involved in the analgesic effects of CBs are thought be based on the activation of CB1 and/or CB2 receptors, causing a decrease in pain signal transmission and/or anti-inflammatory effects [22–24]. Two major endocannabinoids described so far, 2-arachidonylglycerol and anandamide, have been shown to influence the transmission of pain signals by acting on CB1 and CB2 receptors [22]. Additionally, these endogenous receptors in humans may play a role in reducing changes in cognitive and autonomic processing in chronic pain states [25].

Preclinical data demonstrate that the CB1 receptor is expressed in regions of the CNS, such as the dorsal root ganglia [26], periaqueductal gray area and nucleus raphe [27,28], dorsal horn of the spinal cord [29], and forebrain [30]. Additionally, evidence from several animal models demonstrates an upregulation of CB receptors in the CNS following nerve injury, suggesting a role of cannabinoids in the possible treatment of NP conditions [31–33]. Studies examining plant-based and synthetic cannabis-based interventions have provided data suggesting the use of cannabis-based medications as a possible approach for the management of chronic NP of different origins [34].

Given the current challenges in the treatment of chronic NP in combination with the ongoing fear of the long-term effects of the opioid epidemic, chronic pain management physicians as well as orofacial pain specialists need more innovative, effective, and safer options to alleviate NP [35]. Although opiates and non-steroidal anti-inflammatory medications are the primary pharmacological treatments for nociceptive pain, these medications have a modest effect and only in a minority of patients with NP due to the inability to precisely target the underlying mechanisms [36]. High-potency opioids have a number needed to treat one patient to experience a reduction of pain by at least 50% (NNTB) of 4.3 NP (NNTB 3.4-5.8) [37]. Current pharmacological treatments for chronic NP have largely been limited to tricyclic antidepressants (TCAs) and neuromodulators (i.e., sodium channel blockers and anticonvulsants), but these have also only shown partial efficacy in most patients [38], with a NNTB for these first-line drugs falling in the range of 3.5 to 7.7 for one patient to achieve at least a 50% reduction in pain [37]. Individuals with chronic NP conditions struggle to find effective treatment options and often undergo multiple trials with commonly used medications in search for an effective treatment and relief. The financial, social, psychological, and physical toll that poorly treated chronic NP can contribute significantly. Individuals with painful neuropathic disorders show a three-fold increase in healthcare costs compared to the matched control groups [39]. The prevalence of NP in the general population has been reported to be between 7% and 10% in some countries [2,40].

There is a need to explore additional treatment options for NP; with the increasing awareness and use of cannabinoids for medical purposes, a systematic review with meta-analysis is needed to summarize its effectiveness and safety as a therapeutic option for the treatment of chronic NP.

2. Objectives

The objective of this systematic review and meta-analysis was to evaluate the effectiveness of cannabis-based medications, including herbal cannabis

(marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), and pharmacological synthetic cannabinoids (e.g., nabilone, CT-3), as therapeutic agents compared to placebo intervention (i.e., cigarettes with 0% cannabis) in patients with chronic NP.

METHODS

1. Research question

This study follows the preferred reporting elements for systematic reviews and meta-analyses (PRISMA) guidelines [41], and the procedure was registered with PROSPERO #CRD42021234766. The PICOS question was:

- Population: Individuals diagnosed with NP (central NP, cancer-related neuropathy, painful diabetic neuropathy, complex regional pain syndrome (CRPS) type II, postherpetic neuralgia (PHN), peripheral polyneuropathy of other etiologies, trigeminal neuralgia; HIV neuropathy, spinal cord injury; postoperative or traumatic peripheral nerve lesions due to trauma; nerve plexus injury and phantom limb pain).
- Intervention: Cannabis-based medications, either herbal forms of cannabis (marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), or pharmacological (synthetic) cannabinoid formulations (e.g., nabilone, CT-3). Any route of administration (i.e., smoking, vaping, oral administration)
- Comparison: Placebo intervention.
- Primary outcomes: NP intensity and spontaneous pain intensity at baseline and post-treatment or reduction post-treatment.
- Secondary outcomes: Other pain outcomes, quality of life, cognitive decline assessment, sleep quality, qualitative testing, disability status, rescue medications, and adverse events or side effects.
- Setting: Orofacial pain clinic, university hospital, or clinical care center.

2. Inclusion and exclusion criteria

The studies included in this systematic review were limited to publications in English of randomized placebo-controlled trials. Studies identified with no placebo control, abstract only, not in English, with conditions other than NP, where cannabinoid medications were adjuvant only, and duplicate studies were excluded from this review.

3. Search methods for identification of studies

Four electronic databases (EMBASE, MEDLINE through PubMed, Web of Science, and Cochrane) were searched up to 2/1/2021 using the strategies described in Table 1.

4. Data collection and analysis

After removing duplicates, the references were screened by three authors (J.B., B.S., M.P.). The titles and abstracts of all records were analyzed using the inclusion and exclusion criteria. If there was no agreement among the reviewers, the full PDF was retrieved and analyzed. The reference sections of all literature reviews, systematic reviews, meta-analyses, and clinical guidelines in addition to all eligible RCTs were then scanned by three authors (J.B., B.S., M.P.) for any further applicable references. Any new relevant study was screened using the same inclusion and exclusion criteria and subsequently reviewed by the same three authors. If a consensus was not reached by the authors, the full article was reviewed, and a fourth author (R.E.) was involved if there was no consensus.

5. Data Extraction and Management

Three authors (J.B., B.S., M.P.) independently extracted the data obtained from the identified RCTs. Data included participants' demographics, control groups, intervention groups, funding, and outcomes. Any disagreement among the three authors (J.B., B.S., M.P.) was reviewed and resolved by consensus with a fourth author (R.E.).

Table 1. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	**Language: limited to English** **Species: limited to Humans** **Article types: limit to Clinical Trails, Randomized Controlled Trials, Review, Systematic Reviews, Guidelines, Meta-analysis, Practice Guideline** ((neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND ("Cannabis" [Mesh] OR "Medical Marijuana" [Mesh] OR "Cannabidiol" [Mesh] OR "Cannabinoids" [Mesh] OR marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid* OR hash* OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol OR THC)) AND random*
The Web of Science (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	TOPIC: (neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND TOPIC: (marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid* OR hash* OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol) AND TOPIC: random* Limits: Article, Review, Proceedings, Early Access
The Cochrane Library (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	((neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND (marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid OR hash OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol OR THC)) AND (random OR randomly OR randomized)
EMBASE (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	#1 neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy) #2 marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid OR hash OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR "delta9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" #3 randomly OR randomized OR random #4: #1 and #2 and #3 Limits: English, Article, Article in Press, Conference paper,

6. Assessment of risk of bias in included studies

The risk of bias for each eligible trial was independently identified by three reviewers (J.B., B.S., M.P.) and reviewed by a senior author (R.E.), following the recommended guidelines in the Cochrane Handbook [42].

7. Statistical analyses

RCTs on cannabis-based medications compared to placebo groups for NP were included. Means and standard deviations (SD) were calculated based on reported medians (m) and interquartile range (IQR) = (q1, q3), with q1 = 25% quartile, and q3 = 75% quartile, as: mean = (q1 + m + q3)/3; SD = (q3 − q1)/ 1.35. SD was calculated based on the reported standard error of the mean (SEM) as follows: SD = SEM × sqrt (N), where N is the total sample size in the intervention group. For pain intensity, outcomes reported on a 0–10 scale were converted to a 0-100 scale by multiplying by 10.

Treatment effects for pain intensity reported on a 0–100 Visual Analog scale (VAS) or a 0-100 Numerical Rating scale (NRS) were expressed as the difference in means (DM) of the change in outcomes from baseline with 95% confidence intervals (CI). Treatment effects for percent reduction in NP intensity from baseline as well as post-treatment pain disability scores, McGill pain questionnaires, and SF-36 were reported as DM of post-treatment outcomes with 95% CI. For the number of patients with 30% (or 50%) reduction in pain intensity, treatment effects were expressed as risk ratios (RR) with 95% CI.

Cochran's Q test [43] and the I2 statistic [44] were used to test for heterogeneity. A random-effects model was employed when there was heterogeneity (Q-test P<.10); otherwise, a fixed-effect model was used. All statistical analyses were performed using the Comprehensive Meta-Analysis v3 software. (Biostat, Englewood, NJ, USA). Statistical significance was defined as $P \leq .05$.

8. Subgroup and sensitivity analyses

Sensitivity analyses for low risk of bias versus

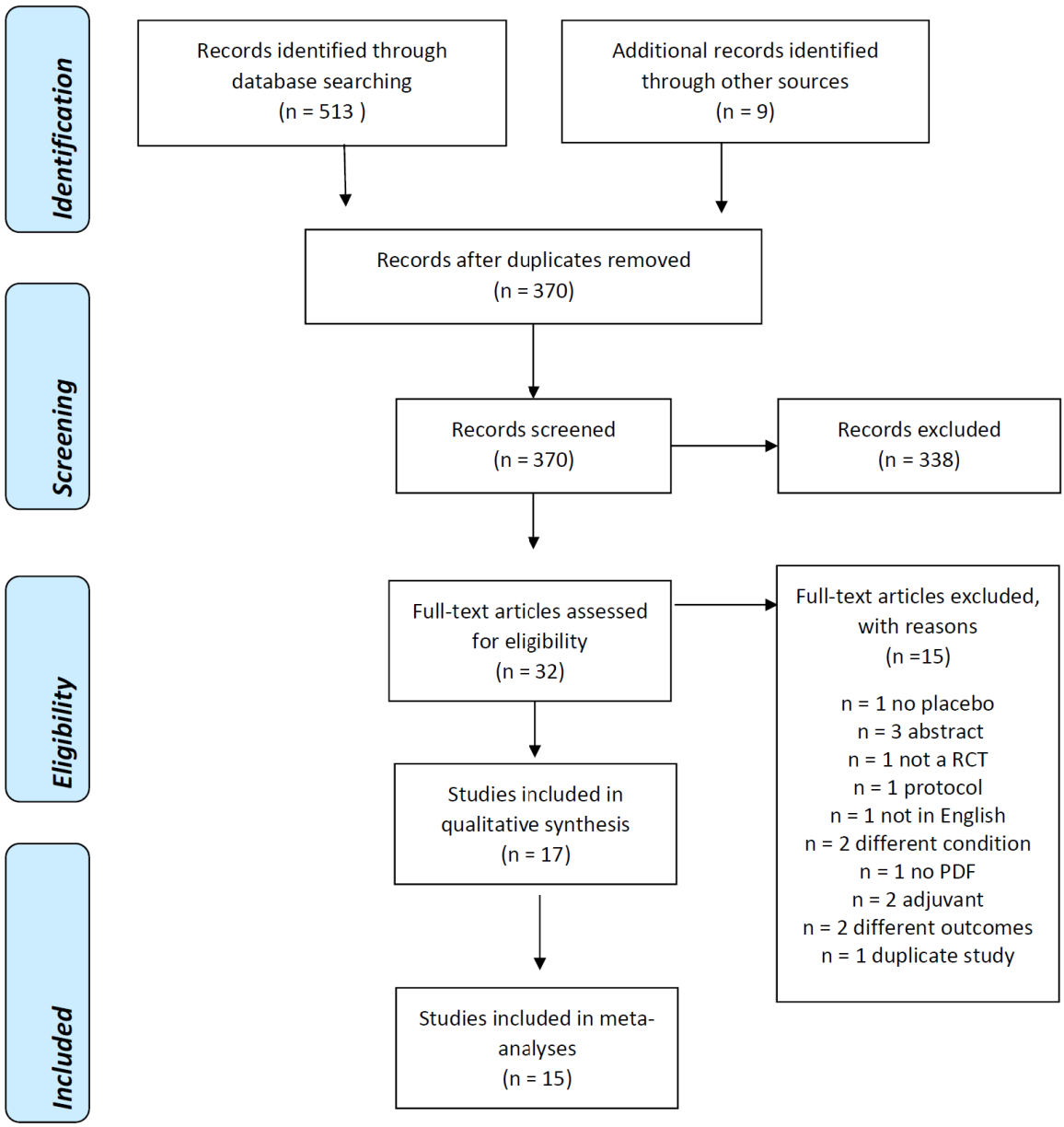

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram [42]. RCT, randomized controlled trials, PDF, portable document format.

unclear/high risk of bias due to the small number of studies could not be conducted, nor a funnel plot to assess for publication bias. Subgroup analyses were conducted for THC/CBD, THC, CBD, cannabidivarin (CBDV), and synthetic cannabis therapies (dronabinol, CT-3).

9. Quality of the evidence

A summary of the quality of the evidence was obtained using the GRADE profiler software (GRADEpro), following the GRADE Working Group guidelines [45].

RESULTS

1. Results of the search

The initial search strategy through databases on February 5, 2020, yielded 513 references, and 9 additional references identified through a manual search. After duplicates were removed, 370 records were screened and reduced to 32 relevant manuscripts. These manuscripts were searched for full-text availability and analyzed for

Table 2. Summary of eligible studies

Reference	Year, Country	Study design, Total sample size	Interventions, sample size per group	Delivery	Tx duration	Washout period for crossover studies	Gender (M/F)	Age (Mean ± SD or range in years)
Abrams, et al. 2007 [63]	2007, USA	DBRPCT parallel design N = 55	• 3.56% THC cigarettes (n = 27) • 0% THC cigarettes (n = 28)	Smoked	5 d	N/A	48M/7F	Tx group: 50 ± 6 Placebo 47 ± 7
Almog, et al. 2020 [47]	2020, Israel	Crossover DBRPC N = 27	• 0.5 mg single inhalation of Δ9-THC • 1 mg single inhalation of Δ9-THC • 0% THC Placebo matched	Inhaler	3 x 150 min sessions	2 d washout	8F/19M	48.3 ± 11.9
Berman, et al. 2004 [49]	2004, England	DBRPCT Crossover N = 48	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100 mL) spray • 2.7 mg THC oromucosal spray • Placebo spray	Spray	14 d	No washout	46M/2F	Mean: 39 23-63
Eibach, et al. 2020 [48]	2020, German	RDBPC Crossover N = 32	• 400 mg/daily oral dose CBDV dissolved in sesame oil • Identical appearing placebo dissolved in sesame oil	Oil	4 weeks	3 weeks washout	31M/1F	CBDV: 52.31 ± 8.06 36-65 Placebo: 48.31 ± 9.62 31-65
Ellis, et al. 2009 [56]	2009, USA	DBRPCT Crossover N = 34	• 1% to 8% THC cigarettes 5xday • Placebo cigarettes 5Xday	Smoked	5 d	2 weeks washout	34M/0F	48.8 ± 6.8
Karst, et al. 2003 [57]	2003, Germany	Crossover study N = 21	• CT-3, 10 mg oral capsules (synthetic THC analog without the psychotropic effects) • Placebo capsules	Oral capsules	1 week	1 week washout	13M/8F	29-65
Nurmikko, et al. 2007 [58]	2007, UK & Belgium	DBRPCT parallel N = 125	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 63) • Placebo spray (n = 62)	Spray	5 weeks	N/A	50M/74F (one patient censored)	Tx group: 52.4 ± 15.8 Placebo: 54.3 ± 15.2
Selvarajah, et al. 2010 [50]	2010, United Kingdom	DBRPCT parallel N = 29	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 15) • Placebo spray (n = 14)	Spray	10 weeks	N/A	18M/11F	Tx group: 58.2 ± 8.8 Placebo: 54.4 ± 11.6
Serpell, et al. 2013 [61]	2013, United Kingdom, Czech Republic	DBRPCT parallel N = 246	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 128) • Placebo spray (n= 118)	Spray	14 weeks	N/A	96M/150F	Tx group: 57.6 ± 14.4 Placebo: 57.0 ± 14.1
Svendsen, et al. 2004 [51]	2004, Denmark	RDBPCT Crossover N = 24	• Dronabinol 2.5 mg capsules (n = 24) • Placebo sesame seed oil capsule (n = 24)	Oral capsules	18-21 d	21 d	10M/14F	Median: 50 23-55
Wade, et al. 2002 [60]	2002, United Kingdom	DBRPC Crossover N = 20	• 2.5 mg THC & 2.5 mg CBD spray • 2.5 mg THC spray • 2.5 mg CBD spray • Placebo spray	Spray	2 weeks	None	10M/10F	Mean: 48
Wallace, et al. 2015 [52]	2015, USA	DBRPC Crossover N = 16	• 7% THC Vaporized cannabis • 4% THC Vaporized cannabis • 1% THC Vaporized cannabis • 0% Vaporized cannabis	Vaporized	4 x 4 hours	2 week	9M/7F	56.9 ± 8.2
Ware, et al. 2010 [62]	2008, USA	RDBPCT Crossover N = 23	• 2.5% THC • 6.0% THC • 9.4% THC • Placebo 0% THC	Inhaled - pipe	5 d	9 d	11M/12F	45.4 ± 12.3 25–77
Wilsey, et al. 2008 [53]	2008, USA	RDBPC Crossover N = 38	• 7% THC • 3.5% THC • 0% THC	Inhaled cigarettes	3 x 6-hour sessions	3 d	20M/18F	Mean: 46 21-71
Wilsey, et al. 2013 [54]	2013, USA	DBRPCT Crossover N = 39	• 3.53% THC • 1.29% THC • Placebo cannabis	Inhaled vapor	3 x 6-hour sessions	3 d	28M/11F	50 ± 11
Wilsey, et al. 2016b [55]	2016, USA	DBRPCT Crossover N = 42	• 0% delta 9-THC, • 2.9% delta 9-THC • 6.7% delta 9-THC	Inhaled vapor	3 x 8-hour sessions	3 d	29M/13F	46.4 ± 13.6
Wilsey, et al. 2016a [59]	2016, USA	RPCT Crossover N = 42	• 6.7% THC cannabis • 2.9% THC cannabis • 0% THC cannabis	Inhaled vapor	3 x 8-hour sessions	3 d	29M/13F	Mean: 46.4

Abbreviations: CBD, cannabidiol; CBDV, cannabidivarin; CRPS, Complex Regional Pain Syndrome; d, day; DBRPCT, Double-blind Randomized Placebo-Controlled Trial; F, female; N, participants; n, participants; NP, Neuropathic pain; M, male; RPCT, Randomized Placebo-Controlled Trial; THC, tetrahydrocannabinol; y, years.

inclusion. Seventeen studies were found to be relevant for inclusion. The main reasons for exclusion were no placebo group (n = 1), abstract proceedings (n = 3), not an RCT (n = 1), protocol (n = 1), not in English (n = 1), not NP (n = 2), no PDF available (n = 1), adjuvant to other treatments (n = 2), different outcomes such as side effects (n = 2), and duplicate studies (n = 1) [46]. All four databases were searched again on February 1, 2021, and two additional references [47,48] were found. The PRISMA flowchart shows a summary of the search and screening results (Fig. 1).

2. Included studies

Seventeen references were included in the qualitative analysis [47–63], as shown in Table 2. Four studies followed an RCT parallel design [50,58,61,63], and 13 studies followed a crossover design [47,48,59,60,62,49,51–57].

1) Types of NP

- Three studies included patients with symptomatic HIV-associated sensory neuropathy [48,56,63].
- Seven studies included patients with NP associated with nerve injury [49,53–55,57,59,62].
- One study reported unilateral peripheral neuropathic pain (PNP) and allodynia [58].
- Two studies included patients with painful diabetic neuropathy (PDN) symptoms [50,52].
- Two studies reported mechanical allodynia and at least one of the following: radiculopathy, complex regional pain syndrome (CRPS) type 2, post-herpetic neuralgia (PHN), and peripheral neuropathy [47,61].
- One study reported that NP was associated with multiple sclerosis (MS) [51].
- One study included patients with a neurological diagnosis of NP pain associated with muscle spasm and tremor, including spinal cord injury (n = 4), brachial plexus damage (n = 1), multiple sclerosis (n = 18), and limb amputation (n = 1) [60].

2) Diagnosis of NP

NP was diagnosed using the following tools (Table 3):

- The diagnosis of NP varied among the studies and was based on clinical symptoms, according to the IASP 2008 criteria [64], Douleur Neuropathique 4 interview (DN4i) [40], Leeds Assessment of Neuropathic Symptoms and Signs [65], and Neuropathy Total Symptom Score 6 [66].
- CRPS was diagnosed using Budapest criteria [67] in one study [47].
- HIV-associated NP was diagnosed using the clinical HIV-associated neuropathy tool [68].
- One study [61] included patients with mechanical allodynia and hyperalgesia with PHN, peripheral neuropathy, focal nerve lesion radiculopathy, or CRPS type II.
- Diagnosis of multiple sclerosis was based on clinical symptoms and laboratory supported diagnosis.
- Painful diabetic peripheral neuropathy was diagnosed using the Michigan Neuropathy Screening Instrument [69].

3) Population

The ages of the participants ranged from 21 to 77 years. The number of participants ranged from a minimum of 16 [52] to 246 research subject [61]. RCTs were conducted in the USA [52–56,59,62,63], Israel [47], and Europe and the UK [48–51,57,58,60,61] (Table 2). Centers providing the intervention varied from pain clinical research centers [47,53,54], university hospitals [49–52,56,58,61,62], and medical schools [55,57,59].

4) Interventions

Cannabinoid medications were administered via a variety of methods and in various dosage forms (Table 2).

- THC/CBD: Oromucosal spray Sativex containing 2.7 mg of THC and 2.7 mg of CBD [49,50,58,61] or a spray containing 2.5 mg of THC and CBD [60].
- THC:
  - Three of the included studies used cannabis cigarettes [53,56,63] with THC varying from 1% to 8%.

Table 3. Diagnosis of neuropathic pain and inclusion criteria

Reference	Dx of NP	Inclusion criteria
Abrams, et al. 2007 [63]	(1) Adults with HIV infection and symptomatic HIV-SN (2) Painful HIV-SN was confirmed by symptoms of symmetric distal pain or dysesthesias in the lower extremities for at least 2 weeks, combined with absent or depressed ankle reflexes or sensory loss of vibration, pin, temperature, or touch on examination by the study neurologist.	(1) Average daily pain score of at least 30 mm on the 100 mm VAS during the outpatient pre-intervention phase. (2) Patients were in stable health. (3) Without current substance abuse (including tobacco) (4) Followed a stable medication regimen for pain and HIV for at least 8 weeks prior to enrollment, (5) All patients were required to have prior experience smoking cannabis.
Almog, et al. 2020 [47]	The diagnoses of NP and CRPS were made by an investigating physician according to IASP 2008 [64], and Budapest criteria [67], respectively.	(1) Adult patients (18 years of age or above), (2) Suffering from chronic pain with a baseline pain intensity of 6 or above on a 10-cm visual analog scale (VAS), (3) Licensed by the Israeli Ministry of Health to receive cannabis-based medications. (4) Active users had to agree to abstain from cannabis-based medications 12 hr. before study intervention. (5) Women of fertile age had to declare using contraception.
Berman, et al. 2004 [49]	(1) At least one avulsed brachial plexus injury (2) at least 18 months duration	(1) Men/women 18 + (2) Stable pain pattern 4 + weeks (3) Stable medication regimen 4 + weeks and during study (4) No cannabis use at least 7 days prior to study
Eibach, et al. 2020	The diagnosis of HIV-associated sensory neuropathy was confirmed by a clinician based on: • patient history, • the Douleur Neuropathique 4 interview (DN4i) [40] • the Clinical HIV-associated Neuropathy Tool [68].	(1) 18 - 65 years old (2) Pain > 4 on a NRS (0 - 10)
Ellis, et al. 2009 [56]	(1) HIV-DSPN diagnosed by a board-certified clinical neurologist included: • the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or • electrophysiological abnormalities (distal leg sensory nerve conduction studies), • symptoms of pain and paresthesia, acquired in the setting of HIcV infection. (2) NP refractory to a least two previous analgesics	(1) Average score of 5 or higher on the pain intensity subscale.
Karst, et al. 2003 [57]	Presentation and examination consistent with hyperalgesia and allodynia. Diagnoses included: • NP of the left arm and right arm due to traumatic cervicobrachial plexus lesions • Neuropathic facial pain due to traumatic lesions of the left maxillary nerve, left trigeminal nerve, and mental nerve bilaterally. • NP behind the left ear due to traumatic lesion of the left great auricular nerve. • NP of the left forearm and hand due to traumatic lesion of the left radial nerve • NP in the left leg and right leg due to lumbar disk protrusion or intraspinal scar tissue after lumbar disk surgery • Pain in one or both legs due to traumatic spinal cord lesions • NP of the sole of the left foot due to compression of the tibial nerve (tarsal tunnel syndrome) • Neuropathic whole-body pain below the shoulders due to tethered cord syndrome after surgical removal of an intrathecal ependymoma • Neuropathic left facial pain (n = 1) of unknown cause.	(1) Stable levels of pain medications for at least 2 months, (2) Age 18 to 65 years, (3) Concomitant pain-relieving medications allowed were antipyretic and opioid analgesics, flupirtine, anticonvulsants, and antidepressants. (4) Pain for at least 6 months.

(continued)

Reference	Dx of NP	Inclusion criteria
Nurmikko, et al. 2007 [58]	(1) Unilateral peripheral NP and allodynia (2) Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination. (3) Patients with CRPS were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II)	(1) Age 18 or over, male or female (2) A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion (3) A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week (4) A stable medication regimen of analgesics for at least 2 weeks prior to study entry
Selvarajah, et al. 2010 [50]	Patients with chronic painful diabetic peripheral neuropathy (Neuropathy Total Symptom Score 6 [66] >4 and <16)	(1) At least 6 months of pain (2) Stable glycemic control (HbA1C <11%) (3) Those with persistent pain, despite an adequate trial of tricyclic antidepressants, were recruited.
Serpell, et al. 2013 [61]	(1) Had mechanical allodynia within the territory of the affected nerve(s) confirmed by either a positive response to stroking the allodynic area with a brush or to force applied by a monofilament. (2) At least one of the following underlying conditions, which caused their Peripheral NP: • post-herpetic neuralgia, • peripheral neuropathy, • focal nerve lesion, • radiculopathy or • CRPS type 2.	(1) Aged 18 or older, (2) At least a 6-month history of PNP and were receiving the appropriate treatment for their PNP. (3) Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) and pain that was not wholly relieved by their current therapy. (4) Analgesic regimen was stable for at least 2 weeks preceding study entry.
Svendsen, et al. 2004 [51]	(1) Diagnosis of multiple sclerosis (clinical definite multiple sclerosis and laboratory supported definite multiple sclerosis), (2) Assessed central pain after a clinical examination by a doctor. The criterion for central pain was: - pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside, - or quantitative sensory testing corresponding to at least one lesion in the central nervous system.	(1) Age between 18 and 55 years, (2) Central pain at the maximal pain site with a pain intensity score ≥3 on a 0-10 numerical rating scale. (3) We allowed concurrent spasm related pain if the patient was able to distinguish spasm related pain and central pain. (4) We allowed additional pain outside the maximal pain site if pain intensity was low and distinguishable from the central pain
Wade, et al. 2002 [60]	(1) Eligible patients had to have a neurological diagnosis and to be able to identify troublesome symptoms which were stable and unresponsive to standard treatments. (2) NP pain associated with muscle spasm and tremor and included multiple sclerosis (n=18), spinal cord injury (n = 4), brachial plexus damage (n=1), and limb amputation (n = 1)	
Wallace, et al. 2015 [52]	(1) Diabetes mellitus type 1 or type 2, who had stable glycemia (HbA1c ≤11%) and were maintained by diet or a stable regimen of diabetic therapy for at least 12 weeks before the evaluation. (2) Presence of both spontaneous and evoked pain in the feet, (3) At least a six-month history of painful diabetic peripheral neuropathy diagnosed according to research diagnostic criteria (using the Michigan Neuropathy Screening Instrument [69]), which included: - the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or electrophysiological abnormalities (distal leg sensory nerve conduction studies), - paresthesia and a pain of intensity of ≥ 4 on the 11-point NRS	(1) Participants were men and women. (2) Age 18 or older
Ware, et al. 2010 [62]	(1) NP of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia, (2) Average weekly pain intensity scores greater than 4 on a 10-cm visual analogue scale.	(1) Men and women aged 18 years or older. (2) Participants had a stable analgesic regimen and reported not having used cannabis during the year before the study. (3) normal liver function normal renal function, normal hematocrit and a negative result on human chorionic gonadotropin pregnancy test (if applicable).

(continued)

Reference	Dx of NP	Inclusion criteria
Wilsey, et al. 2008 [53]	(1) Patients with CRPS type I, spinal cord injury, peripheral neuropathy, or nerve injury. (2) The specific historic and physical findings included burning pain, skin sensitivity to light touching or cold, skin color changes, swelling, limited movement of the affected body part, motor neglect or abnormalities in skin temperature, hair growth, nail growth, and/or sweating.	(1) Previous cannabis exposure was required of all participants. (2) Refrain from smoking cannabis or taking oral synthetic delta-9-THC medications for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to confirm this provision.
Wilsey, et al. 2013 [54]	NP disorder: (1) CRPS type I, formerly known as reflex sympathetic dystrophy. (2) thalamic pain, (3) spinal cord injury, (4) peripheral neuropathy, (5) radiculopathy, or (6) nerve injury	(1) Required to refrain from smoking cannabis or taking oral synthetic THC medications for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to confirm this provision as much as was feasible. (2) Previous cannabis exposure (3) No depression.
Wilsey, et al. 2016b (exploratory) [55]	Individuals with injury and disease of the spinal cord	(1) Age >18 and <70 yrs. (2) Pain intensity >4 on a scale of 10
Wilsey, et al. 2016a (preliminary) [59]	NP as defined by Leeds Assessment of Neuropathic Symptoms and Signs [107]	(1) 18-70 yrs. (2) Pain intensity of 4/10.

Abbreviations: CRPS, complex regional pain syndrome; Dx, diagnosis; HbA1C, glycated hemoglobin; HIV-DSPN, human immunodeficiency virus associated distal sensory predominant polyneuropathy HIV-SN, human immunodeficiency virus associated sensory neuropathy, hr, hour; NP, neuropathic pain; NRS, numeral rating scale; PNP, peripheral neuropathic pain; THC, tetrahydrocannabinol; VAS, visual analog scale; yrs, years.

  - One study used a novel hand-held, battery-operated inhaler with software control to accurately control different doses of pharmacologically active granulated pharmaceutical-grade 22% THC (0.5 mg or 1.0 mg) [47].
  - One trial studied 2.5% to 9.4% THC concentrations administered via inhalation using a titanium pipe [62].
  - Four studies used inhaled vaporized cannabis as the treatment comparison [52,54,55,59] with THC concentrations ranging from 1% to 7%.
- CBDV: One study used 8 mL (400 mg) doses of CBDV dissolved in sesame oil taken orally [48].
- Synthetic cannabinoid: Two of the studies used capsules (synthetic cannabinoid analog CT-3 in 10 mg capsules [57] and synthetic THC molecule dronabinol in 2.5 mg capsules [51]).

5) Co-interventions

Due to the nature of NP conditions and the use of medications to relieve the pain burden by those experiencing it, patients continued taking medications in an attempt to reduce pain. All included studies, except three [49,51,59], required stable use of concomitant medications without adequate relief for a period of time leading up to the study and throughout the study. Two studies specifically excluded patient receiving medications including levodopa, sildenafil, and fentanyl [49], and those with the use of concomitant tricyclic anti-depressants, anticholinergics, antihistamines, and CNS depressants [51]. One study did not state any co-interventions [59]. One study [47] reported the use of concomitant medications for pain management, including anticonvulsants, benzodiazepines, antidepressants, analgesics, and anti-inflammatory drugs. Another trial [48] reported that the use of concomitant analgesics (including antidepressants and anticonvulsants) was allowed throughout the study. Participants in each study were asked not to use any non-study cannabinoid medication during the course of their study.

6) Outcomes

The primary outcomes of the included studies were NP intensity and spontaneous pain intensity at baseline and post-treatment, or baseline NP pain and reduction from baseline at post-treatment.

Table 4. Summary of Risk of bias for eligible studies

Study	Random Seq. Generation	Allocation Concealment	Blinding participants/ personnel	Blinding assessors/statistician	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Abrams, et al. 2007 [63]	-	-	?	?	-	-	?	?
Almog, 2020 [47]	-	-	?	-	-	-	+	+
Berman, et al. 2004 [49]	-	-	?	?	-	-	+	+
Eibach, et al. 2020 [48]	-	-	?	?	?	-	?	?
Ellis, et al. 2009 [56]	-	-	+	-	-	-	?	+
Karst, et al. 2003 [57]	-	-	-	?	-	-	+	+
Nurmikko, et al. 2007 [58]	-	-	-	+	-	-	+	+
Selvarajah, et al. 2010 [50]	?	-	?	?	-	-	?	?
Serpell, et al. 2013 [61]	-	-	-	?	+	-	+	+
Svendsen, et al. 2004 [51]	-	-	?	-	-	-	?	?
Wade, et al. 2002 [60]	-	-	-	?	?	-	+	+
Wallace, et al. 2015 [52]	-	-	?	-	-	-	?	?
Ware, et al. 2010 [62]	-	?	?	?	-	-	?	?
Wilsey, et al. 2008 [53]	-	-	?	?	-	-	?	?
Wilsey, et al. 2013 [54]	-	-	?	?	?	-	?	?
Wilsey, et al. 2016b (exploratory) [55]	-	-	?	-	-	-	?	?
Wilsey, et al. 2016a (preliminary) [59]	?	+	+	+	?	-	?	+

KEY: + High risk of bias; - Low risk of bias; ? Unclear risk of bias

Secondary outcomes for reported pain included percentage improvement in NP intensity [70], responders with a 30% or more reduction in pain intensity, responders with a 50% or more reduction in pain intensity, brief pain inventory [71], pain disability index [72], painDETECT [73], McGill Pain Questionnaire [74], and Douleur Neuropathique 4 interview (DN4i) [40].

The included RCTs also reported quality of life outcomes: SF-36 [75], brief symptom inventory (BSI) [76], general health questionnaire (GHQ-12 or GHQ－28) [77], patient global impression change (PGIC) [78], and Euro quality of life (EQ-5D) [79]. For cognitive decline assessment, studies reported the Cambridge Neuropsychological Test Automated Battery (CANTAB) [80], trail-making test [81], and the short orientation-memory-concentration test [82]. Sleep quality was assessed using several recording methods, such as the insomnia severity index (ISI) [83], sleep disturbances, sleep disruption, and Leeds sleep evaluation questionnaire 65, and the box score 11 point scale (BS-11) [84]. Other secondary outcomes included expanded disability status (EDSS) [85], profile of mood states (PMOS) [86], and qualitative testing (allodynia, cold/hot threshold). Other outcomes reported included rescue medications, medication quantification scale [87], and adverse events [48] using common terminology criteria for adverse events version 4.03 (CTCTAE) [88].

3. Risk of bias in included studies

The trials included in this review were analyzed for the presence of risk of bias, including but not limited to allocation concealment, random sequence generation, blinding of investigators and participants, selective reporting, incomplete outcome data, and other potential sources of bias. Overall, the risk of bias was unclear in nine of the 17 RCTs (52.9%) [48,50–55,62,63], and a high risk of bias was found in eight of the 17 RCTs (47.1%) [47,49,56–61] (Tables 4 and 5; Fig. 2).

4. Adverse events

Adverse events (AEs) and side effects for the RCTs [47,49,62,63,51–54,56,58,60,61] included but were not limited to anxiety, sedation, dizziness, nausea, and fatigue. Two publications [55,59] reported that there were no serious side effects related to the study. One study [48] reported that thirty-one patients, (91.2%) had at least one study related AE, stating that diarrhea and dry mouth of mild severity were the most common AEs, and one

Table 5. Analysis of risk of bias for included studies

RISK OF BIAS	SUMMARY
Random sequence generation	Random sequence generation methods were found to be low risk of bias in fifteen studies as a computerized random generator [48,49,51,56–58,61,63] random number permutations [52], Latin square design [62], William's square [47,60], and web-based number generator [53–55] were used. An unclear risk of bias was identified in two of the studies as they stated the goal was randomization but the strategy for randomization was not specifically stated [50,59].
Allocation concealment	Allocation concealment was identified as low risk in fifteen trials. The interventions were prepared and packaged by a third party in identical packaging in seven [47,50,52,57,60,61,63], key study assignments were withheld in one 56, sealed envelopes were used in four [48,49,51,58] and the allocation was kept concealed in the pharmacy in three [53–55] trials. The risk of bias was unclear in two studies. One paper 62 stated "We have shown the feasibility of a single-dose delivery method for smoked cannabis, and that blinding participants to treatment allocation is possible using this method", but does not describe how. High risk of bias was given to one trial [59] for having no description of allocation concealment.
Blinding of participants/personnel	Blinding of participants and personnel was identified as low risk in four studies [57,58,60,61]. Placebo capsules were identical and randomization, labeling, and packaging in high-density polyethylene bottles and dispensed under blinded conditions in one study [57]. Study spray medication and placebo were taste- and color-matched with peppermint oil and coloring in three studies [58,60,61]. An unclear risk assessment was assigned to eleven studies [47,48,63,49–55,62]. Although there were identical pre-rolled cigarettes in one study, participants were required to have previous experience smoking cannabis63. Seven studies did not give enough information to determine level of blinding [47–50,53,55,62]. In one study although medication and placebo were in identical containers 67% of participants correctly identified active medication [51]. Similarly 89% of the subjects correctly identified the active medication in another study [54]. One study was assigned unclear risk of bias because of psychoactive effects of both placebo and treatment [52]. A high risk of bias for participants and personnel was assigned to two trials [56,59]. In one study all but one participant correctly identified the active treatment [56]. One study was assigned a high risk of bias because no blinding description was given [59].
Blinding assessors/statistician	Blinding of assessors and statisticians was identified as low risk in five studies with the key for study assignment withheld from investigation until analysis was completed [47,51,52,55,56]. Blinding of assessors and statisticians was assigned unclear risk bias for ten studies as they stated the trial was "double-blinded" but gave no description of blinding methods for assessors and/or statisticians [48–50,53,54,57,60–63]. Two studies were identified as high risk of bias for assessors and statisticians [58,59]. In one study the sponsor of the study participated in the analysis [58]. Another study did not indicate that blinding of assessors and/or statisticians was performed [59].
Incomplete outcome data	Twelve of the studies were assigned low riskof bias for incomplete outcome data; these studies had no missing outcome data reported [47,49,62,63,50–53,55–58]. Fourof the studies were identified as unclear risk of bias due to incomplete outcome data reporting [54,59,60]. Two studies lacked information on intent-to-treat analysis adherence [59,60]. One study had participants who were not included in the analysis, although reasons for non-inclusion were stated [54]. One study had patients drop out during the study that were not excluded from analysis and no information was given on point of study during which they withdrew [48]. One study was identified as high risk of bias of incomplete outcome data reported due to a withdrawal rate of 29.7% for the study [61].
Selective reporting	A low risk of bias was assigned to all studies [47,48,57–63,49–56] because all outcomes were described and presented as pre-specified.
Other potential sources of bias	An unclear risk of bias was assigned to eleven [48,50,63,51–56,59,62] studies. Nine had co-interventions (patients used concomitant medications for pain) [48,50,52–56,62,63] One studydid not state the co-interventions [59] and one trial [51] was funded by the drug company that manufactures the intervention, however the statistical analyses were blinded. A high risk of bias was identified in six studies [47,49,57,58,60,61] as the authors received funding by the intervention manufacturer with a proprietary interest in the medications used.
Overall bias	Overall, the risk of bias was unclear in nine of the seventeen RCTs (52.9%) [48,50–55,62,63], and a high risk of bias was found in eight of the seventeen RCTs (47.1%) [47,49,56–61].

Abbreviations: RCT, randomized controlled trial.

patient withdrew due to an AE (cough) during CBDV treatment. Another RCT [57] reported side effects of the trial in a subsequent paper [46]. One study [50] did not list the adverse events but stated that, of the 30 patients randomized, six withdrew because of adverse events.

5. Meta-analyses

1) THC/CBD

Five studies [49,50,58,60,61] reported a change in pain

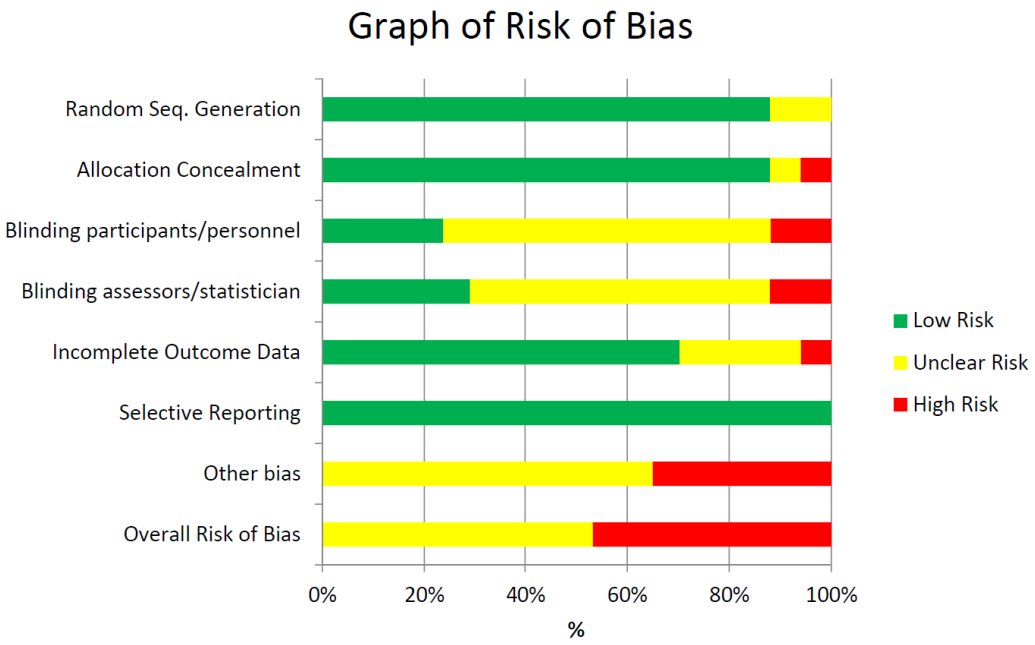

Fig. 2. Summary of risk of bias of eligible randomized controlled trials.

intensity (VAS or NRS 0-100) from baseline. Overall, THC/CBD significantly improved pain intensity by -6.6 units compared to placebo on a 0–100 scale (P < .001; Fig. 3a). Two studies [58,61] reported the number of patients with a 30% reduction in pain intensity. Patients who used THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain compared to patients receiving placebo (P = .008; Fig. 4a). Patients receiving THC/CBD intervention were 1.422 times more likely to achieve a 50% reduction in pain, although the difference was not statistically significant [58] (P = .37; Fig. 4b). There were no significant differences in the change in pain disability index (0-70) from baseline with THC/CBD compared to placebo in two studies [49,58] (P = .06; Fig. 5a), nor in the change in Brief Pain Inventory (BPI) pain intensity score [61](P = .29) and BPI pain interference score (P = .184).

Two studies [49,50] reported the McGill Pain Questionnaire (MPQ) post-treatment data. There were no statistical differences between THC/CBD and placebo in post-treatment MPQ VAS pain (P = .92; Fig. 5b), MPQ total score [49] (P = .08), present pain intensity (P = .19), sensory scale(P = .46), or affective scale (P = .67) [50]. Finally, this study reported changes in quality of life using the SF-36 questionnaire [50]. There were no statistically significant differences in any of the SF-36 subscales between the THC/CBD and placebo interventions (P = .37; Fig. 6a).

2) THC

Six studies [49,52,56,60,62,63] reported a change in pain intensity (VAS or NRS 0–100) from baseline. Overall, THC at varying dosages (1% to 9.4%) significantly improved pain intensity by -8.7 units on a 0–100 scale (P < .001; Fig. 3a). Two studies [52,63] reported a difference in the percent reduction in pain intensity from the baseline. Patients receiving THC had a -21% significantly higher improvement in pain intensity from baseline than patients in the placebo group (P = 0.005; Fig. 3c). Five studies [47,52,54–56,63] reported the number of patients with a 30% reduction in pain intensity. Patients receiving THC were 1.855 times more likely to achieve a 30% reduction in pain than patients in the placebo group (P < .001; Fig. 4a). One study [49] reported a change in the Pain Disability Index (0-70) from baseline. Overall, THC did not significantly improve the pain disability index on a 0–70 scale compared to placebo (P = .82; Fig. 5a).

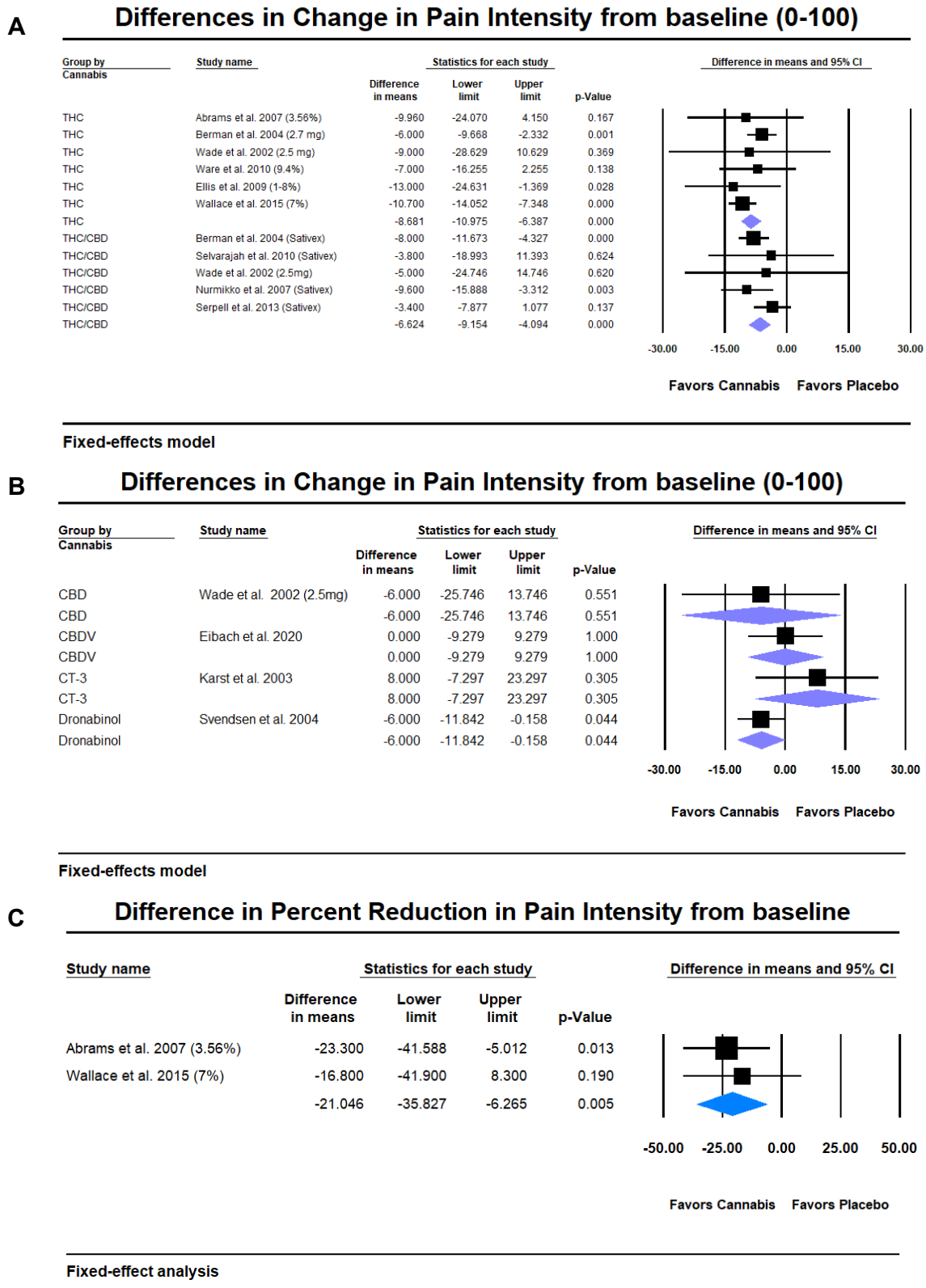

Fig. 3. Results of meta-analysis comparing cannabis to placebo intervention for neuropathic pain patients. Subgroup analyses for differences of change in pain intensity from baseline for (a) THC and THC/CBD studies and (b) CBD and synthetic cannabis interventions; (c) Percent reduction in pain intensity with THC. A $p \leq 0.05$ denotes a statistically significant difference. CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol.

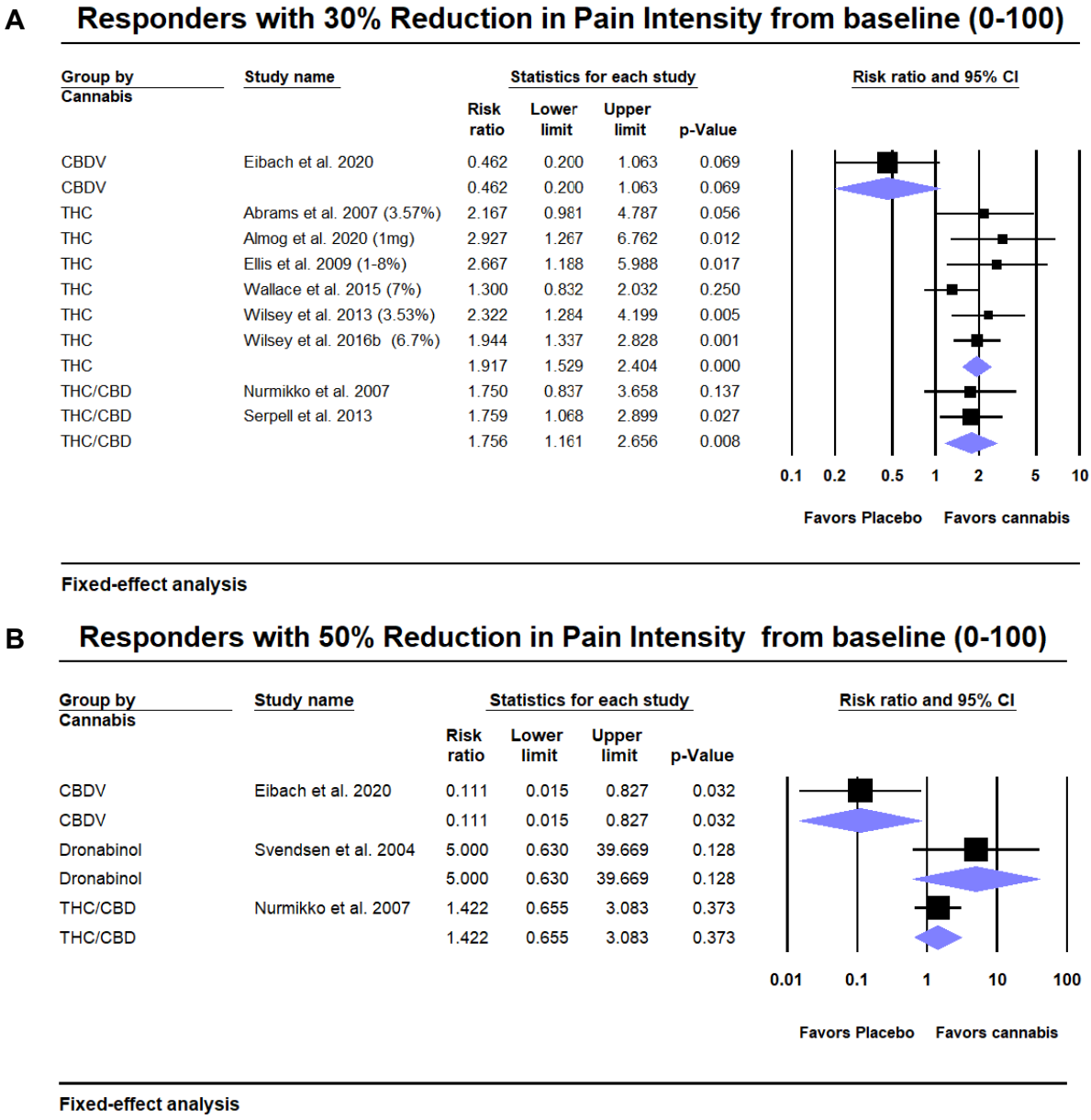

Fig. 4. Subgroup analyses for differences in number of responders with (a) 30% reduction and (b) 50% reduction in pain intensity from baseline (score 0-100). CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol.

Overall, THC significantly improved post-treatment MPQ VAS pain [49] (P = .02; Fig. 5b) and total score [49,62] (P = .03). One study [62] reported a non-significant improvement in post-treatment MPQ present pain intensity (P = .40), sensory scale (P = .59), and affective scale (P = .60).

3) CBD and CBDV

CBD: Overall, CBD [60] slightly improved pain intensity by -6.0 units on a 0–100 scale from baseline, and the difference was not significant with placebo (P = .55; Fig. 3b).

CBDV: One study [48] reported no difference in VAS pain intensity between the CBDV and placebo groups (P = 1.00; Fig. 3b). Patients who used CBDV were 53.8% less likely to achieve a 30% reduction in pain (P = .07; Fig. 4a) and 88.9% less likely to achieve a 50% reduction in pain compared to patients receiving placebo (P = .03;

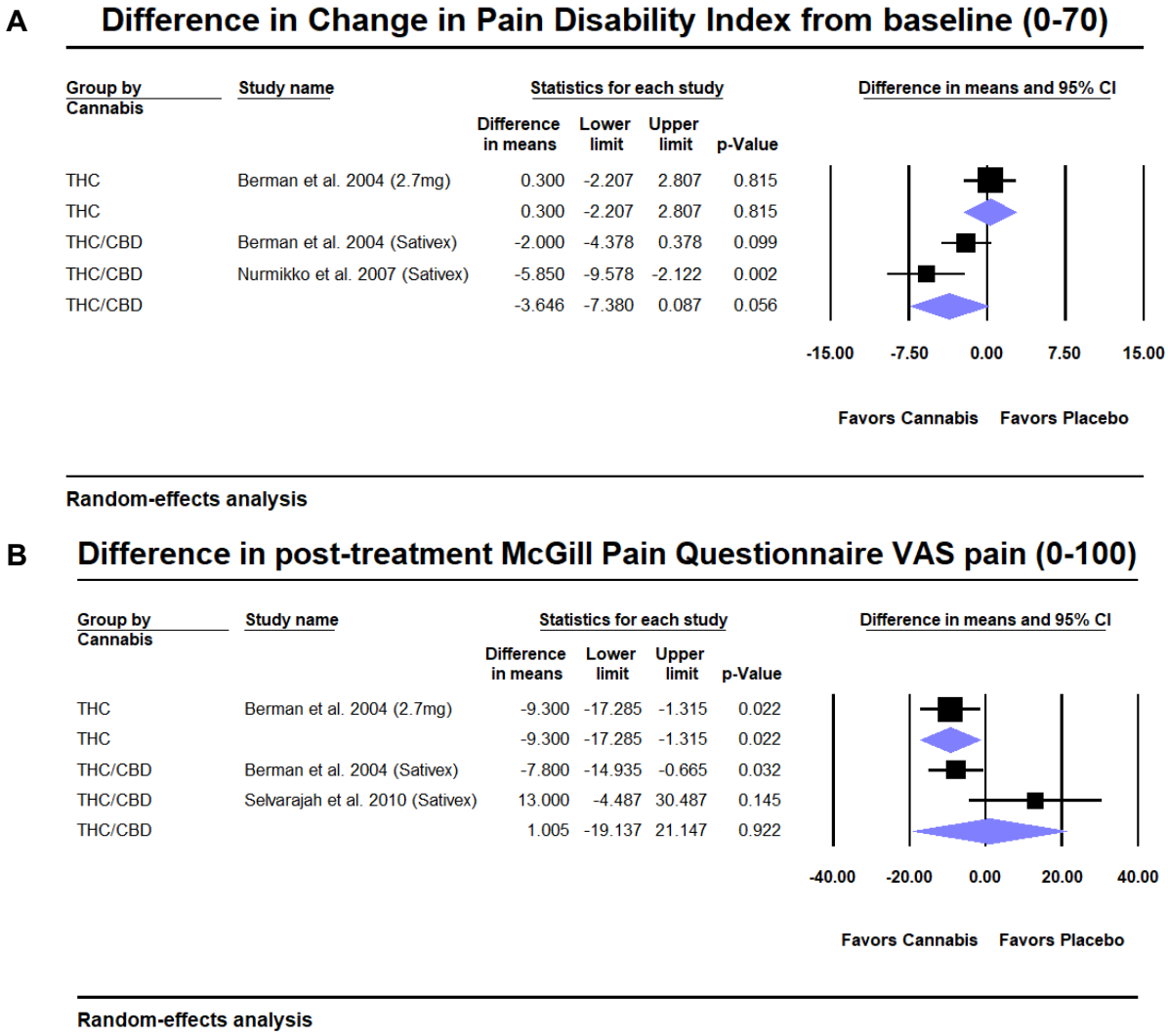

Fig. 5. Subgroup analyses for (a) differences of change in Pain Disability Index from baseline on a 0-70 scale; (b) differences in post-treatment McGill Pain Questionnaire Visual Analog Scale score on a 0-100 scale. CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol; VAS, visual analog scale.

Fig. 4b). There were no significant differences in BPI pain intensity score (P=.65) or BPI pain interference score between the CBDV and placebo groups (P = .36).

4) Synthetic cannabis

CT-3: One study [57] reported a change in pain intensity (0–100) from the baseline. There were no significant differences in the change in pain intensity between the CT-3 and placebo groups (P = .31; Fig. 3b).

Dronabinol: In one study [51], 2.5 mg capsules of dronabinol significantly improved pain intensity by -6.0 units on a 0–100 scale compared to placebo (P = .04; Fig. 3b). Patients receiving dronabinol were 5 times more likely to achieve a 50% reduction in pain than patients in the placebo group; however, this was not statistically significant (P = .13; Fig. 4b). There was a significant improvement in SF-36 reported mental health scores (P < .001), physical functioning (P < .001), and social functioning (P = .04) in the dronabinol group than in the placebo group (Fig. 6b).

6. Quality of the Evidence (GRADE)

1) THC/CBD

The quality of the evidence was moderate for THC/CBD interventions for the outcomes of change in

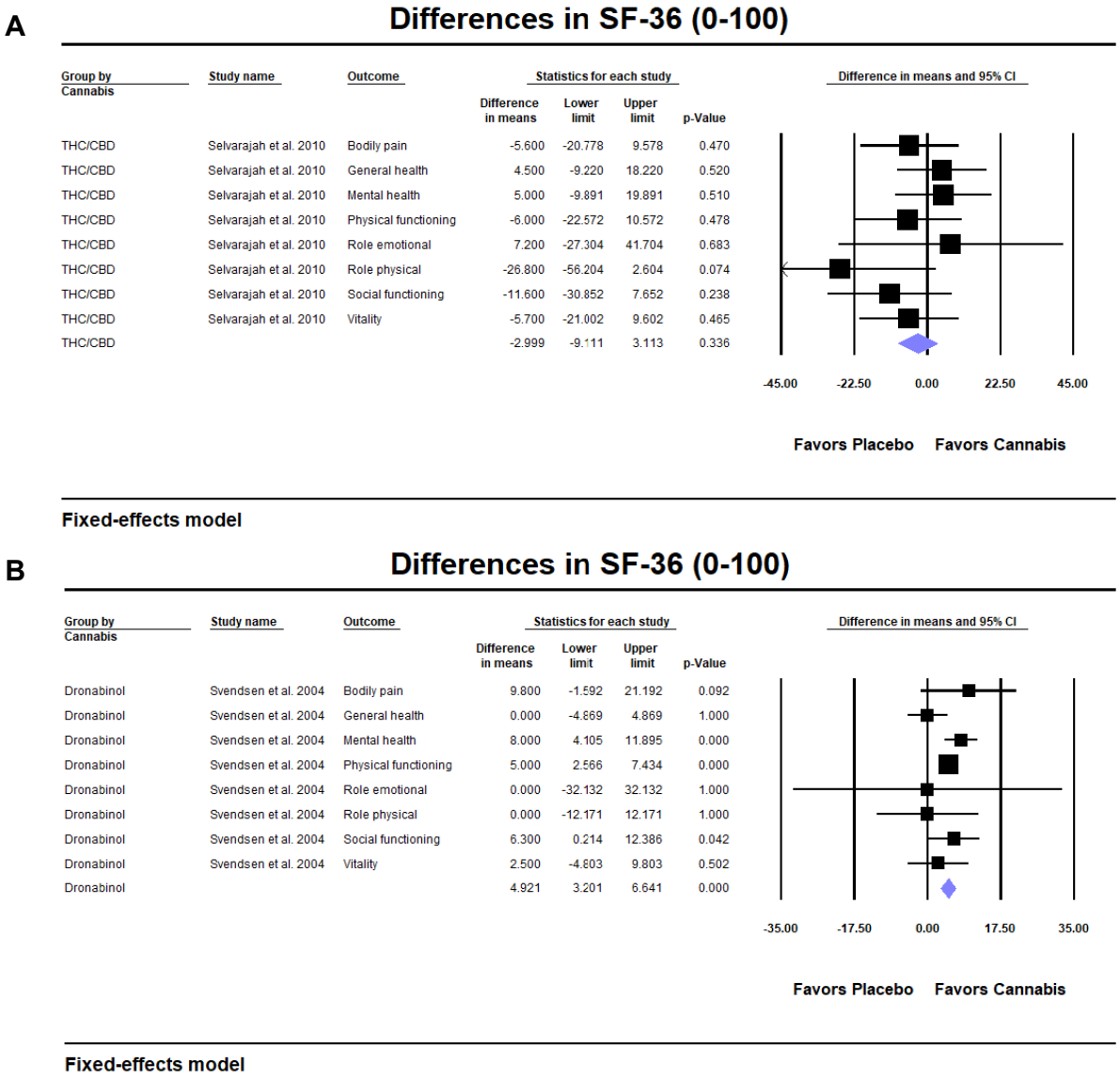

Fig. 6. Subgroup analyses for differences in post-treatment SF-36 subscales with (a) THC/CBD and (b) dronabinol. Higher SF-36 scores represent favorable quality of life. CBD, cannabidiol; CI, confidence interval; SF-36, 36 item short form survey; THC, tetrahydrocannabinol.

pain intensity from baseline (0–100) due to the unclear/high risk of bias of the studies pooled in the subgroup analyses. The quality of the evidence was low for the number of responders with a 30% reduction in pain and the change in pain disability index (Table 6) due to (a) the unclear/high risk of bias of the studies pooled in the subgroup analyses, (b) small sample size of participants in each analysis (<400), and (c) the small number of studies pooled (only two).

2) THC

Due to unclear or high risk of bias in the studies pooled in the subgroup analyses, the quality of the evidence was moderate for THC interventions for the outcomes of change in pain intensity from baseline (0–100) and number of responders with a 30% reduction in pain. The quality of the evidence was low for difference in percent reduction of pain intensity and MPQ total score (Table 6) due to the unclear/high risk of bias, small total sample size, and the small number of studies pooled (only two).

3) Other cannabis interventions

Only one study reported outcomes for dronabinol, CBD, CBDV, and CT-3; further studies are needed to

Table 6. Quality of the Evidence (GRADE [45]) for THC/CBD and THC interventions.

THC/CBD Interventions compared to Placebo for Neuropathic pain					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with THC/CBD (95% CI)
Change in pain intensity from baseline Scale from: 0 to 100.	522 (5studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias			The mean change in pain intensity from baseline in the intervention groups was -6.624 lower (-9.154to-4.094lower)
Responders with 30% reduction in pain intensity	359 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision	RR 1.756 (1.161to2.656)	157 per 1000	119 more per 1000 (from25moreto260more)
Change in pain disability index Scalefrom:0to70.	219 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean change in pain disability index in the intervention groups was 3.646 lower (7.380lowerto0.087higher)
McGill pain questionnaire VAS pain Scalefrom:0to100.	71 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean McGill pain questionnaire VAS pain in the intervention groups was 1.005 higher (19.137lowerto21.147higher)
THC interventions compared to Placebo for Neuropathic Pain					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with THC (95% CI)
Change in pain intensity from baseline Scalefrom:0to100.	332 (7studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias			The mean change in pain intensity from baseline in the cannabis groups was -8.681 lower (-10.975to-6.387lower)
Difference in percent reduction of pain intensity	87 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean difference in percent reduction of pain intensity in the cannabis groups was –21.046 lower (-35.827to-6.265lower)
Responders with 30% reduction in pain intensity	353 (6studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias	RR 1.917 (1.529to2.404)	309 per 1000	283 more per 1000 (from163moreto434more)
McGill pain questionnaire - Total score Scalefrom:0to45.	137 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean McGill pain questionnaire - total score in the intervention groups was 2.197 lower (4.219to0.176lower)

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.

[1]All studies at unclear or high risk of bias
[2]Only two studies, wide confidenc eintervals, small sample size

Abbreviations: CBD, cannabidiol; CI, confidence interval; GRADE, grading of recommendations assessment, development and evaluation; RR, Risk ratio; THC, tetrahydrocannabinol; VAS, visual analog scale.

confirm our results, and the quality of the evidence was very low.

DISCUSSION

1. Main findings

This systematic review included 17 studies involving 861 adult participants. Each of the included studies compared cannabis-based medications with placebo controls. The studies varied in methods of delivery,

concentration, and dosage of cannabis-based medications and included both plant-based and synthetic cannabinoids. Subgroup analyses were undertaken to provide overall estimates for THC, THC/CBD, CBD, CBDV, and synthetic cannabinoid medications (CT-3 and dronabinol) used as interventions. A significant reduction in NP intensity from baseline was observed in studies of THC and THC/CBD with moderate quality of evidence (Table 6); however, the decrease in VAS pain was not clinically significant (-6 units for THC/CBD and -9 units for THC on a 0–100 scale). Participants in two studies with THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain (low quality evidence) and 1.422 times more likely to achieve a 50% reduction in pain in one study (very low evidence). Those receiving THC were 1.917 times more likely to achieve a 30% reduction in pain (moderate-quality evidence) compared to placebo. Due to the unclear/high risk of bias of the included studies, small sample sizes, and wide confidence intervals, the quality of the evidence was moderate to low. Low to moderate quality of evidence indicated inconclusive results that THC and THC/CBD may be efficacious in reducing chronic NP.

Only one study reported a change in VAS pain from baseline for dronabinol, CBD, CBDV, and CT-3; further studies are needed to confirm our results. Dronabinol showed a significant decrease in pain of -6 units compared to placebo in one study, as well as significant improvements in quality of life measured with the SF-36. CBD, CBDV, and CT-3 did not show a significant reduction from baseline pain compared to placebo in the included studies.

The most common AEs and side effects were anxiety, sedation, dizziness, nausea, and fatigue. Two publications [55,59] reported that there were no studies related to serious side effects. One study [48] reported that 91.2% of the patients had at least one study related AE, stating that diarrhea and dry mouth of mild severity were the most common AEs, and one patient withdrew due to an AE (cough) during CBDV treatment. One study [50] stated that, of the 30 patients randomized, six withdrew because of adverse events.

2. Agreements and disagreements with other studies or reviews

Several reviews [89–91] share optimistic conclusions that the use of cannabis-based medications is moderately effective, tolerable, and safe in the treatment of patients with NP. In a qualitative systematic review of cannabis-based medications for non-cancer pain [89], which included 11 RCTs on chronic NP, the authors reported that cannabis-based medications were “modestly” effective in the treatment of NP, and that it was “reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain.” Several of the included trials also demonstrated a significant improvement in sleep without serious adverse events, which were generally described as well tolerated, short lived, or mild-to-moderate [89].

In a review of the effectiveness of cannabinoids in the management of chronic nonmalignant NP [90], the authors concluded that cannabinoids provided significant pain reduction in both the short and long term, and that cannabinoids should be considered as an effective add-on, if not an alternative therapy, for the treatment of chronic NP. Their review also suggested that cannabis-based therapies may provide effective analgesia in chronic NP conditions that are refractory to other interventions, and that cannabinoids also improve nausea, sleep quality, anxiety, and appetite. Adverse events were described as minor in nature [90].

In an individual patient data meta-analysis of inhaled cannabis for the treatment of chronic NP [91], data from 178 participants in five RCTs provided evidence that inhaled cannabis resulted in short-term reductions in chronic NP for every five to six patients treated (NNTB = 5.6, CI = 3.4 to 14) for a more than 30% reduction in pain scores compared to placebo. From their data, they inferred that this effect applies to chronic painful neuropathies of different etiologies. They also reported that withdrawals due to adverse events were rare. Other

clinical guidelines and systematic reviews consider cannabis-based medications as third-or fourth-line therapy for chronic NP if the already accepted therapies (tricyclic antidepressants (TCAs), anticonvulsants) have failed to achieve effective results [92,93].

On the other hand, there are also reviews [21,94,95] that do not support cannabis-based medications for the treatment of NP. The Neuropathic Pain Special Interest Group (NeuPSIG) conducted a systematic review of randomized double-blind studies of oral and topical pharmacotherapy for NP [94]. The authors identified nine trials of Sativex (an oromucosally applied spray containing 27 mg/ml of THC and 25 mg/ml of cannabidiol) in NP. Only two of these studies were found to be favorable, leading to a weak recommendation against their use in NP. Abuse, negative results, diversion, potential misuse, and long-term mental health risks in susceptible individuals were all reasons for their recommendation against the use of Sativex in NP.

In a systematic review of cannabis-based medications for chronic NP in adults [21], the authors analyzed eight studies with 1,001 participants. A total of 20.9% of participants in the cannabis-based medications and 17.3% in the placebo group reported pain relief of 50% or greater (NNTB = 20). According to their predefined categories, there were no clinically relevant benefits of cannabis-based medications. Cannabis-based medications were superior to placebo in the reduction of mean pain intensity (P =.008). According to Cohen's categories, there was a small effect size, indicating minimal clinically important improvement. Finally, 39.4% of participants in the cannabis-based medications and 32.7% of participants in the placebo group reported pain relief of 30% or greater (NNTB = 11). The quality of evidence was determined to be moderate to low due to indirectness, imprecision, and inconsistency. They concluded that there is "no high-quality evidence for the efficacy of any cannabis-based medicine (herbal cannabis, plant-derived THC (dronabinol), synthetic THC (nabilone), and plant-derived THC/CBD combinations) in any condition with chronic NP". Mücke et al. [21] stated that they performed a quantitative analysis, which included unpublished studies with negative results, while the authors of the studies with more favorable outcomes did not include the data of studies that are only available in databases; they also excluded studies with a very short duration. In addition, the same authors found that using cannabis-based medications for chronic NP showed moderate-quality evidence that more participants dropped out due to AEs with cannabis-based medications compared to placebo, and low-quality evidence that more participants reported any AEs and AEs of the central nervous system and psychiatric disorders with all cannabis-based medications pooled together than with placebo. This was also in accordance with another systematic review [96] that analyzed eight trials of cannabis-based medicine in chronic NP.

Another systematic review and meta-analysis that examined cannabis treatment for chronic pain [95] concluded that the current evidence might suggest that treatment of chronic pain with cannabinoid compounds may pose a greater risk than benefit to the patient because of the possible appearance of the pain as a secondary problem in the subject.

3. Overall completeness and applicability of evidence

Parallel RCTs or crossover placebo-controlled studies were identified from electronic databases including MEDLINE, Web of Science, EMBASE, and the Cochrane library limited to English language up to 2/1/2021. Cannabis-based medications included THC, THC/CBD, CBD, CBDV, CT-3, and dronabinol. The results of this systematic review apply to patients with chronic NP between ages 18–77. The trials were conducted in the USA, UK, Europe, and Israel, and may not reflect or apply to other countries.

These results are applicable to NP conditions including central NP (MS, brachial plexus avulsion), complex regional pain syndrome (CRPS) type II, HIV-related neuropathy, painful diabetic neuropathy, peripheral polyneuropathies of other etiologies, phantom limb pain, postherpetic neuralgia, postoperative or traumatic

peripheral nerve lesions, spinal cord injuries, nerve plexus injuries, and trigeminal neuralgia (TN).

The applicability of the evidence to routine care is limited because some of the included studies excluded individuals with current or past alcohol and/or substance abuse, significant medical issues (cardiovascular disease, poorly controlled hypertension, active epilepsy), significant psychiatric illnesses, and those naïve to cannabis-derived products.

The reliability of the combined results is limited because of the small sample size, short duration, different types of interventions, routes of administration, doses and dose schedules, and the different types of NPs.

4. Heterogeneity of the review

This systematic review included only RCTs comparing cannabis-based medications with a placebo. There was heterogeneity in terms of the intervention (THC/CBD, CBD, CBDV, synthetic cannabis), for which the review authors conducted subgroup analyses. Review authors conducted subgroup analyses with similarly reported outcomes. Different types of cannabis were utilized in the included studies, with varied mechanisms of action, routes of administration, dosages, and schedule. The route of administration of cannabis varied from smoked, inhaled, vaping, spray, and oil. The minimum and maximum doses of THC were 1% and 9.4%, respectively. NP types varied from HIV distal sensory predominant polyneuropathy, CRPS II, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, focal nerve lesion, radiculopathy, multiple sclerosis, injury and disease of the spinal cord, nerve plexus injury, and postoperative or traumatic peripheral nerve lesions due to trauma. The diagnosis of NP was based on clinical symptoms and various tools depending on the diagnosis (see Results section).

5. Implications for research

This systematic review and meta-analyses demonstrated low to moderate quality of evidence due to high or unclear risk of bias, small number of studies, and limited duration. The quality of the evidence was low to moderate because of the unclear blinding of samples. Some studies received funding from drug companies, while others had co-interventions. However, a few studies have not completely reported the outcome data. In conclusion, a high overall risk of bias was assigned to six studies, and an unclear overall risk of bias was assigned to eight studies. The meta-analyses highlight the need for future high-quality double-blinded randomized, placebo-controlled studies receiving cannabis-based medications with intent-to-treat analyses and full reporting of outcome data as stated in published protocols without biases.

The present systematic review has several limitations that will be valuable for future studies. These limitations included the variability in the length of the studies evaluated, the short trial durations, small sample sizes, variability of route of administration, multiple doses, concomitant therapies, and lack of knowledge of possible drug-drug interactions or long-term effects.

The Committee for Medicinal Products for Human Use (CHMP) published guidelines on clinical medicinal products intended for the treatment of neuropathic pain [97]. These guidelines require that the study duration for chronic NP trials be at least 12 weeks after a stable dose is achieved to exclude a transient effect. Due to the increasing number of drugs approved for NP, they also recommend that a three-arm study (study drug – comparator–placebo) should be undertaken to assess the comparative efficacy and safety of a new product. Long-term clinical trials may also help to determine whether the effect of cannabis on chronic NP is sustainable.

The optimal dose and ratio of THC/CBD need to be determined for different types of NPs. Determining the optimal dose, treatment duration, and individual titrations would allow for a better balance between beneficial and adverse effects, especially in older vulnerable and young populations [98,99].

Medicinal cannabis is controversial and remains illegal and is unavailable in many states in the United States.

There may also be a long-lasting stigma associated with smoking cannabis [100]. Some individuals may prefer not to take cannabis-based medications if the route of administration is inhaled due to social stigmas or if long-term adverse effects of smoked cannabis outweigh the benefits [99,101-104]. Determining the most beneficial route of administration and type of cannabinoid with these factors in mind would allow individuals with an interest in medicinal cannabis to select or decline this treatment option, especially if the reduction in pain intensity is modest. There may also be differences in efficacy, adverse effects, or abuse potential among the different types of cannabinoids and routes of administration.

The use of cannabis for other medical conditions should also be investigated in high-quality randomized placebo-controlled clinical trials. Clinical evidence will help with appropriate prescribing, prevent misuse and harm, and possibly reduce the use of opioids and their associated risks [105,106].

One study [63] in this review required that participants have experience using cannabis-containing products, while another excluded patients with prior experience [54]. Future studies should include individuals who have not used cannabis-based medications and those that used them to study the efficacy, safety, and tolerability of all types of patients. Future studies should also explore other cannabis-based agents that may be useful in reducing pain, such as CT-3.

The types of NP varied greatly in this systematic review with meta-analysis due to a lack of RCTs on cannabis-based medications in the treatment of any specific type of NP. Future research on the efficacy of cannabis-based medications should focus on the specific causes of NP because the mechanisms are different.

6. Implications for clinical practice

Currently, therapeutic options for the treatment of NP often provide inadequate relief. A review of the current research indicates that, although there is moderate and low-quality evidence to support significant changes in pain intensity from baseline in NP with the use of some forms of THC, THC/CBD, and the synthetic cannabinoid dronabinol, there is currently no high-quality evidence for the efficacy of any form of cannabis-based medication for the treatment of NP. Clinical research to determine the efficacy of cannabinoid medications in the treatment of NP is confounded by the variable etiologies of NP as well as factors such as varying doses, routes of administration, concurrent medications of NP patients, potential adverse effects, and lack of uniform testing across studies. This makes statistical analysis to determine the efficacy difficult and clinical recommendations for its use tenuous. Additional long-term studies with more uniform study parameters are needed to achieve more clinically relevant recommendations. Potential adverse events often related to psychoactive effects may limit the clinical use of cannabis-based medications for some patients. A high degree of variability among study participants warrants caution with its use as a potential therapeutic option for patients with NP.

In conclusion, THC/CBD and THC interventions provided statistically significant improvements in pain intensity in NP patients and were more likely to provide a 30% reduction of NP when smoked or vaped at different concentrations (3.56% to 9.4% THC) or using a spray (THC 2.5-2.7 mg & CBD 2.5 mg per 100mL) compared to placebo. The evidence for THC/CBD and THC was moderate to low quality. Therefore, Further studies are needed for CBD, CBDV, and the synthetic cannabinoids dronabinol and CT-3, as only one study reported outcomes on these cannabis-based interventions compared to placebo.

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