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ORIGINAL RESEARCH

Systematic Review and Meta-analysis Seem to Indicate that Cannabinoids for Chronic Primary Pain Treatment Have Limited Benefit

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ABSTRACT

Introduction: The IASP ICD-11 chronic primary pain (CPP) definition includes 19 different painful conditions. In recent years, interest in the potential role of cannabinoids in the management of CPP has increased, since they demonstrated a possible efficacy in treating pain, especially in secondary pain conditions. However, limited evidence is available for patients with CPP. The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of cannabinoid administration in CPP.

Methods: PubMed, EMBASE, and Cochrane Library were searched form the beginning up to 31 October 2021 to retrieve published articles of randomized controlled trials (RCTs) or observational, retrospective or prospective, studies, investigating cannabinoids in CPP. The study screening process was completed during November 2021. The primary outcome was pain reduction by means of the visual analogue scale (VAS). Secondary outcomes were quality of life by means of the fibromyalgia impact questionnaire (FIQ) or other available scales, appetite, anxiety, depression, and sleep by means of any available scales. Safety was assessed with the reporting of serious adverse events (SAE) and discontinuation due to adverse events. Risk of bias was assessed. The weighted generic inverse

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variance method and Mantel–Haenszel method were used to estimate the mean difference (MD) and odds ratios (OR) with 95% confidence intervals (CI) for continuous and dichotomous outcomes, respectively. For outcome measures reported with different scales (pain, anxiety, depression), we used the standardized MD (SMD) as the effect measure and then converted it into units of the VAS scale for pain, the Beck Anxiety Inventory (BAI) for anxiety, and the Beck Depression Inventory (BDI) for depression. Summary of findings was produced using GRADEproGDT.

Results: From 3007 identified records, we included eight articles reporting the results of eight different RCTs (four parallel and four crossover studies; seven compared to placebo and one to amitriptyline), with a total population of 240 patients. VAS pain reduction was non-significant for cannabinoids against placebo (MD = − 0.64; 95% CI − 1.30 to 0.02) or amitriptyline (MD = − 0.19; 95% CI − 0.58 to 0.19). More than 4 weeks cannabinoid treatment significantly reduced pain compared to placebo in parallel studies with more than 4 weeks of treatment duration (MD = − 1.28; 95% CI − 2.33 to − 0.22). Differences for the FIQ (MD = − 21.69; 95% CI − 46.20 to 2.82), BAI (MD = − 2.32; 95% CI − 7.99 to 3.08), and BDI (MD = 2.32; 95% CI − 1.71 to 6.35) were non-significant, likewise for discontinuation due to adverse events (OR = 2.15; 95% CI 0.44–10.65), when comparing cannabinoids to placebo. The quality of the evidence was generally low mainly as a result of imprecision and risk of bias.

Conclusion: Cannabinoid treatment in patients with CPP had limited benefit on pain relief; however, it might improve pain with long-term administration.

Keywords: Cannabis; Cannabinoids; Chronic primary pain; Fibromyalgia; Meta-analysis; Systematic review

Key Summary Points

Chronic primary pain (CPP) is a new ICD-11 diagnostic definition including several painful conditions such as fibromyalgia, chronic regional pain syndrome, irritable bowel syndrome, and chronic migraine among others.

While interest in the potential role of cannabinoids in painful conditions has increased and previous systematic reviews found they are effective in treatment of chronic, especially secondary, non-cancer pain, limited evidence is available on the effects of cannabinoids on CPP and for this reason we performed a systematic review and a meta-analysis to evaluate the role of cannabinoids in CPP.

We found limited benefit of cannabinoids compared to placebo on pain relief in patients with CPP in the overall analysis, while we observed a significant reduction of pain in clinical trials with a long-term treatment.

Cannabinoids might improve pain and quality of life in patients with fibromyalgia.

The quality of the available evidence for cannabinoids use in CPP is generally low and future, long-term trials are needed.

INTRODUCTION

In 2019, the International Association for the Study of Pain (IASP) proposed the new diagnosis of chronic primary pain (CPP) for ICD-11. CPP is defined as pain in one or more anatomical regions, persisting or recurring for more than 3 months, associated with significant emotional distress and/or significant functional disability, and with symptoms that are not better accounted for by another diagnosis. By contrast, chronic secondary pain is the consequence or

the symptom of an underlying disease (e.g., rheumatoid arthritis, multiple sclerosis, diabetic neuropathy, chronic pancreatitis). The CPP definition encompasses 19 different conditions, including fibromyalgia, chronic regional pain syndrome (CRPS), irritable bowel syndrome (IBS), and chronic migraine, among others. Thus, CPP can involve any body system, site, and even a combination of body sites while the emotional distress can assume the forms of catastrophism, depressed mood, anxiety, anger, or frustration. Functional disability could widely interfere with daily-life activities such as working, sleeping, and taking part in social activities. Recently, it has been suggested that the concept of nociplastic pain, a third neurophysiological mechanism proposed in addition to neuropathic and nociceptive pain, may be suitable for CPP [1, 2]. Limited treatments are available for CPP and often they do not provide adequate symptom control.

In recent years, interest in the potential role of cannabinoids in the management of pain has increased. Cannabinoids are a large group of compounds found in *Cannabis sativa* and *Cannabis indica* plants, whose two major constituents are tetrahydrocannabinol (THC) and cannabidiol (CBD). Different categories of cannabinoid medicines are currently used: cannabis-derived pharmaceuticals, including synthetics (e.g., nabilone and dronabinol) and botanical cannabinoids (e.g., nabiximols), and various phytocannabinoid plant-derived preparations (i.e., medical cannabis or marijuana) [3]. Cannabinoids can be administered orally (ingested, topically, or sublingually), smoked, inhaled, mixed with food, or assumed as a decoction [4]. The therapeutic use of cannabis and its derivatives has been evaluated for a variety of health conditions including pain, side effects of chemotherapy, anorexia, multiple sclerosis, and symptomatic relief of spasticity [5, 6]. The mechanisms of the analgesic effect of cannabinoids include the inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve terminals, the modulation of postsynaptic neuron excitability, the activation of descending inhibitory pain pathways, and the reduction of neural inflammation [7]. These effects are thought to be obtained by the different cannabinoids on the endocannabinoid system, involving the two cannabinoid receptors, CB_1 and CB_2, both coupled to inhibitory G proteins. CB_1 is mostly present in the central and peripheral nervous system, but also in other organs such as heart, some endocrine glands, and the gastrointestinal tract. CB_2 is more present in the periphery and on immune system cells [8, 9]. THC acts as a partial agonist both on CB_1 and CB_2 and can both activate or inhibit cannabinoid receptors depending on the expression of receptors in different tissues or on the presence of other cannabinoids. Although CBD has low affinity for cannabinoids receptors, it has shown antagonist properties on CB_1 and CB_2, acting as an inverse agonist. However, its mechanism of action on the endocannabinoid system is less understood and it is believed that CBD exerts its functions on other receptor systems, potentiates the activity of the endogenous cannabinoid anandamide, and reduces the psychotropic effects of THC [8–10]. Besides being generally well tolerated in long-term medical use, cannabinoid administration is not free of potential unwanted and adverse effects (e.g., dysphoria, depersonalization, hallucinations, induction or aggravation of psychotic states, impaired motor coordination, tachycardia, both hypotension and hypertension, and impairment of cognitive function in exposed newborns and children) [8].

Previous systematic reviews and meta-analyses showed that cannabinoids are effective in pain reduction in patients with chronic non-cancer pain. However, the analgesic effect was small and with limited clinical significance, while the efficacy in pain reduction was similar between patients affected by neuropathic or non-neuropathic chronic pain. Moreover, the evidence was in general moderate to low, and meta-analyses included both CPP and chronic secondary pain, without differentiating these different conditions, with the majority of included studies having enrolled patients with the latter condition [11–18]. Also, other systematic reviews evaluated and included studies without comparators [17, 19], which may limit the possibility to evaluate the presence of the placebo effect and thus estimate the real efficacy

or effectiveness of cannabinoids. Albeit limited by some clinical and methodological constraints, recent studies and systematic reviews on fibromyalgia suggested that cannabinoids might be useful and safe in the treatment of CPP [20–22]. Since the effect sizes from previous meta-analyses including mainly secondary pain conditions are estimated and strongly depend on the data of patients with these conditions, it is not possible to generalize those results to the CPP population [11–14]. For this reason, we conducted a systematic review with a meta-analysis to investigate the role of cannabinoids in the treatment of CPP, compared to placebo or other active compounds. The results of this systematic review could provide clinicians and patients with the current evidence about the potential efficacy of cannabinoids in CPP, improving the clinical decision process at the time of therapeutic choices. Also, this study could provide useful information for researches, identifying knowledge gaps in the topic and suggesting potential future studies to provide further and high-quality evidence.

METHODS

Search Strategy and Selection Criteria

We performed a literature search on PubMed, EMBASE, and Cochrane Library (CENTRAL) from the beginning up to 31 October 2021, to retrieve clinical studies investigating the efficacy and safety of cannabinoids in CPP. The study screening process was completed during November 2021. The search strategy included "chronic primary pain", all the 19 conditions included in the CPP definition according to the ICD-11 IASP dedicated publication [1], and "cannabinoids" as search terms combined with Boolean operators and without any applied filters. Refer to Supplementary Material S1 for the detailed search strategy and keywords used.

We included randomized controlled trials (RCTs) and longitudinal, prospective or retrospective, observational studies to evaluate the efficacy and safety of any type and preparation of cannabinoid treatments in adult or pediatric patients with CPP, compared to placebo or any other active treatment. In order to classify studies for inclusion we adhered to the ICD-11 IASP CPP definition [1]. Only articles in English were included. Studies enrolling patients either with CPP or chronic secondary pain were included only if the subgroup of patients with CPP was at least 50% of the overall population. Cross-sectional studies, single-arm studies without a comparator, and conference abstracts were excluded.

Two study authors independently screened the retrieved citations by title and abstract. Full-text versions of potentially eligible articles were read to make the final decision for inclusion or exclusion, with reasons. Disagreements were resolved by collegial discussion. This systematic review was registered on PROSPERO (CRD42021281840) and we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for the realization of this work [23, 24]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Assessed Outcomes

The primary prespecified outcome of this study was pain reduction, assessed with the visual analogue scale (VAS) or another dedicated scale or questionnaire. For the pain outcome evaluation, we intended to evaluate spontaneous pain; thus, we did not collect data on this outcome if studies investigated experimentally induced pain or pain thresholds. Secondary prespecified outcomes were quality of life (QoL), appetite, anxiety, depression, and sleep. For QoL, in this systematic review and meta-analysis we used the fibromyalgia impact questionnaire (FIQ) and the IBS-36 questionnaire. Anxiety and depression were analyzed using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI), respectively. Safety was assessed with discontinuation due to adverse events (AE) and occurrence of serious adverse events (SAE).

Data Extraction

Data were collected from included study papers and extracted independently by two authors on an Excel spreadsheet, and discrepancies were resolved by collegial discussion. The Excel spreadsheet was divided into dedicated sheets for each different outcome. We used rows for studies and columns for each different piece of information extracted (e.g., number of patients, effect size, standard deviation, standard error, lower and upper limits of the 95% CI, etc.). One sheet was dedicated to design details of included studies with rows for studies and columns for different collected information. The following information was extracted: first author, year of publication, countries involved, recruitment period, study duration, patients age and sex, included conditions, inclusion and exclusion criteria, total patients included and by treatment arm, the baseline VAS for pain, and results of prespecified review outcomes.

Assessment of Risk of Bias

Two pairs of authors independently assessed risk of bias (RoB) using the Cochrane RoB 2 tool for RCTs. The RoB 2 tool includes the following domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Discrepancies were resolved by collegial discussion. For observational non-randomized studies, we intended to use the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.

Statistical Analysis

A meta-analysis was performed when there were at least two included studies with available data for assessed outcomes. For continuous outcomes, the weighted generic inverse variance on mean difference (MD) method was used to estimate MD and 95% confidence intervals (95% CI). For studies reporting the same outcome measure with different scales (pain, anxiety, depression), we used the standardized MD (SMD) as the effect measure. We then re-expressed SMD to the corresponding MD units of the VAS scale for pain, the BAI for anxiety, and the BDI for depression. When studies did not report standard deviations, standard errors, or 95% CI, these were estimated from MD, study arm populations, and p values. For dichotomous outcomes, the Mantel–Haenszel method was used to calculate measures of effect as odds ratios (ORs) with 95% CI. Results were pooled using a random-effect meta-analysis. Heterogeneity was assessed with I-squared statistic. Analyses were performed comparing cannabinoids to placebo or any active comparator. When possible, for efficacy outcomes we conducted several subgroup analyses based on the investigational product administration schedule (studies with daily administration of the same compound for a determined period—longitudinal daily-dose studies; studies with the administration of different compounds in different single days—single doses studies) and the different condition of included patients. We performed two sensitivity analyses excluding studies that enrolled also chronic secondary pain patients and grouping studies by design (parallel or crossover) and by treatment duration (at least 4 weeks or less than 4 weeks). Publication bias was assessed through the creation of a funnel plot. The different forest plots and funnel plot are available in the Supplementary Material. Analyses were performed with the use of Cochrane RevMan 5.4 software.

Summary of Findings

Summary of findings was produced using GRADEproGDT by two review authors independently and discrepancies were resolved by discussion.

Role of the Funding Source

The study was funded by the Postgraduate School of Clinical Pharmacology and Toxicology, Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Milan, Italy. The corresponding author had full access to all the data in the

study and had final responsibility for the decision to submit for publication.

RESULTS

Search Results and Study Characteristics

We identified 3007 records (1242 from PubMed, 1765 from EMBASE, and 0 from Cochrane Library) from the initial search strategy. After the removal of duplicates, 2518 records were screened and 2452 of these were excluded by title and abstract. Sixty-six potentially eligible studies were read in full text and 58 were excluded for various reasons. Eight studies were included in the qualitative synthesis and in the meta-analysis [25–32] (Fig. 1). The percentage of agreement was 99.8% and the Cohen's kappa was 0.73, implying substantial agreement. All included studies were RCTs, published between 2008 and 2021, four with a parallel design and four with a crossover design. Among them, two crossover studies evaluated cannabinoids as single-dose administrations of different compounds on different days (single doses studies), while the remaining six RCTs administered the same compounds daily for a determined period (longitudinal daily-dose studies) (Table 1). The overall population consisted of 240 patients across eight studies. A total of 115 patients had fibromyalgia [25, 27, 28, 31], 19 had chronic primary chest pain [26], and 68 had IBS [29, 30]. One study enrolled 22 patients with CRPS type I (57.9%) among a total population of 38 subjects, with the remaining having various chronic secondary pain conditions (Table 1) [32]. For this reason, we performed a sensitivity analysis excluding this study.

Among included RCTs, seven studies administered different cannabinoid compounds and preparations, including sublingual cannabis THC-rich oil [25], dronabinol oral capsules [26, 29], oral nabilone [27], CBD gums [30], inhaled vaporized pharmaceutical-grade medicinal cannabis (Bedrocan, Bediol, Bedrobinol) [31], different doses of delta-9-THC pharmaceutical-grade medicinal cannabis smoked cigarettes [32], all compared to matching placebo. One RCT compared nabilone to amitriptyline oral capsules [28].

Outcomes extracted and included in our meta-analysis are outlined in Table 1.

Risk of Bias

Overall, we considered one study at low risk of bias; five studies had some concerns regarding risk of bias, and two studies were at high risk of bias (Fig. 2). We considered all studies at low risk of bias for the randomization process. We considered two studies to have some concerns [25, 30] and two others to be at high risk of bias [26, 27] because of deviations from intended interventions, mainly due to the exclusion of patients from the analyses or a large dropout from the study, without accounting for the missingness of the patients and performing the analysis itself in a per-protocol fashion. For the missing outcome data domain, we considered three studies to have some concerns [26, 30, 31] and one was at high risk of bias [27]. We considered all studies at low risk of bias for measurement of the outcome. One study was considered at low risk of bias [28] in the selection of the reported result while we considered the others to have some concerns of risk of bias [25–27, 29–32] for this domain since we did not find information on whether the analyses were performed according to a prespecified plan.

Pain Reduction

Overall, we were able to extract data on pain reduction from seven studies, six evaluated cannabinoids efficacy against placebo and one against amitriptyline, with a total population of 182 patients included in the analyses. Among these patients, 46 were from the crossover RCT comparing nabilone to amitriptyline in fibromyalgia. Pain was re-expressed in VAS units. In a primary analysis, we assessed cannabinoids efficacy against placebo or any active comparator. When comparing cannabinoids to placebo the difference was non-significant (MD = − 0.64 95% CI − 1.30 to 0.02) (Fig. S1A, Table 2). Nabilone and amitriptyline were not significantly different in pain

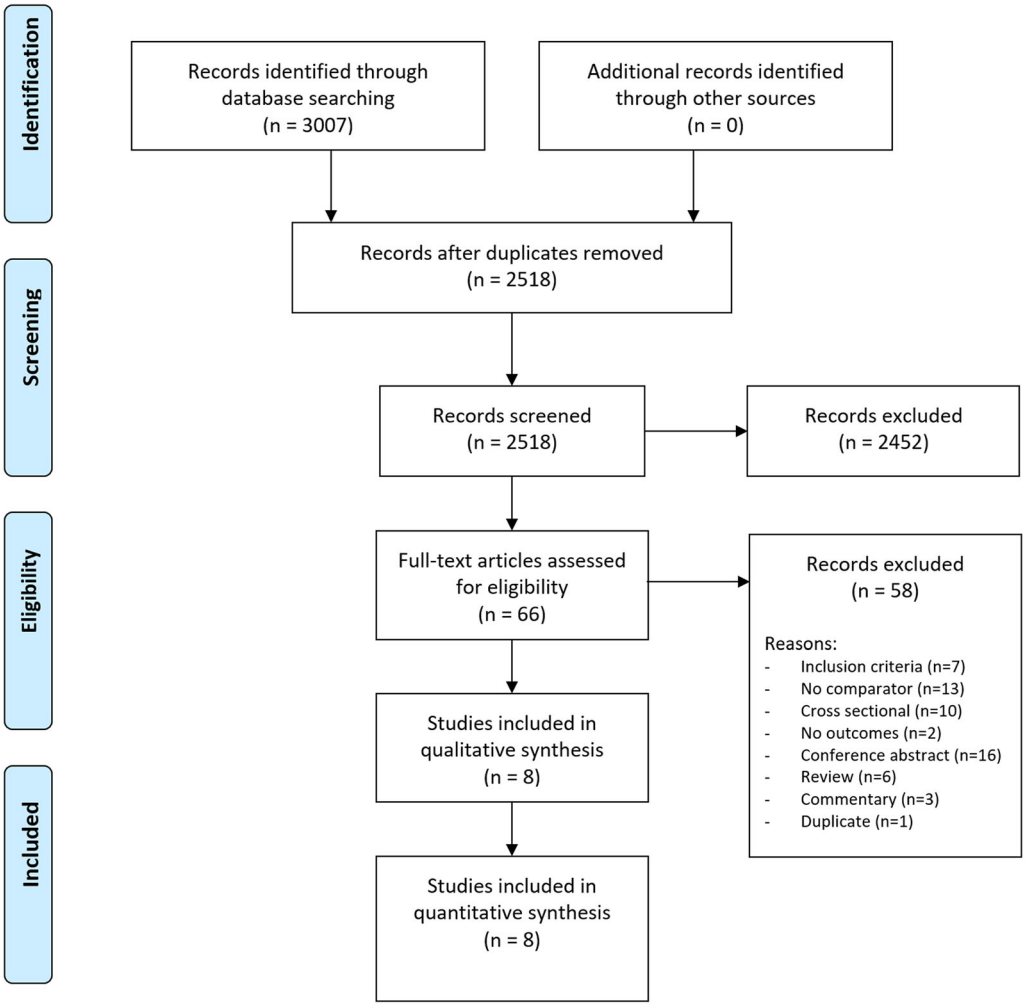

Fig. 1 PRISMA flow chart

reduction (MD = – 0.19; 95% CI − 0.58 to 0.19) (Fig. S1B). When grouping included studies by study design (parallel or crossover) and by treatment duration (at least 4 weeks or less than 4 weeks), we observed a significant reduction of pain in parallel studies with more than 4 weeks of cannabinoid treatment compared to placebo (MD = – 1.28; 95% CI − 2.33 to − 0.22). This difference was not significant for crossover studies with a treatment duration less than 4 weeks compared to placebo (MD = – 0.34; 95% CI − 1.1 to 0.42) (Fig. S2A, Table 2). These results were confirmed after a sensitivity analysis excluding the study that also enrolled chronic secondary pain patients (Fig. S3).

In a subgroup analysis, we evaluated the efficacy of cannabinoids against placebo by different CPP conditions. No significant differences were observed in patients with fibromyalgia (MD = – 0.70; 95% CI – 1.54 to 0.12), chronic primary chest pain (MD = 0.00; 95% CI − 2.19 to 2.19), and IBS (MD = 0.34; 95% CI − 1.06 to 1.73), while we observed a significant reduction in patients with CRPS type I (MD = – 1.62; 95% CI − 3.01 to − 0.26) (Fig. S4, Table 2). However, a sensitivity analysis including studies on fibromyalgia showed that cannabinoids significantly reduced pain compared to placebo in parallel RCTs with more than 4 weeks of follow-up (MD = – 0.82; 95% CI − 1.41 to − 0.24) while it was non-significant in

Table 1 Characteristics of included studies

Data	Longitudinal daily-dose studies						Single-dose studies	
Author (year)	**Chaves (2020) [25]**	**Malik (2017) [26]**	**Skrabek (2008) [27]**	**Ware (2010) [28]**	**Wong (2012) [29]**	**van Orten-Luiten (2021) [30]**	**Van de Donk (2019) [31]**	**Wilsey (2008) [32]**
Study design	RCT-P	RCT-P	RCT-P	RCT-Co	RCT-P	RCT-Co	RCT-Co	RCT-Co
Included condition	FM	CPCP[a]	FM	FM	IBS-D	IBS	FM	CRPS type I + secondary chronic neuropathic pain
Study years	2019–2019	NA	2006–2006	2005–2006	2008–2011	NA	NA	2004–2006
Inclusion criteria	Male or female, age 18+ years, with FM, no previous cannabis medication. Mild analgesics and AID allowed	Male or female, age 18–75 years, with functional chest pain, no previous narcotics or other pain medications. Concomitant pain medications not allowed	Male or female, age 18–70 years, with FM, no previous cannabis medication. Previous pain medication, including opioids, maintained	Male or female, age 18+ years, with FM and chronic insomnia, stable analgesic therapy, negative urine test for cannabinoids at baseline	Male or female, age 18–69 years, with IBS-D, without previous use of cannabinoids	Male or female, age 18–65 years, with IBS, without cannabis use in the last 3 months and no concurrent use of opioids	Female, age 18+ years, with FM, no recent cannabis. No opioid use. Paracetamol and ibuprofen allowed	Male or female, age 21+ years, with CRPS type I, spinal cord injury, peripheral neuropathy, or nerve injury, and previous cannabis exposure. Previous pain medications maintained
Study drug	THC-rich cannabis oil[b]	Dronabinol 5 mg BID	Nabilone 0.5–2.0 mg daily	Nabilone 0.5–1.0 mg before bedtime	Dronabinol 5 mg BID; dronabinol 2.5 mg BID	CBD gums[c]	Bedrocan; Bediol; Bedrolite;[d]	Delta-9-THC 7%; delta-9-THC 3.5% (cigarettes)
Control	Placebo	Placebo	Placebo	Amitriptyline 10–20 mg before bedtime	Placebo	Placebo	Placebo	Placebo
Follow-up, weeks (Tr/Wo)	8 (8Tr)	4 (4Tr)	8 (4Tr; 4Wo)	10 (2Wo; 2Tr; 2Wo; 2Tr; 2Wo)	2 days	8; (1Bl; 3Tr; 1Wo; 3Tr)	4 days in separate sessions	3 days in separate sessions
Population	18	19	40	32	36	40 (32 analyzed)	25	38
Age, mean	52	43	49	50	42	31[e]	39	46
Female, *n* (%)	17 (100)	11 (84.6)	47 (92.5)	26 (83.9)	34 (94.4)	32 (100)[e]	25 (100)	18 (47.4)

Table 1 continued

Data	Longitudinal daily-dose studies						Single-dose studies	
Author (year)	Chaves (2020) [25]	Malik (2017) [26]	Skrabek (2008) [27]	Ware (2010) [28]	Wong (2012) [29]	van Orten-Luiten (2021) [30]	Van de Donk (2019) [31]	Wilsey (2008) [32]
Baseline pain, VAS, mean	NA	NA	6.53	2.3 (McGill PPI)	NA	5.8	7.2	5.6
Extracted outcomes	Pain, FIQ, discontinuation due to AEs	Daily chest pain, SAE, discontinuation due to AEs	VAS, FIQ, SAE, discontinuation due to AEs	McGill PPI, FIQ, SAE, discontinuation due to AEs	SAE, discontinuation due to AEs	VAS, IBS36, discontinuation due to AEs	VAS 180 min change from baseline, SAE, discontinuation due to AEs	VAS, discontinuation due to AEs

For follow-up, total duration and treatment and washout periods duration are both presented

AE adverse events, *AID* anti-inflammatory drugs, *BAI* Beck anxiety inventory, *BDI* Beck depression inventory, *BID* bis in die, *CBD* cannabidiol, *CPCP* chronic primary chest pain, *CRPS* chronic regional pain syndrome, *FIQ* fibromyalgia impact questionnaire, *FM* fibromyalgia, *GI* gastrointestinal, *GIC* global impression of change, *IBS* irritable bowel syndrome, *IBS-36* 36-items IBS quality of life scale, *NA* not available/not applicable, *RCT* randomized controlled trial, *RCT-P* parallel arm RCT, *RCT-Co* crossover RCT, *SAE* serious adverse events, *SF-36* 36-items short form survey, *THC* tetrahydrocannabinol, *Tr* treatment period, *VAS* visual analogue scale, *Wo* washout period

[a]Referred to as "functional chest pain" in the article

[b]THC-rich cannabis oil: 24.44 mg/mL THC + 0.51 mg/mL CBD. The initial dose was one sublingual drop (1.22 mg of THC and 0.02 mg of CBD) a day with subsequent increases according to symptoms

[c]CBD gums: 1–6 daily if VAS pain 4 or more. CBD-PBO sequence consumed 5.4 gums week, while PBO-CBD consumed 6.3 gums week in the first period, then 6.5 and 5.3, respectively

[d]Bedrocan (22% THC + 1% CBD); Bediol (6.3% THC + 8% CBD); Bedrolite (1% THC + 9% CBD)

[e]Data for baseline were available only for the 32 patients who completed the study on the originally randomized 40 patients population

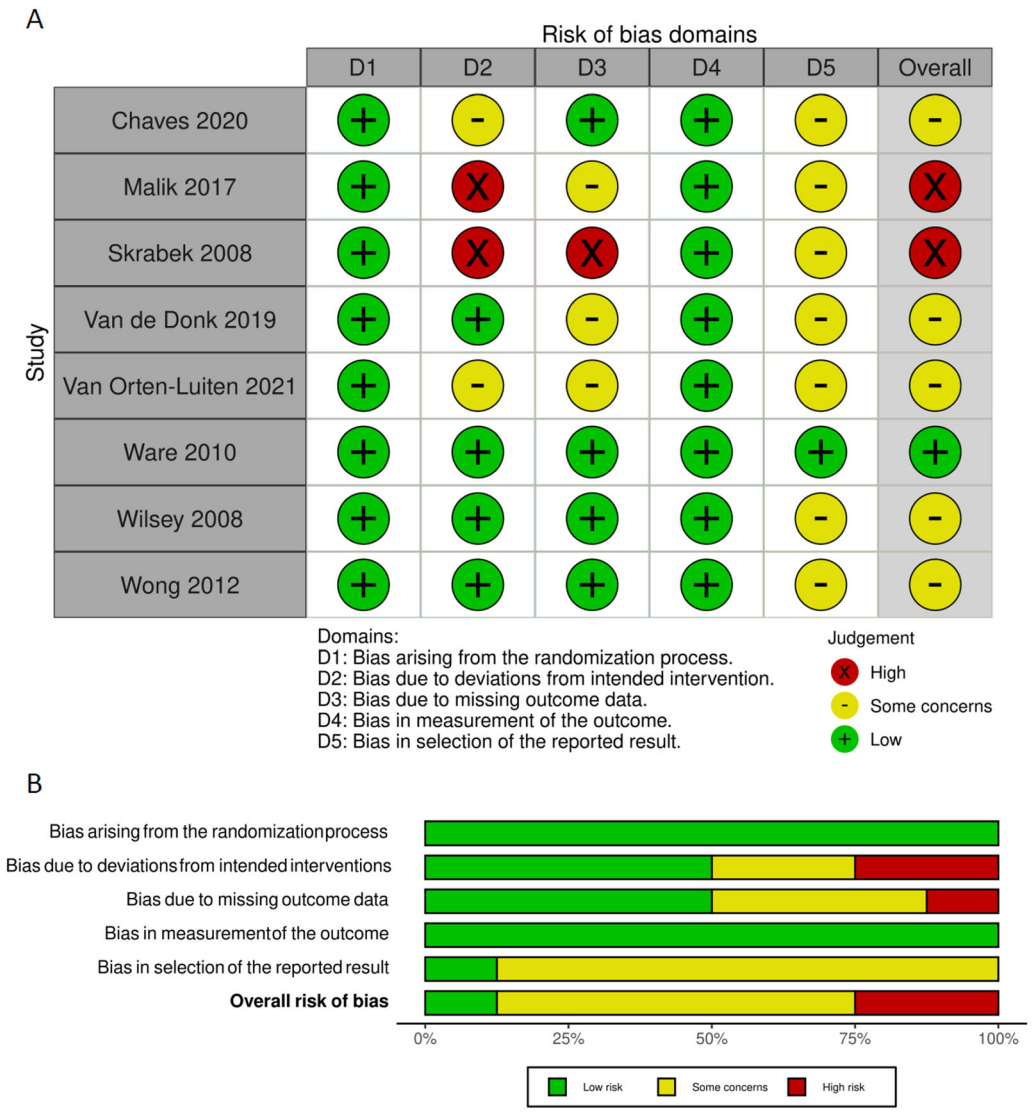

Fig. 2 Risk of bias of included studies **a** for individual studies and **b** across risk of bias domains

crossover RCTs with less than 4 weeks of follow-up (MD = – 0.01; 95% CI – 0.52 to 0.50) (Fig. S2B, Table 2).

Quality of Life

We extracted QoL outcomes from three studies enrolling patients with fibromyalgia, two evaluating cannabinoids against placebo, and one against amitriptyline, with a total population of 79 patients included in the analyses. To evaluate the quality of life, the FIQ was used in all the three studies. We found statistically non-significant differences when comparing cannabinoids against placebo (MD = – 21.69; 95% CI – 46.20 to 2.82) or amitriptyline (MD = – 0.70; 95% CI – 7.30 to 5.90). Another crossover study comparing CBD to placebo reported QoL data from 30 patients with IBS who completed the IBS-36 questionnaire. No significant differences were observed between CBD and placebo (MD = – 1.0; 95% CI – 6.8 to 4.9) (Fig. S5, Table 2).

Table 2 Summary of findings for cannabinoids compared to placebo

Outcomes	Risk/effect difference (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pain (overall CPP)	MD – 0.64 cm (– 1.3 to 0.02)	151 (6 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests that cannabinoids result in little to no difference in pain reduction compared to placebo
Pain (overall CPP parallel RCT)	MD – 1.28 cm lower (– 2.33 to – 0.22)	63 (3 RCTs)	⊕⊕◯◯ Low[a,b]	Cannabinoids may result in a slight reduction in pain
Pain (overall CPP crossover RCT)	MD – 0.34 cm (– 1.1 to 0.42)	90 (3 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggests that cannabinoids result in little to no difference in pain reduction
Pain (fibromyalgia)	MD – 0.70 cm (– 1.54 to 0.12)	83 (3 RCTs)	⊕⊕◯◯ Low[a,b]	Cannabinoids may not reduce pain in fibromyalgia
Pain (fibromyalgia parallel RCT)	MD – 0.82 cm (– 1.41 to – 0.24)	58 (2 RCTs)	⊕⊕◯◯ Low[a,b]	Cannabinoids may result in a slight reduction in pain
Pain (fibromyalgia crossover RCT)	MD – 0.01 cm (– 0.52 to 0.50)	25 (1 RCT)	⊕◯◯◯ Very low[c,d]	Cannabinoids may have little to no effect on pain but the evidence is very uncertain
Pain (chronic primary chest pain)	MD 0.00 cm (– 2.19 to 2.19)	13 (1 RCT)	⊕◯◯◯ Very low[c,d]	Cannabinoids may have little to no effect on pain in chronic primary chest pain but the evidence is very uncertain
Pain (CRPS type I + CSP)	MD – 1.62 cm lower (– 3.01 to – 0.26)	38 (1 RCT)	⊕⊕◯◯ Low[c,e]	The evidence suggests cannabinoids may result in a slight reduction in pain in CRPS type I and chronic secondary pain conditions
Pain (IBS)	MD 0.34 cm higher (– 1.06 to 1.73)	32 (1 RCT)	⊕⊕◯◯ Low[c,f]	Cannabinoids (CBD) may not reduce pain in IBS
QoL (fibromyalgia)	MD – 21.69 points (– 46.2 to 2.82)	50 (2 RCTs)	⊕⊕◯◯ Low[a,b]	Cannabinoids may result in a slight improvement of QoL (FIQ) in fibromyalgia
QoL (IBS)	MD 1.00 points lower (– 6.8 to 4.9)	30 (1 RCT)	⊕⊕◯◯ Low[c,f]	The evidence suggests that cannabinoids (CBD) may not improve QoL (IBS-36) in IBS

Table 2 continued

Outcomes	Risk/effect difference (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Anxiety assessed with: BAI	MD – 2.42 points lower (– 7.99 to 3.08)	63 (3 RCTs)	⊕◯◯◯ Very low[a,c,g]	Cannabinoids may reduce/have little to no effect on anxiety but the evidence is very uncertain
Depression assessed with: BDI	MD 2.32 points higher (– 1.71 to 6.35)	30 (2 RCTs)	⊕⊕◯◯ Low[a,c]	Cannabinoids may increase/have little to no effect on depression
SAE	Not estimable	152 (5 RCTs)	⊕◯◯◯ Very low[a,c]	No SAE were reported both in cannabinoids and any comparator. The evidence is very uncertain about the effect of cannabinoids on SAE
Discontinuation due to AE	OR 2.15 (0.44–10.65)	171 (6 RCTs)	⊕⊕◯◯ Low[h]	The evidence suggests cannabinoids result in a slight increase in discontinuation due to AE

Pain is expressed in VAS units; QoL is expressed in FIQ units and IBS-36 units for fibromyalgia and IBS, respectively; anxiety and depression are expressed in BAI and BDI units, respectively

BAI Beck anxiety inventory, *BDI* Beck depression inventory, *CI* confidence interval, *CPP* chronic primary pain, *CRPS* chronic regional pain syndrome, *CSP* chronic secondary pain, *FIQ* fibromyalgia impact questionnaire, *IBS* irritable bowel syndrome, *IBS-36* 36-item IBS quality of life scale, *MD* mean difference, *OR* odds ratio, *QoL* quality of life, *RCT* randomized controlled trial, *VAS* visual analogue scale

[a]Overall some concerns and high risk of bias in the majority of included studies, mainly due to deviations from intended interventions and missing outcome data

[b]Imprecision due to limited sample size

[c]Imprecision due to severely limited sample size

[d]High risk of bias due to deviations from intended interventions and missing outcome data

[e]Indirectness due to not homogeneous population including 57.9% of patients with CRPS type I, with the remaining having various chronic secondary pain conditions

[f]Some concerns of risk of bias due to deviations from intended interventions, missing outcome data, and selection of the reported result

[g]Serious inconsistency

[h]Imprecision due to limited sample size and wide 95% CI that include substantial benefit and harm

Anxiety and Depression

Data on anxiety were available from three studies with a total sample of 63 patients, while two studies reported data on depression with a total sample of 30 patients. Anxiety and depression were re-expressed in BAI and BDI units, respectively, and all studies compared cannabinoids to placebo. A non-significant difference was observed for anxiety (MD = – 2.32; 95% CI – 7.99 to 3.08) and depression (MD = 2.32; 95% CI – 1.71 to 6.35) (Fig. S6A, B, Table 2).

Sleep and Appetite

Other study outcomes were sleep and appetite. We did not extract and analyze data on sleep since they were reported with different and incomparable outcome measures by two studies

evaluating cannabinoids against two different comparators; thus, we provide only a description of reported results. One study, comparing cannabis oil to placebo in patients with fibromyalgia, did not find significant differences in the FIQ subscale for morning tiredness [25]. The other, comparing nabilone to amitriptyline, showed that nabilone was superior to amitriptyline in improving the Insomnia Severity Index (MD = – 3.25; 95% CI − 5.26 to − 1.24). Also, nabilone marginally improved restfulness assessed with the Leeds Sleep Evaluation Questionnaire, while other subscales showed no marked differences [28].

Appetite was not evaluated in included studies.

Safety

We managed to extract data on SAE from five studies, with a total population of 152 patients, of whom 95 were from three parallel RCTs and 57 from two crossover RCTs. One crossover RCT compared cannabinoids to amitriptyline, while the remaining four studies used placebo as a comparator. No SAEs were reported.

All eight studies reported data on discontinuation due to AEs. However, two crossover studies did not separate the events by the treatment patients were receiving at the moment of the discontinuation: in one RCT, comparing nabilone to amitriptyline, one patient discontinued the trial after the first dose because of the onset of arm and leg edema, decreased concentration, dizziness, nausea, hyper-alert state, and insomnia; in the other study, which evaluated CBD gums compared to placebo gums, two patients discontinued the treatment because of unpleasant air ingestion. The remaining six studies were included in the meta-analysis. A non-significant difference was found between cannabinoids and placebo in discontinuation due to AEs (OR = 2.15; 95% CI 0.44 to 10.65) (Fig. S6C).

Summary of findings and Publication bias

We produced a summary of findings for cannabinoids compared to placebo (Table 2). We did not observe signs of possible publication bias. The funnel plot evaluating publication bias for studies reporting the primary outcome is presented in Fig. S7.

DISCUSSION

We conducted a systematic review and a meta-analysis on RCTs including patients with CPP. Of the 19 conditions included in the IASP ICD-11 CPP definition, we found studies enrolling only four conditions (fibromyalgia, IBS, CRPS type I, and chronic primary chest pain), mainly fibromyalgia. The novelty of our study is the inclusion of the conditions encompassed in the new IASP ICD-11 CPP definition. Differently from previous studies, this would allow a better estimate of the effect size of cannabinoids in reducing pain in CPP. Compared to previous meta-analyses on chronic non-cancer pain, enrolling also and mainly patients with chronic secondary pain, the number of available studies in CPP and the total included population was inferior by one order of magnitude [11]. In our analysis, we found that cannabinoid treatment yielded a statistically non-significant reduction in pain for the overall CPP population. The magnitude of this reduction was of limited clinical meaning and the quality of the evidence was low. Also, we observed, with data from a single study, a non-significant difference between nabilone and amitriptyline in reducing pain in patients with fibromyalgia [28]. A recent meta-analysis on chronic non-cancer pain produced similar results. In particular, from a total of over 3000 included patients, affected by several conditions such as multiple sclerosis, fibromyalgia, neuropathic pain, and mixed populations of unspecified chronic non-cancer pain, overall cannabinoid treatment resulted in a statistically significant VAS reduction of 0.63 ($p < 0.001$), which is in line with our results. Conversely, we observed a larger and statistically significant absolute reduction in pain in long-term studies (follow-up of 4 weeks or more) compared to both their short-term (VAS MD = – 0.76; $p < 0.001$) and long-term (VAS MD = – 0.46; $p < 0.01$) follow-up analysis (follow-up of less than 12 weeks or more than

12 weeks, respectively) [11]. A subsequent meta-analysis including about 4000 patients affected with several different painful conditions (e.g., multiple sclerosis, HIV neuropathy, post-traumatic pain, diabetic neuropathy, fibromyalgia, cervical dystonia) showed similar results in pain reduction (2-week VAS MD = – 0.54; 95% CI − 0.76 to − 0.31) with moderate quality of evidence. Similar results were obtained also for the 2-month (VAS MD = – 0.68, 95% CI − 0.96 to -0.4) and 6-month (VAS MD = – 0.43, 95% CI − 0.75 to − 0.10) follow-up analysis, with low and moderate quality of evidence, respectively. In the same study, the reporting of SAE was non-significantly different between cannabinoids and placebo, as in our study [13]. Also, another meta-analysis evaluating nabiximols against placebo in chronic neuropathic pain (e.g., multiple sclerosis, plexus/nerve lesion, post-herpetic neuralgia, peripheral neuropathy) and a limited number of patients with CRPS type II yielded similar results [12].

Our study population consisted mainly of patients with fibromyalgia. We observed a modest, statistically non-significant effect in pain reduction in fibromyalgia, with low quality of evidence. A critical review without meta-analysis concluded that superficial evidence exists on the efficacy and safety of cannabinoids in the treatment of fibromyalgia and it was not possible to draw firm conclusions given the low quality of available studies and methodological concerns, including the diverse evaluated cannabis preparations [20]. Interestingly, although at the limits of statistical non-significance, we observed a large reduction in the FIQ for cannabinoid treatment, indicating a possible role of cannabinoids in improving quality of life in patients with fibromyalgia and the impact of the condition. Also, in a sensitivity analysis, we observed that cannabinoid administration in patients with fibromyalgia enrolled in long-term, longitudinal daily-dose, parallel RCTs was significantly superior to placebo in pain relief. However, the quality of the evidence was low and severely limited by the small sample size. We found a significant reduction in patients with CRPS type I from a single study. However, that study also enrolled patients with other secondary (mainly neuropathic) pain conditions, which may have contributed to the magnitude of the effect. CRPS type I is a borderline primary pain condition since a traumatic lesion preceded the onset of chronic pain, thus a neuropathic process is expected to participate in the pathogenesis of the condition [1]. Also, neuropathic pain has been observed to be more responsive to cannabinoid treatment compared to mixed and non-neuropathic pain [33]. Conversely, we did not observe any significant pain reduction with cannabinoid treatment in chronic primary chest pain and IBS. Other authors suggested a potential role of the endocannabinoid system and cannabinoids in the treatment of IBS [34]. Literature data are scarce in this context and we managed to include only one study which showed substantially no effect of CBD gums compared to placebo in reducing pain in patients with IBS. Participants in a study on IBS we analyzed reported a significant reduction in pain threshold after experimental mechanical stimulation. However, we did not include the data in our analysis since it was experimentally induced pain [28, 30]. Finally, we observed a non-significant trend in anxiety reduction and depression increase for cannabinoid treatment; differences were non-significant for discontinuation due to AEs analyses and no SAE were reported in included studies.

Limitations

In our study, the quality of evidence was in general low to very low, mainly for imprecision due to limited sample size and risk of bias. Indeed, risk of bias from unclear to high was observed also in previous systematic reviews on cannabinoids in various primary and secondary pain conditions, indicating the need for higher-quality studies to better define cannabinoids' role in chronic pain treatment [11–13].

Another limitation of our analysis associated with the short term of some included studies was the administration of single doses. Notably, the administration of single doses of a treatment for pain is generally intended as an "as-needed" intervention. On the contrary and especially for chronic pain, the pharmacological

control of pain should be in the long-term period. For this reason and to check for possible distortions in the effect size estimate, we performed subgroup analyses based on administration schedules and study design. Indeed, our results showed that parallel studies, which were all longitudinal daily-dose studies, were the only ones capable of identifying a significant and clinically meaningful pain reduction in CPP with low quality of evidence, especially in fibromyalgia. This finding is relevant, since it indicates that future RCTs should administer the intervention as longitudinal daily doses and that study designs should have a long-term follow-up either in parallel or in crossover trials, the latter with an adequate duration of the study periods and with an adequate washout between them.

We could not perform analyses on different ways of administration, active principle, or pharmaceutical form since the treatment regimens of included studies were very different between one another. This is a limitation in particular for our efficacy analysis, which is due to the limited available literature on cannabinoids in CPP, further indicating the need for future studies to better address this issue. Other systematic reviews including various secondary and primary pain conditions showed contrasting results about the superiority of oral administration compared to smoked or oro-mucosal administration [11, 13]. Regardless, the generalizability of these findings could not be applied specifically to patients with CPP since they were obtained mainly from patients with chronic secondary pain.

Eventually, available studies included only four out of 19 conditions of the IASP ICD-11 definition of CPP. This limits the generalizability of our findings to all patients with CPP and indicates that the potential efficacy of cannabinoids should be investigated also in the remaining, not yet studied, conditions.

CONCLUSION

Overall cannabinoid treatment in patients with CPP had limited benefit on pain relief, with generally low quality of evidence. Long-term administration studies showed limited evidence of efficacy of cannabinoids in pain reduction while crossover, short-term studies did not. This limited efficacy was present only in fibromyalgia and CRPS type I, while no beneficial effect was found for IBS and chronic primary chest pain. Our results confirm that cannabinoids might improve pain and FIQ in fibromyalgia with long-term administration. Cannabinoids displayed a safety profile comparable to placebo or amitriptyline. Good-quality evidence on use of cannabinoids is limited and lacking for the majority of CPP conditions, and large, well-designed RCTs—and importantly with a long-term follow-up—are urgently needed.

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