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REVIEW ARTICLE

Long-term observational studies with cannabis-based medicines for chronic non-cancer pain: A systematic review and meta-analysis of effectiveness and safety

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Abstract

Background and Objective: This systematic review evaluated the effectiveness, tolerability and safety of cannabis-based medicines (CbMs) for chronic non-cancer pain (CNCP) in long-term observational studies.

Databases and Data Treatment: CENTRAL, EMBASE and MEDLINE were searched until December 2021. We included prospective observational studies with a study duration ≥26 weeks. Pooled estimates of event rates of categorical data and standardized mean differences (SMD) of continuous variables were calculated using a random effects model.

Results: Six studies were included with 2686 participants, with study duration ranging between 26 and 52 weeks. Pain conditions included nociceptive, nociplastic, neuropathic and mixed pain mechanisms. The certainty of evidence for every outcome was very low. The weighted mean difference of mean pain reduction was 1.75 (95% confidence interval [CI] 0.72 to 2.78) on a 0–10 scale. 20.8% (95% CI 10.2% to 34.0%) of patients reported pain relief of 50% or greater. The effect size for sleep problems was moderate and for depression and anxiety was low. Study completions was reported for 53.3% (95% CI 26.8% to 79.9%) of patients, with dropouts of 6.8% (95% CI 4.3% to 9.7%) due to adverse events. Serious adverse events occurred in 3.0% (95 CI 0.02% to 12.8%) and 0.3% (95% CI 0.1% to 0.6%) of patients died.

Conclusions: Information included in observational studies should be regarded with caution. Within the context of observational studies. CbMs had positive effects on multiple symptoms for some CNCP patients and were generally well tolerated and safe.

Significance: There is very low quality evidence for the long-term effectiveness (pain, sleep, mood, health-related quality of life), tolerability and safety of medical cannabis for chronic non-cancer pain (CNCP) according to reports of prospective observational studies. Predefined criteria of a large magnitude of effect size in these types of studies were not met. Nevertheless, long-term medical cannabis therapy can be considered in some carefully selected and monitored patients with CNCP.

1 | INTRODUCTION

Discrepant views on the efficacy and role of cannabis-based medicines (CbMs) (plant-based cannabinoids, pharmacological [synthetic] cannabinoids and medical cannabis) for management of chronic pain are held by the evidence-based and pain medicine communities (Eisenberg et al., 2022). A systematic review of randomized trials commissioned by the International Association of the Study of PAIN (IASP) concluded that randomized controlled trials (RCTs) in this field have unclear or high risk of bias and with Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) rating outcomes assessed as low- or very low-quality evidence (Fisher et al., 2021).These shortcoming have led to the conclusion that the current evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CbMs in the management of pain (Fisher et al., 2021). In addition, especially in view of the opioid crisis in some countries, there are ongoing concerns about the long-term safety of CbMs, particularly for increased risks of accidents and CbMs use disorder (Mohiuddin et al., 2021). In contrast, another systematic review of RCTs concluded that there is moderate to high certainty evidence that non-inhaled medical cannabis or cannabinoids results in a small to very small improvement in pain relief, physical functioning, and sleep quality among patients with chronic pain, along with several transient adverse side effects, compared with placebo (Wang et al., 2021).

Based on a lack of evidence from high-quality research, the IASP does not endorse the general use of cannabinoids to treat pain (IASP, 2021). The European Pain Federation (EFIC) stated that CbMs can be used as third-line therapies for chronic neuropathic pain and as an individual therapeutic trial in all other chronic pain conditions if established treatment options have failed (Häuser et al., 2018).

Historically, cannabis research has been limited by strict legal regulations and insufficient access to standardized and well-characterized products (Incze et al., 2021). However, recent federal legislation in selected countries has expanded access to CbMs for clinicians and patients (Krcevski-Skvarc et al., 2018), outside the context of the usual drug approval path (Fitzcharles & Eisenberg, 2018). Licensing of new producers has allowed a wider variety of cannabis products to be used in clinical research. Likewise, some states in the United States have funded cannabis-related research in their medical cannabis legislation (Incze et al., 2021). Registries of patients prescribed CbMs have been established in some countries by governments or medical associations, for example in Germany (Schmidt-Wolf & Cremer-Schaeffer, 2021), in Israel (Bar-Lev Schleider et al., 2018) and in Italy (Salaffi et al., 2020). Thus, the real-world effectiveness of CbMs as evaluated in non-randomized and non-controlled trials in a naturalistic setting can be used to complement the efficacy data derived from RCTs.

It is noteworthy that the quality of evidence derived from non-randomized interventional (observational) studies is very low according to the GRADE approach because of risks of bias due to a lack of randomisation and blinding (Guyatt et al., 2011). However, a large magnitude of effect in observational studies should increase confidence in the effectiveness estimate according to GRADE. In addition, real-world data from non-randomized interventional studies counterbalance the limited applicability to clinical practice of RCTs because of their indirectness (study population is not representative of the population in clinical practice) due to the restrictive exclusion criteria (Mücke et al., 2018).

In view of the uncertainties on the effectiveness and safety of CbMs in routine clinical care, the aim of this review was to assess the long-term effectiveness, tolerability and safety of CbMs in the management of chronic non-cancer pain (CNCP) in patients of any age in long-term observational studies. We were specifically interested to examine the magnitude of effect of CbMs on chronic pain and other pain-associated outcomes and to determine whether the study populations are representative of patients in routine clinical care. We also examined whether aberrant drug behaviour was assessed by the studies analysed.

2 | METHODS

The review was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) (see Table S1).

2.1 | Study protocol

Methods of analysis and inclusion criteria were specified in advance (PROSPERO CRD 42021293251). To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, the registration record has been automatically published exactly as submitted and eligibility has not been checked by the PROSPERO team.

2.1.1 | Criteria for considering studies for this review

Types of participants

Patients of any age with CNCP lasting for at least 3 months prior to trial enrolment. We excluded studies with cancer pain.

Types of interventions

We included studies with cannabinoids (either phytocannabinoids such as herbal cannabis [hashish, marihuana], plant-based cannabinoids [cannabidiol, nabiximole] or pharmacological [synthetic] cannabinoids [e.g. dronabinol, levonantradol, nabilone]), at any dose, by any route, administered for the relief of CNCP. We did not include studies that manipulate the endocannabinoid system by inhibiting enzymes that hydrolysed endocannabinoids and thereby boosted the levels of the endogenous molecules (e.g. blockade of the catabolic enzyme fatty acid amidehydrolase [FAAH]) and are currently under development.

Types of studies

We included long-term (≥6 months) prospective observational studies. We selected a trial duration of at least 6 months guided by the guideline on the clinical development of medicinal products intended for the treatment of pain by the European Medicines Agency (EMA). The EMA has recommended an open label treatment of at least 6 months for the investigation of maintenance of effect and development of tolerance—before including responders into a randomized withdrawal trial design (European Medicines Agency, 2015). We excluded open-label extension studies of RCTs.

Types of outcome measures

The selection of outcomes was guided by the IMMPACT core outcome domains for clinical trials in CNCP (Turk et al., 2003). The selection of specific adverse events was guided by an overview of systematic reviews on general risks of harm with cannabinoids, cannabis and CbMs possibly relevant to patients receiving these for pain management (Mohiuddin et al., 2021).

Primary outcomes. Change in pain intensity from baseline to last follow-up.

Proportion of patients with pain relief of 50% or greater from baseline to last follow-up.

Proportion of patients reporting to be much or very much improved at last follow-up.

Change in disability from baseline to last follow-up.

Proportion of patients with drop out due to side effects.

Proportion of patients with serious adverse events.

Proportion of patients with pain relief of 30% or greater from baseline to last follow-up.

Proportion of patients that completed the study (retention rate).

Proportion of patients who dropped out due to lack of efficacy.

Secondary outcomes. Change in sleep problems from baseline to latest follow-up.

Change in depression from baseline to latest follow-up.

Change in anxiety from baseline to latest follow-up.

Change in health-related quality of life from baseline to last follow-up.

Proportion of patients who completely terminated opioid therapy.

Proportion of patients with nervous system disorders as adverse events.

Proportion of patients with psychiatric disorders as adverse events.

Proportion of patients with gastrointestinal disorders as adverse events.

Proportion of patients with pulmonary disorders as adverse events.

Proportion of patients with aberrant drug behaviour.

Proportion of deaths. In addition, we assessed whether studies performed analysis of treatment success related to the type of pain mechanism (nociceptive, neuropathic, nociplastic, mixed), to CbMs dosage and to previous cannabis experience.

2.1.2 | Electronic searches

The search included CENTRAL, EMBASE, PubMed, US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) from inception to 22 December 2021. The search strategy for PubMed is outlined in Table S2.

Our search included all languages. We reviewed the bibliographies of any observational studies identified.

2.2 | Measures of treatment effect

The mean difference (MD) of the continuous variable pain intensity, standardized to a 0–10 scale, and standardized mean differences (SMD) of other continuous variables were calculated using means and standard deviations for each intervention using a random effects model. Pooled estimates of event rates of categorical data (e.g. drop out due to adverse events) were calculated using a random effects model. Confidence intervals (95% CI) were calculated for all summary data. We used the I^2 statistic to identify heterogeneity. Combined results with $I^2 > 50\%$ were considered substantially heterogeneous (Deeks et al., 2021).

2.2.1 | Criteria of a large treatment effect

There is no accepted definition on how to define a large magnitude of effect size in observational studies. A systematic review found that the median of minimally clinically important difference (MCID) from baseline to the end of study and defined in chronic pain trials was 23 mm on a 100 mm scale (interquartile range 12–39) (Olsen et al., 2018). This number varied considerably according to baseline pain and methodological factors. We assumed a large magnitude of effect size in case of a reduction of 2.0 points or more on a 0–10 pain scale.

In RCTs with CbMs for chronic neuropathic pain, 39% of patients reported a pain relief of 30% or greater from baseline to the end of therapy (Mücke et al., 2018). A systematic review including all chronic pain conditions found that 29% of the patients in the CbMs groups reported a pain relief of 30% or greater from baseline to the end of therapy (Stockings et al., 2018). We assumed a large magnitude of effect size in the case that >50% of patients reported pain relief of 30% or greater from baseline to last follow-up.

For non-pain continuous outcomes, we used Cohen's categories to classify the magnitude of effect size (Cohen, 1988).

2.3 | Dealing with missing data

Where means or standard deviations (SDs) were missing, we attempted to obtain these data by contacting trial authors. Where SDs were not available from trial authors, we calculated them from *t* values, *p* values, CIs, or standard errors or medians where reported by the studies. Where rates of pain relief of 30% and of 50% or greater were not reported or provided on request, we calculated them from means and SDs using a validated imputation method (Furukawa et al., 2005).

2.4 | Data collection and analysis

2.4.1 | Selection of studies

Two authors (BP and WH) independently selected the studies. Disagreements on study selection were resolved by consensus. If needed, a third review author was involved (MAF).

2.4.2 | Data extraction and management

Two review authors (WH and MAF) independently extracted the data from the full-text articles and entered the data in standard extraction forms. Characteristics of patients and studies, description of interventions, conflicts of interest declared by the authors and sponsoring of the study were extracted. Disagreements were resolved by consensus. If needed, a third review author was involved (BP).

2.4.3 | Assessment of risk of bias in included studies

One pair of review authors (WH and MAF) independently assessed the risk of bias in each trial assessed using the eight domains of the Methodological Index for Non-Randomized Studies (MINORS) (Slim et al., 2003). MINORS has been recommended as an excellent tool for assessing methodology quality of non-randomized interventional studies (Zeng et al., 2015). Each item (a clearly stated aim; inclusion of consecutive patients; prospective collection of data; endpoints appropriate to the aim of the study; unbiased assessment of the study endpoint; follow-up period appropriate to the aim of the study; prospective calculation of the study size) is scored from 0 to 2. The total score (0–16) is a measure of overall methodological quality. We classified study quality as follows: excellent (12–16), fair (6–11) or poor (0–5). Any disagreements were resolved by discussion. If needed, a third review author was involved ()PB).

2.4.4 | Grading of evidence

Two review authors (WH and PB) independently rated the certainty of the body of evidence for the outcomes. They used the GRADE system to rank the certainty of the evidence according to the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann et al., 2021). The GRADE system considers study design as a marker of quality. It uses the following criteria for assigning a quality level to a body of evidence:

1. High: randomized trials; or double-upgraded observational studies
2. Moderate: downgraded randomized trials; or upgraded observational studies
3. Low: double-downgraded randomized trials; or observational studies
4. Very low: triple-downgraded randomized trials; or downgraded observational studies; or case series/case report.

Factors that may decrease the certainty level of a body of evidence are as follows:

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias. We

assumed that there were limitations in study design if more than 50% of participants were from poor quality studies, as defined by the MINORS tool.
2. Indirectness of evidence (indirect population, intervention, control, outcomes). We assessed whether the study population was different from the population in routine clinical care by assessing if patients with relevant medical conditions (cardiovascular, hepatic, renal and endocrine system, psychiatric disorders except substance dependence/abuse and psychosis) had been excluded. If 50% or more of the total number of participants with clinically relevant medical conditions were excluded, we decreased the certainty of evidence.
3. Unexplained heterogeneity ($I^2 > 50\%$) or inconsistency of results.
4. Imprecision of results (wide confidence intervals; confidence interval including zero; low number of events).
5. High probability of publication bias. We assumed a potential publication bias if all studies were initiated and funded by the manufacturer of the drug tested in the trial.

2.5 | Subgroup analysis

Provided that at least two studies were available, subgroup analyses were predefined for type of CbMs (medical cannabis, synthetic and plant-based cannabinoids) and the type of chronic pain syndrome for the outcomes of pain intensity, retention rate and drop out due to adverse events. These subgroup analyses were also used to examine potential sources of clinical heterogeneity.

2.6 | Sensitivity analyses

Sensitivity analyses were predefined by excluding studies with imputed means and SDs for responder analysis.

2.7 | Assessment of publication bias

We planned to use the Egger intercept test (Egger et al., 1997) and the Begg rank correlation test for funnel plot asymmetry (Begg & Mazumdar, 1994) at the significance level $p < 0.05$.

2.8 | Software

MedCalc (MedCalc, 2022) and RevMan Analysis (RevMan 5.4.1) of the Cochrane Collaboration software (RevMan, 2020) were used for statistical analyses.

3 | RESULTS

3.1 | Search

The search produced 3662 records after duplicates were removed. After removing duplicates and reading the full reports, we included six studies with 2641 participants into the qualitative and quantitative analysis (Aviram et al., 2021; Giorgi et al., 2020; Haroutounian et al., 2016; Safakish et al., 2020; Sagy et al., 2019; Ware et al., 2015). (see Figure 1).

We excluded five studies after full-text review. One Italian study (1845 patients with multiple sclerosis over 18 months; Chisari et al., 2020) and one German study (52 patients with multiple sclerosis over 12 months; Flachenecker et al., 2014), using THC/CBD oromucosal spray (nabiximols) were excluded because no pain outcomes were reported. Two other studies with nabiximols for multiple sclerosis were excluded for the following reasons: One Italian study (144 patients over 48 weeks) reported outcomes separately, but not pooled, for responders and non-responders (Ferrè et al., 2016). Another Italian study (102 patients) reported a mean follow-up of 48 ± 28 weeks (Paolicelli et al., 2016). One Canadian study included 1145 participants treated with medical cannabis for various diseases and did not report outcomes for patients with pain separately at 6-month follow-up (Lucas et al., 2021).

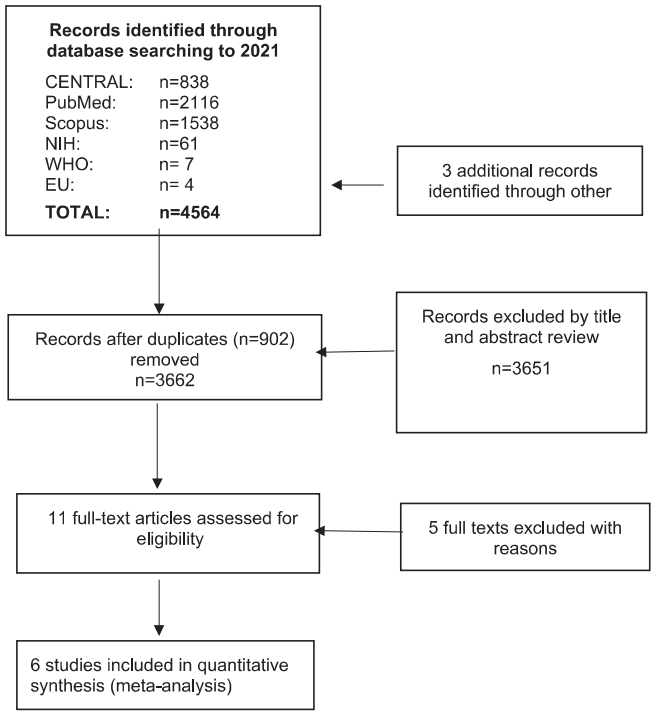

FIGURE 1 PRISMA flow diagram

3.2 | Included studies

The main characteristics of the studies are summarized in Table 1; for details, see Table S3.

3.2.1 | Settings

Two studies each were conducted in Canada, Israel and Italy. Latest follow-up was 12 months in four studies and 6 months for two studies.

3.2.2 | Types of CbMs

All studies used medical cannabis, either inhaled (smoking or vaporiser) and/or oral (drops). Five studies reported on dosages, which was 1.5 g/day in three studies without giving details on average THC and CBD content and their range. One study reported an average daily dosage of 140 mg THC and 39 mg CBD.

3.3 | Types of chronic pain

Two studies included only patients with fibromyalgia syndrome (FMS). Three studies included patients with different types of CNCP. One of these three studies included 7% patients with non-terminal cancer pain. One study identified the pain mechanism (nociceptive, neuropathic and mixed mechanisms), but did not specify a diagnosis.

3.3.1 | Participants

All studies included only adults. The number of patients included ranged from 102 to 751. The mean age of the participants ranged between 43 and 57 years. The proportion of female patients ranged from 36% to 82%. Four studies reported on the percentage of cannabis-naïve patients which ranged from 7% to 55%.

3.3.2 | Exclusion of clinically relevant internal diseases or mental disorders

Two studies did not report exclusion criteria. Two studies defined (medical) cannabis use in the last 3 months as a criterion for exclusion. Two studies excluded pregnant and breastfeeding women. Two studies excluded patients with a history and/or risk for psychosis and substance dependence. One study excluded patients with unstable ischemic heart disease or arrhythmia or unstable bronchopulmonary disease.

3.3.3 | Funding and conflicts of interest

Two studies did not report on funding. One study each received public funding, by cannabis-producing enterprise, by public funding and by cannabis-producing enterprise and no funding. One author group did not declare their conflicts of interest. Three author groups declared that they have no conflicts of interest.

3.4 | Risk of bias in included studies

Detailed information regarding risk of bias assessments of each study is given in electronic Table S4. The methodological quality of all studies was fair.

3.5 | Effects of intervention

The certainty of evidence for all outcomes was downgraded by two levels due to limitations of inconsistency (high heterogeneity) and imprecision (large confidence intervals of effects sizes). The quality of evidence could not be increased because the predefined criteria of a large magnitude of effect size was not met. Thus, the certainty of evidence was very low for all outcomes.

The results are summarized in Tables 2 and 3. Effect sizes are reported with 95% confidence interval in brackets. The forest plots of all analyses are included in Figure S1.

3.5.1 | Primary outcomes

The predefined criterion of a large effect size for the outcome for change of pain intensity from baseline to latest follow-up of 2.0 or more on a 10- point scale (WMD 1.75 [0.72, 2.78]); $I^2 = 96\%$ was not met.

Twenty point eight percentage (20.8%) (10.2%, 34.0%), $I^2 = 98\%$ of patients reported pain relief of 50% or greater.

No study assessed the number of patients that reported to be much or very much improved at latest follow-up.

The effect size for the change of disability from baseline to last follow-up was moderate (SMD 0.45 [0.05, 0.88]) $I^2 = 95\%$.

There were 6.8% (4.3%,9.7%) $I^2 = 68\%$ of patients who dropped out due to side effects.

TABLE 1 Main characteristics of the included studies (alphabetical order)

First author Year of publication Country of the study	Number of participants at baseline Female gender (%) Mean age (years) Cannabis naïve (%)	Most frequent diseases and pain mechanisms	Study medication Route of administration Mean dosage at the end of the study	Duration study (months)
Aviram 2021 Israel	1045 47 43 41	Neuropathic pain (31%); musculoskeletal pain (11%); other pain (4%); visceral pain (2%); headache (2%); combinations (49%)	Medical cannabis: Mostly THC dominant cultivar/s ($n = 133$, 74%), followed by THC/CBD balanced cultivar/s ($n = 44$, 24%), and only a small fraction consumed only CBD dominant cultivar/s ($n = 4$, 2%). 86% by smoking or inhaling Average dosage: 30 ± 20–30 g/months	12
Giorgi 2020 Italy	102 91 52 Not reported	Fibromyalgia syndrome (FMS) (100%)	Medical cannabis: Bedrocan, which contains 22% tetrahydrocannabinol (THC) (220 mg/g) and less than 1% cannabidiol (CBD), and Bediol, which contains 6.3% THC (63 mg/g) and 8% CBD (80 mg/g). 100% orally (drops) Mean dosages not reported; maximum 200 drops/day	6
Haroutounian 2016 Israel	206 51 36 Not reported	93.2% non-cancer pain (30.1% chronic widespread musculoskeletal pain; 23.8% peripheral neuropathic pain; 18.9% radicular low back pain; 20.4% other pain pain conditions) and 6.8% cancer pain	Medical cannabis: THC concentration in the smoked product was 6% to 14% (11% to 19% in oral formulations, eg, cookies), and the CBD concentration is 0.2% to 3.8% (0.5% to 5.5% in oral formulation). At the follow-up, 136 participants received cannabis cigarettes, 8 participants received a combination of cigarettes and drops, 17 participants received only drops, 9 participants received only cookies, and 6 received a combination of cookies and drops. Mean prescribed dosage 43.2 (17.9) g/month	6
Safakish 2020 Canada	751 50 57 35	Back pain (46.7%), osteoarthritis (28.5%), chronic headaches (21.3%), FMS (17.6%)	Medical cannabis: THC and/or CBD from 7% to 29% THC No information provided Mean dose: 1, 5 g/d (SD 0.55)	12
Sagy 2019 Italy	367 53 82 55	Primary FMS in 77% of patients; secondary FMS (other primary diagnosis such as cancer and posttraumatic stress disorder) in 23% of patients.	Medical cannabis: No additional information provided No information provided The median THC and CBD dosages at 6 months were 140 mg/day (interquartile range 90–200 mg) and 39 mg/day (inter-quartile range 10–69 mg), respectively.	6

(Continues)

TABLE 1 (Continued)

First author Year of publication Country of the study	Number of participants at baseline Female gender (%) Mean age (years) Cannabis naïve (%)	Most frequent diseases and pain mechanisms	Study medication Route of administration Mean dosage at the end of the study	Duration study (months)
Ware 2015 Canada	215 46 49 7	Nociceptive pain 16.3%, neuropathic pain 38.6%, both 45.1% ; no diagnoses reported	Medical cannabis: THC 12.5 ± 1.5% 27% used smoking as the only route of administration, 61% used a combination of smoking, oral, and vaporization, and 8% consumed cannabis orally only. Median dosage 2.5 g/d (range 0.1–13.4)	12

Serious adverse events were recorded in 3.0% (0.02%,12.8%) of patients.

The predefined criterion of a large effect size of 50% or more patients with pain relief of 30% or greater from baseline to last follow-up (38.3% (21.2%, 57.1%), I2 = 99% was not met.

Seven point four percentage (7.4)% (1.8%, 16.1%); I^2=95.3% dropped out due to lack of efficacy.

3.5.2 | Secondary outcomes

The effect sizes for reduction of depression (SMD 0.33 [0.05, 0.60]), I^2 = 84% and anxiety (SMD 0.36 [0.26, 0.46]), I^2 = 0% from baseline to last follow-up were small, of sleep problems moderate (SMD 0.56 [0.33, 0.80]), I^2 = 84% and of limitations of health-related quality of life (SMD 1.05 [0.20, 1.89]), I^2 = 96% large.

The retention rate was 53.9% (26.8%, 79.9%) I^2 = 95).

The number of patients reporting organ specific adverse events ranged from 17.8% (0.7%,50.4%) (pulmonary system), I^2 = 98% to 28.2% (12.8%, 46.9%), I^2 = 97% (gastrointestinal system).

For those on opioid medication at baseline, 16.2% (6.2%, 29.8%), I^2 = 94% had completely discontinued opioids at follow-up.

Aberrant drug behaviour was not assessed by any study.

The death rate was 0.27% (0.09%, 0.55%), I^2 = 0%.

3.5.3 | Subgroup analyses and predictors of response

Efficacy of CbMs was similar according to a different pain conditions (nociceptive, neuropathic and mixed pain mechanisms) in one study. In another study, neuropathic pain predicted lower rates of treatment success. Previous cannabis experience was significantly associated with treatment response in one study.

3.6 | Subgroup analyses

The 95% CI of the outcome of mean pain intensity of the two studies with FMS patients included zero: WMD 2.15 (−1.48, 5.79), I^2 = 99%. The WMD for mean pain intensity for the studies with mixed pain syndromes was 1.54 (0.97, 2.11), I^2 = 81%.

Retention rate of the two studies with FMS patients was 44.6% (6.3%, 87.5%), I^2 = 99% and that of the studies with mixed pain syndromes was 35.2% (16.6%, 56.4%); I^2 = 99%.

TABLE 2 Effect sizes (baseline to latest follow-up) of cannabis-based medicines for chronic pain on continuous outcome variables

Outcome title	Number of studies	Number of patients in analysis	Effect size WMD or SMD (95% CI)	Test for overall effect *p*-value	Heterogeneity (I^2)
Mean pain intensity	6	2571	1.75 (0.72, 2.78) (WMD)	0.0009	96.6
Disability	5	2201	0.45 (0.05, 0.88) (SMD)	0.03	95.5
Sleep problems	5	2213	0.56 (0.33, 0.80) (SMD)	<0.0001	84.4
Depression	4	2007	0.33 (0.05, 0.60) (SMD)	0.02	84.4
Anxiety	2	1147	0.36 (0.26, 0.46) (SMD)	<0.0001	0
Health-related quality of life	2	1412	1.05 (0.20, 1.89) (SMD)	0.02	98.2

[a]Abbreviations: CI, confidence interval; SMD, standardized mean difference; WMD, weighted mean difference.

TABLE 3 Effect sizes (baseline to latest follow-up) of cannabis-based medicines for chronic pain on dichotomous outcome variables

Outcome title	Num-ber of studies	Number of patients	Proportion (%) (95% CI)	Heterogeneity (I^2)
Pain relief of 50% or greater	6	2686	20.8 (10.2, 34.0)	98.0
Pain relief of 30% or greater	6	2686	38.3 (21.2, 57.1)	98.9
Opioid cessation	3	594	16.2 (6.2, 29.8)	93.2
Drop out due to lack of efficacy	4	1568	7.4 (1.8, 16.1)	95.3
Retention rate	6	2686	53.9 (26.8, 79.9)	99.5
Drop out due to adverse events (AE)	3	1568	6.8 (4.3, 9.7)	68.0
Central nervous system AE	3	1005	25.1 (9.8, 44.6)	97.5
Psychiatric AE	4	1051	23.6 (10.9, 39.3)	96.2
Gastrointestinal AE	4	1051	28.2 (12.8, 46.9)	97.1
Pulmonary AE	3	500	17.8 (0.7, 50.4)	99.7
Serious adverse events	3	1466	3.0 (0.02, 12.8)	97.3
Deaths	5	1935	0.3 (0.09, 0.6)	0

[a]Abbreviatons: AE, adverse events.

3.7 | Sensitivity analyses

After removing the four studies for which an imputation method was used to calculate responder rates, the proportion of patients with a pain relief of 30% or greater fell to 20.5% (18.3%, 22.9%), $I^2 = 0\%$.

3.8 | Heterogeneity

There was substantial heterogeneity of all outcomes except anxiety and number of deaths.

We did not perform the prespecified tests due to the small number of studies.

4 | DISCUSSION

4.1 | Summary of main results

In this first systematic review of prospective long-term observational studies of CbMs for treatment of various chronic pain conditions, we found that 21% of patients reported pain relief of 50% or greater and 38% reported pain relief of 30% or greater. These findings are, however, based on very low-quality evidence. Other than effect on pain, CbMs had positive effects on symptoms such as anxiety, depression, sleep problems and health-related quality of life with effect sizes ranging from small to large. These associated symptoms contribute considerably to the global suffering of patients with chronic pain and any improvement in these domains should be considered an advantage. Continued use of CbMs was reported for 54% of patients at last follow-up, with less than 10% discontinuing use due to lack of effect. Contrary to other pharmacological intervention studies, CbMs in the studies examined were not reimbursed and required out-of-pocket expenses for the patients, a factor than may have contributed to dropouts. The observation that opioid medications were completely discontinued by 16% of patients treated with opioids at baseline, is both noteworthy and encouraging. CbMs were generally well tolerated and safe. However, two studies did not report on serious adverse events. In addition, there were no reports of events that may not have been captured such as motor vehicle accidents,

impact on interpersonal relationships and specific social and work functioning. No study assessed aberrant drug behaviour. Therefore, information included in observational studies should be regarded with caution.

4.2 | Overall completeness and applicability of evidence

We cannot rule out the possibility that negative study results had not been published or had been missed by our search strategy.

The applicability (external validity) of evidence is partially limited for the following reasons:

1. The majority of the participants were middle-aged and probably Caucasian. No studies were conducted in Asia, Africa or South America.
2. The positive effects of CbMs in non-controlled studies cannot be disentangled from uncontrolled co-therapies, from non-specific (placebo) effects (due to lack of a placebo group), and from spontaneous improvement (due to absence of a no treatment group).

4.3 | Potential biases in the review process (limitations and strengths)

We have used median and interquartile ranges instead of means and standard deviations for the calculation of outcomes in three studies because these data were not reported in the papers and were not provided on request by the authors.

Three studies did not report a cumulative number of adverse events (at all assessments) but only at last assessment. In addition. Most t studies did not systematically assess and report all adverse events according to the International Conference on Harmonization guidelinescoded within organ classes using the Medical Dictionary for Regulatory Activities (International Council for Harmonisation, 2021). When adverse events were more systematically assessed (Ware et al., 2015), there was a higher prevalence of (serious) adverse events. Therefore, we might have underestimated the prevalence of adverse events.

We have included a study in which 9% of participants suffered from cancer pain.

There was a high heterogeneity of all outcomes except for two probably due to the heterogeneity of the study samples and of the settings of the studies. Therefore, we have downgraded the certainty of evidence by one level due to inconsistency (high heterogeneity).

Despite these limitations, we hope that our systematic review has met the items outlined by Moore et al. (2022) to consider when reading a systematic review of efficacy of interventions for pain.

4.4 | Agreements with other systematic reviews of cohort studies

In the systematic review, cannabis and cannabinoids for the treatment of people with CNCP pain conditions, by Stockings et al. (2018), observational studies were also included. However, the comparisons of CbMs with gabapentin, placebo and non-cannabis use were pooled for the analyses of nearly all outcomes. The only outcome measurement comparable to that reported in our current review is the pooled prevalence for achieving a 30% reduction in pain was 72% (95% CI 66%,78%), although the specific studies analyses for this outcome were not identified.

Kurlyandchik et al. (2021) provided a narrative analysis of RCTs and observational studies with CbMs for FMS. All five studies without control reported a clinically meaningful pain reduction.

Our review confirms that the use of medical cannabis can be associated with gastrointestinal, neurological, psychiatric and pulmonary harms as found by Mohiuddin et al. (2021) in an analysis of studies with recreational cannabis use. Serious adverse events were generally rare in the studies analysed in this review, but clinically relevant events such as confusion leading to admission in the emergency department and two deaths due to pneumonia were reported. The authors of this study (Aviram et al., 2021) did not report whether the two deceased patients had smoked medical cannabis with or without tobacco. Based on the known risks of cardiovascular harms of smoking cannabis, the Canadian practice guideline (Allan et al., 2018) and the position paper of the European Pain Federation recommend that oral or oromucosal use of CbMs is preferred (Häuser et al. (2018). Unfortunately, no study assessed aberrant drug behaviour (e.g. diversion of cannabis flowers to friends or black market) and cannabis dependence/cannabis use disorder.

In contrast to other long-term studies with other pain medications, usually supported by the manufacturer of the drug, for example opioids (Bialas et al., 2020), most patients in the studies with CbMs analysed were not reimbursed for CbMs costs. Therefore, it is remarkable that the pooled retention rate of 54% is higher than the 31% that was found in an analysis of long-term observational studies with opioids (Bialas et al., 2020).

5 | CONCLUSIONS

Twenty one percentage of patients reported ≥50% pain reduction, and 38% reported ≥30% pain reduction. In the

systematic review of Fisher et al. (2021), the placebo response was 24% and 31% respectively. One might argue that the responder rates in our systematic review of observational studies was not substantially higher than the placebo response rate in RCTs. However, RCT populations are likely to be different from observational studies. The pain consultant is interested in people reporting reduced pain whatever the reason, while drug agencies want to know the extent of an intervention-specific effect.

The findings of this review do support the IASP statement that general use of cannabinoids cannot be endorsed for treatment of pain due to lack of evidence from high-quality research (ISAP, 2021). However, we do not know any medication which is recommended to be generally used for any chronic pain. Therefore, recommendations should be more specific. The findings of this review support the more specific recommendations of the European Pain Federation position paper that CbMs can be used in properly selected and supervised patients with chronic pain within a multicomponent management approach when established treatment options have failed (Häuser et al., 2018)

6 | TASKS FOR FUTURE RESEARCH

To increase the internal and external validity of observational studies or registries of patients prescribed CbMs for chronic pain, we suggest the following actions: (1) Patient characteristics should include diagnoses based on the International Classification of Diseases of the World Health Organization and pain mechanisms (nociceptive, nociplastic, neuropathic, mixed) should be identified. (2) All patients included should report at least moderate pain intensity at baseline. (3) The dosage of ingested THC and CBD should be reported to assess which dosages and which molecular combinations of THC/CBD work best for a specific pain condition. (4) Adverse events should be assessed systematically (spontaneous reports, open questions, questionnaires) and reported using the International Conference on Harmonization guidelines, and coded within organ classes using the Medical Dictionary for Regulatory Activities (International Council for Harmonisation, 2021). (5) Internationally accepted definitions of dependence and use disorder of prescribed CbMs should be used. However, there are currently no validated instruments available to assess dependence and use disorder of CbMs. f) One size does not fit all. We hypothesize that CbMs are not equally effective for any or every pain type. Therefore, we recommend subgroup analyses for chronic pain conditions with evidence of efficacy in RCTs such as for neuropathic pain (Mücke et al., 2018) or nociplastic pain such as FMS (Kurlyandchik et al. (2021). g) Studies with an EERW design with responders as recommended by EMA (European Medicines Agency, 2015) are necessary to confirm the effectiveness of CbMs for CNCP in order to meet the criteria for approval by drug agencies.

AUTHOR CONTRIBUTIONS

PK and WH performed the search of literature. PB and WH selected the studies. PB, MAF and WH extracted data. WH entered the data into Revman. PB checked the data entry. WH wrote the manuscript. All authors discussed the results and commented on the manuscript.

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CONFLICTS OF INTEREST

Patric Bialas has received one honorarium for an educational lecture by Spectrum cannabis. The other authors declare no financial conflicts with regards to the manuscript. Winfried Häuser was the head of EFIC's task force of a position paper on cannabis-based medicines and medical cannabis for chronic pain and member of the task force of the German Pain Society on the same topic. Mary-Ann Fitzcharles was the head of a task force of the Canadian Association of Rheumatology of a position paper on medical cannabis for rheumatic diseases.

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