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REVIEW ARTICLE

Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management – An overview of systematic reviews

W. Häuser[1,2], F. Petzke[3], M.A. Fitzcharles[4,5]

1 Internal Medicine 1, Klinikum Saarbrücken gGmbH, Germany
2 Department Psychosomatic Medicine and Psychotherapy, Technische Universität München, Germany
3 Schmerzmedizin, Universitatsmedizin Gottingen, Germany
4 Alan Edwards Pain Management Unit, McGill University Health Center, Montreal, QC,Canada
5 Division of Rheumatology, McGill University Health Centre, Montreal, QC, Canada

Correspondence
Winfried Häuser
E-mail: whaeuser@klinikum-saarbruecken.de

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Abstract

Medicinal cannabis has already entered mainstream medicine in some countries. This systematic review (SR) aimed at evaluating the efficacy, acceptability and safety of cannabis-based medicines for chronic pain management. Qualitative systematic review of SRs of randomized controlled trials with cannabis-based medicines for chronic pain management. The Cochrane databases of SRs, Database of Abstracts of Reviews of Effects and PubMed were searched for SR published in the period January 2009 to January 2017. Assessment of the methodological quality of SR was performed by the AMSTAR checklist. Out of 748 papers identified, 10 SRs met the inclusion criteria. The methodological quality was high in four and moderate in six SRs. There were inconsistent findings of four SRs on the efficacy of cannabis-based medicines in neuropathic pain and of one SR for painful spasms in multiple sclerosis. There were consistent results that there was insufficient evidence of any cannabis-based medicine for pain management in patients with rheumatic diseases (three SRs) and in cancer pain (two SRs). Cannabis-based medicines undoubtedly enrich the possibilities of drug treatment of chronic pain conditions. It remains the responsibility of the health care community to continue to pursue rigorous study of cannabis-based medicines to provide evidence that meets the standard of 21st century clinical care.

Significance: We provide an overview of systematic reviews on the efficacy, tolerability and safety of cannabis-based medicines for chronic pain management. There are inconsistent findings of the efficacy of cannabinoids in neuropathic pain and painful spasms in multiple sclerosis. There are inconsistent results on tolerability and safety of cannabis-based medicines for any chronic pain.

1. Introduction

The recreational and medical use of cannabis products is under debate worldwide. Some cannabinoid preparations such as plant-derived 9-tetrahydrocannabinol (THC) oil or tablets, THC/Cannabidiol (CBD) oromucosal spray and synthetic analogues like nabilone are legally available for a variety of medical conditions in selected countries (e.g. United States, Canada, Germany). Herbal cannabis has recently been legalized for therapeutic use in over 20 states in the United States, in Canada, Israel and some European countries (Ablin et al., 2016). Patient advocates and some politicians promote even early use of medical cannabis for management of chronic

pain as well as other conditions. Propelled by the unprecedented step of governments in these various countries to sanction and legalize herbal cannabis for medicinal use with a wide range of potential indications, thereby abandoning the due diligence process required to ensure efficacy and safety, the medical community is encumbered with the responsibility to examine the current available evidence so as to competently advise and inform other jurisdictions, health care workers and patients about the effects of cannabis-based medicines not only in specific indications but in general.

The therapeutic use of synthetic and plant-based cannabis-based medicines has been widely reviewed with conflicting results regarding the efficacy and safety of cannabis products in pain medicine. Within the discussion on potential indications for the medical use of cannabis-based medicines in some European countries and to prepare an European Federation of IASP Chapters (EFIC) position paper on this topic, this review aims to summarize the efficacy, tolerability and safety of cannabis-based medicines as a treatment for chronic pain (non-cancer and cancer pain) in patients of all ages compared to placebo or other analgesics as assessed by SRs of randomized controlled trials (RCT).

2. Methods

This review was conducted according to the recommendations of the Cochrane Collaboration for systematic reviews (SRs) of previously published reviews (Higgins & Green, 2011) and the recommendations of the Joanna Briggs Institute for umbrella reviews (Joanna Briggs Institute, 2014). Methods of analysis and inclusion criteria were specified in advance (PROSPERO 2017; CRD42017058875).

2.1 Systematic survey of the literature

The Cochrane databases of SRs, Database of Abstracts of Reviews of Effects (DARE) and PubMed were searched for SRs published in the period January 2009 to January 2017. The following search terms were used: 'review', 'meta-analysis', 'cannabis' and 'cannabinoids'. We searched Pubmed with ((‘Chronic Pain’[Mesh]) AND (‘Cannabis’[Mesh] OR ‘Medical Marijuana’[Mesh]) OR ‘Cannabinoids’[Mesh]) AND ((‘Review Literature as Topic’ [Mesh] OR ‘Review’ [Publication Type] OR ‘Meta-Analysis as Topic’[Mesh])). Moreover, the reference lists of the SRs identified were inspected for further SRs and pain medicine experts were contacted.

2.2 Inclusion criteria

The following conditions regarding type of cannabis-based medicines, study type, indications, setting and study population had to be fulfilled:

2.2.1 Cannabis-based medicines

Cannabis-based medicines, either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-derived cannabinoids (dronabinol; THC/CBD = nabiximole), (synthetic) cannabinoid analogues (e.g. levonantradol, nabilone) or synthetic drugs which manipulate the endocannabinoid system, at any dose and by any route.

2.2.2 Indications

We included SRs on any type of chronic pain (non-malignant and cancer pain). We included SRs on spasticity in multiple sclerosis (MS) and excluded studies for palliative care other than chronic pain (e.g. cachexia).

2.2.3 Study type

We included SRs with quantitative analysis (meta-analysis) of study results of (quasi-)RCTs of cannabinoid as defined above as intervention compared to placebo or any active comparator. We included qualitative SR which reported why data synthesis was not reasonable. We excluded qualitative SRs which did not explicitly report the reasons not to perform meta-analysis.

2.2.4 Outcomes

The endpoints of the SRs had to include at least one measure of efficacy for pain reduction, and/or of tolerability (drop-out rate due to adverse events) and/or of safety (frequency of serious adverse events).

2.2.5 Setting and study population

No restrictions were imposed with regard to setting, age or country.

2.3 Review selection

At first, all duplicates were removed from the references. Two reviewers (WH and FP) then screened the abstracts of the remaining papers individually and went on to obtain the full papers for potentially eligible reviews. The reviews were then checked in detail with eligible papers being included in this overview. Disagreements were checked with a third reviewer (MAF) and resolved by agreement.

2.4 Data extraction

The following characteristics of the SRs were extracted independently by two of the authors (WH and MAF) and discrepancies were resolved by consensus:

(1) The type of chronic pain
(2) The number of RCTs/patients included
(3) The type and dosages of cannabis-based medicines
(4) The nature of the control groups
(5) The instrument for and results of measurement of methodological quality of the included RCTs
(6) The databases searched and the period covered
(7) Overall effect estimates of efficacy, tolerance and safety as defined above
(8) The authors' conclusions.

2.5 Methodological quality

Methodological quality of SRs was determined using the assessment of the methodological quality of systematic reviews (AMSTAR) by two independent reviewers (WH and MAF). The AMSTAR instrument is an 11-item assessment tool mainly for intervention reviews with good validity and reliability. The AMSTAR determines whether most important contents of SRs have been provided, such as an a priori design, a comprehensive literature search, information about study selection and data extraction, a list of included and excluded studies, characteristics of studies, a quality assessment of included studies, an appropriate method of combining findings or forming conclusions and a conflict of interest statements (Shea et al., 2009). AMSTAR scores 0–4 were rated as low, AMSTAR scores 5–8 as moderate and AMSTAR scores 9–11 as high quality (Seo and Kim, 2012). Disagreements were checked with a third reviewer (FP) and resolved by agreement.

3. Results

3.1 Literature search

The search of literature yielded 748 hits. After removing 10 duplicates, papers were assessed for eligibility. Finally, 720 manuscripts did not fulfil inclusion criteria as they did not meet criteria for SRs or focused on other indications for cannabis-based medicines. We excluded eight SRs which did not report the reasons for not performing a quantitative analysis of the data (Turcotte et al., 2010; Lynch and Campbell, 2011; Tsang and Giudice 2016; Koppel et al., 2014; Boychuk et al., 2015; Deshpande et al., 2015; Hill, 2015; Lynch and Ware, 2015). Finally 10 SRs were included: Martín-Sánchez et al. (2009), Jahawar et al. (2013), Andreae et al. (2015), Finnerup et al. (2015), Whiting et al. (2015), Fitzcharles et al. (2016a,b), Mücke et al. (2016), Petzke et al. (2016) and Walitt et al. (2016) (see Fig. 1).

These SRs included medical cannabis, plant-derived cannabinoids (THC; THC/CBD), synthetic cannabinoid analogue (nabilone) and synthetic drugs which manipulate the endocannabinoid system.

3.2 Characteristics of included studies and of systematic reviews

AMSTAR quality of four SRs was high (Andreae et al., 2015; Finnerup et al., 2015, Petzke et al., 2016; Walitt et al., 2016) and moderate in the remaining SRs (see Table 1).

Details of the RCTs included and of the results of the SRs are presented in Tables 2–5. The most recent literature search in the reviews covered publications up to April 2017. Included RCTs were published between 1948 and 2016. One SR required a study duration of 3 weeks and more (Finnerup et al., 2015), two SRs required a study duration of 2 weeks and more (Mücke et al., 2016; Petzke et al., 2016) and one SR required a study duration of 4 weeks and more (Fitzcharles et al., 2016b) for inclusion. The remaining SRs did not define a minimal study duration for inclusion.

3.2.1 Any type of chronic pain

Two SRs analysed covered 38 studies with 2838 participants with any type of chronic pain (see Tables 2 and 3; Supporting Information Table S2).

Martín-Sánchez et al. (2009) included 18 studies with 1809 participants and a study duration between 3 days and 5 weeks which tested plant-based cannabinoids (THC, THC/CBD) and synthetic THC congener (nabilone). Whiting et al. (2015) included 28 studies with 2454 participants. Study duration ranged between 4 h and 14 weeks. Studies tested plant-based cannabinoids (THC, THC/CBD), smoked/vaporized cannabis and synthetic THC congener. Maximum dosages in the RCTs included ranged from 4% to 7% THC content of smoked or sprayed THC, 5–40 mg/day of THC capsules, 5–20 mg/day dronabinol, 1.5–4 mg/day nabilone and 11/10–130/120 mg THC/CBD oromucosal spray.

Study quality was rated by the Jadad score (Martín-Sánchez et al., 2009) and the Cochrane Risk of bias (ROB) tool (Whiting et al., 2015). The majority of studies had a high risk of bias.

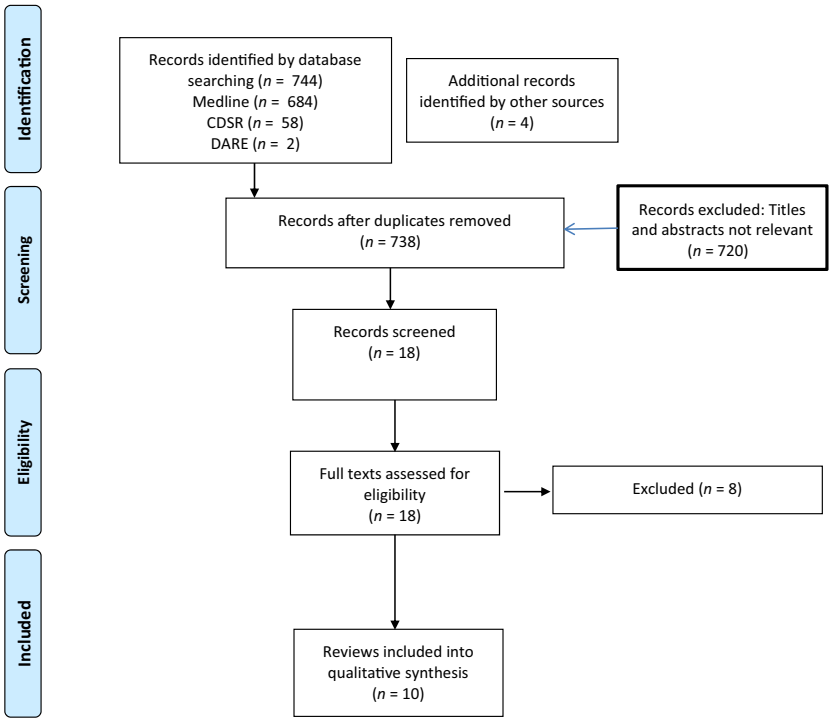

Figure 1 PRISMA flow diagram.

Martín-Sánchez et al. (2009) calculated a standardized mean difference (SMD) change from baseline for intensity of pain −0.61 (−0.84 to −0.37). Whiting et al. (2015) calculated an odds ratio for 30% or greater pain relief of 1.41 (0.99 to 2.00) and a weighted mean difference compared to placebo (WMD) of −0.46 (95% confidence interval [CI]: −0.80 to −0.11) with reference to pain assessment by a numerical 0–10-point scale.

Martín-Sánchez et al. (2009) found an elevated risk for euphoria OR 4.11 (95% CI: 1.33 to 12.72) and NNTH 8 (95% CI: 5 to 19), but not of dissociation/acute psychosis OR 6.17 (95% CI: 0.28 to 136). Whiting et al. (2015) gave a pooled analysis of adverse events of all studies reviewed (chronic pain, spasticity, mental disorders, glaucoma, Tourette syndrome), but no separate analysis of the studies for chronic pain. OR for drop-out for adverse events was 1.41 (95% CI: 1.04 to 1.92). OR for serious adverse events was 2.94 (95% CI: 2.18 to 3.96).

Both SRs did not perform subgroup analyses of cannabis-based medicines and dosages.

Martín-Sánchez et al. (2009) stated that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms. Whiting et al. (2015) concluded that there was moderate-quality evidence to support the use of cannabis-based medicines for the treatment of chronic pain.

3.2.2 Chronic neuropathic pain

Six SRs covered a total of 25 RCTs with 1837 participants (see Tables 2 and 4; Supporting Information Table S3). Andreae et al. (2015) included five RCTs and 178 participants with smoked/vaporized cannabis for which individual patient data were available. Study duration ranged between 5 h and 2 weeks. Finnerup et al. (2015) included nine studies (eight studies with THC/CBD oromucosal spray and one study with dronabinol) with 1110 participants. Study duration ranged between 3 and 14 weeks. Jawahar et al. (2013) included four RCTs of patients with MS and neuropathic pain with 565 participants and a study duration between 4 and 12 weeks, three with nabiximols oromucosal spray and one with THC capsules. Studies addressing spasticity in these patients were excluded. Petzke et al. (2016) included 15 studies and 1619 participants with dronabinol, nabilone, smoked cannabis and THC/CBD oromucosal spray with a study duration of 2–15 weeks. The dosages of dronabinol ranged from 2.5 to 10 mg/day, of nabilone from 2 to 5 mg/day, of THC/CBD oromucosal spray from 32/30 mg to 130/120 mg/day.

Table 1 Assessment of the methodology quality of systematic reviews on cannabis-based medicines in chronic pain by AMSTAR (Shea et al., 2009) instrument

Reference	A priori design?	Duplicate study selection and data extraction ?	Comprehensive literature search?	'Grey' literature included?	List of studies (included and exclu-ded) provided?	Characteristics of the included studies provided?	Scientific quality of the included studies assessed and documented ?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias?	Conflict of interest included ?	Sum
Andreae et al. (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Finnerup et al. (2015)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	9
Fitzcharles et al. (2016a)[a]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	8
Fitzcharles et al. (2016b)[a]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	7
Jawahar et al. (2013)	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	6
Martín-Sánchez et al. (2009)	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	7
Mücke et al. (2016)	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	8
Petzke et al. (2016)	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Walitt et al. (2016)[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	10
Whiting et al. (2015)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	8

[a]No meta-analysis performed.

Table 2 Characteristics of the randomized controlled studies of cannabis-based medicines included in the systematic reviews

Reference	Diseases with chronic pain	Number of studies/participants	Trial duration of randomized phase (range)	Cannabis-based medicines tested (Number of studies) Controls	Methodology quality of the studies included
Andreae et al. (2015)	Chronic neuropathic pain	5/178	5 h to 2 weeks	Smoked cannabis (5) Placebo (5)	Cochrane risk of bias tool: 1 study with low, 2 studies with moderate and 2 studies with high risk of bias
Finnerup et al. (2015)	Chronic neuropathic pain	9/1110	3–14 weeks	THC/CBD (nabiximols) (8) Nabilone (1)	Jadad score reported for 5 fully published studies: One study with score 3 and two studies each with scores of 4 and 5
Fitzcharles et al. (2016a)	Fibromyalgia (2) Rheumatoid arthritis (1) Musculoskeletal pain (1)	4/159 71 fibromyalgia, 58 rheumatoid arthritis and 30 musculoskeletal pain patients	4–8 weeks	Nabilone (3) THC/CBD (nabiximols) (1) Placebo (3), Amitriptyline (1)	Cochrane risk of bias tool: 3 studies with a high risk of bias and one study with a low risk of bias
Fitzcharles et al. (2016b)	Fibromyalgia (2) Rheumatoid arthritis (1) Osteoarthritis (1)	4/203 71 fibromyalgia, 58 rheumatoid arthritis and 74 osteoarthritis patients	4–8 weeks	Nabilone (2) THC/CBD (nabiximols) (1) Fatty acid amide hydrolase (FAAH) inhibitor (1) Placebo (3), Amitriptyline (1)	Cochrane risk of bias tool: 3 studies with a high risk of bias; risk of bias could not be assessed in one study
Jahawar et al. (2013)	Central pain in multiple sclerosis (MS) (3)	3/400	4–12 weeks	Dronabinol (1) THC/CBD spray (2) Placebo (3)	American Academy of Neurology classification scheme: Two class one and one class three studies
Martín-Sánchez et al. (2009)	Cancer pain (6) MS (5) Neuropathic pain syndromes (3) Musculoskeletal pain (1) Rheumatoid arthritis (1) Fibromyalgia (1) Mixed pain syndromes (1)	18/809	3 days to 6 weeks	(Benzopyranopyridine THC congener (1) Dronabinol (2) Nabilone (3) THC capsules (2) Nitrogen analogue of THC (2) THC/CBD spray (8) Placebo (14) Codeine/secobarbital (4)	Jadad score: 6 studies with 2, 8 studies with 3, 2 studies each with 4 and 5
Mücke et al. (2016)	Cancer pain (2)	2/537	16 days to 9 weeks	THC/CBD (2) Placebo (2)	Cochrane risk of bias tool: One study each with a moderate and high risk of bias

Table 2 (*Continued*)

Reference	Diseases with chronic pain	Number of studies/participants	Trial duration of randomized phase (range)	Cannabis-based medicines tested (Number of studies) Controls	Methodology quality of the studies included
Petzke et al. (2016)	Chronic neuropathic pain	15/1619	2–15 weeks	Dronabinol (1) Nabilone (2) Smoked cannabis (2) THC/CBD (10) Placebo (14) Dihydrocodeine (1)	Cochrane risk of bias tool: Two studies had a low and 13 studies had a moderate risk of bias
Walitt et al. (2016)	Fibromyalgia	2/72	4 and 6 weeks	Nabilone (2) Placebo (1), Amitriptyline (1)	Cochrane risk of bias tool: 2 studies with moderate risk of bias
Whiting et al. (2015)	Spasticity due to MS (11 studies) or paraplegia (3 studies)	14/2280	3 days to 5 weeks	THC/CBD (10) Dronabinol (3) Nabilone (1) ECP002A (1) Smoked THC (1) Placebo (14)	Cochrane risk of bias tool Two studies were at low risk of bias, 5 were at unclear risk of bias, and 7 were at high risk of bias
Whiting et al. (2015)	Chronic pain: Neuropathic pain (12) Cancer pain (3) Fibromyalgia (2) Diabetic peripheral neuropathy (3) HIV-associated neuropathy (2) Refractory pain due to MS or other neurological conditions (1) Rheumatoid arthritis (1) Non-cancer pain (1) Central pain (not specified further) (1) Musculoskeletal problems (1) Chemotherapy-induced pain (1)	28/2454	4 h to 14 weeks	THC/CBD (15) Smoked THC (4) Nabilone (5) (as an adjunctive treatment to gabapentin in 1 study) Dronabinol (2) Vaporized cannabis (1) Ajuvenic acid capsules (1) Placebo (28)	Cochrane risk of bias tool: Two studies were at low risk of bias, 9 at unclear risk, and 17 at high risk of bias.

Table 3 Results of the systematic reviews of randomized controlled trials of cannabis-based medicines for any type of chronic pain included in the systematic reviews

Reference	Databases and period covered by search of literature	Results for efficacy (pain relief (95% CI) Number of studies/patients in case of quantitative synthesis	Results for tolerability and safety (95% CI) Number of studies/patients in case of quantitative synthesis	Conclusions of the authors
Martín-Sánchez et al. (2009)	Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (TRIALS CENTRAL) International Association for Cannabis as Medicine, Medical Marijuana Information Resource Centre, Center for Medicinal Cannabis Research (University of California) American Society of Clinical Oncology, Allied and Complementary Medicine Database, and GW Pharmaceutical. And ClinicalTrials.gov to February 2008	SMD change from baseline intensity of pain −0.61 (−0.84 to −0.37); 7/275	OR mood disturbance 4.11 (1.33 to 12.72); euphoria NNTH 8 (5 to 19); 4/202 OR dissociation/acute psychosis 3.18 (.89 to 11.33); 4/285	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms
Whiting et al. (2015)	Twenty-eight databases and grey literature sources were searched from inception to April 2015	OR 30% and more pain relief 1.41 (0.99 to 2.00); 8/465 WMD Numerical rating scale pain assessment (on a 0–10-point scale −0.46 [−0.80 to −0.11]; 6 trials/Not reported	No separate analysis	There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain

CI, confidence interval; NNTH, number needed to harm; OR, odds ratio; SMD, standardized mean difference; WMD, weighted mean difference.

Table 4 Results of the systematic reviews of randomized controlled trials of cannabis-based medicines for chronic neuropathic pain included in the systematic reviews

Reference	Databases and period covered by search of literature	Results for efficacy (95% CI) Number of studies/patients in case of quantitative synthesis	Results for tolerability and safety (95% CI) Number of studies/patients in case of quantitative synthesis	Conclusions of the authors
Andreae et al. (2015)	Cochrane Central, PubMed, EMBASE and AMED; no date reported Hand search in the conference abstracts of the Conference on Retroviruses and Opportunistic Infections 2011, the International AIDS Conference and the World Congress of Pain 2010	OR 30% pain relief or more 3.2 [1.59, 7.24] NNT 5.55 [3.35 to 13.7] 5/509	No quantitative analysis	Inhaled cannabis appears to provide short-term relief from chronic neuropathic pain for one in five to six patients treated
Finnerup et al. (2015)	PubMed/Medline Cochrane CENTRAL EMBASE FDA website EMEA website Clinicaltrials.gov Additional studies Date of end of search not reported	RD 30% and more pain relief 0.03 (−0.03 to 0.09); 5/815	NNH drop-out due to adverse events 12 (9 to 20)	Cannabinoids have weak recommendations against their use in neuropathic pain
Jawahar et al. (2013)	CINAHL, PubMed, CPCI-S, clinicaltrials.gov to December 2012	SMD 0.08 (95% CI: −0.74 to 0.89); 3/565	No quantitative analysis	The relatively small number of trials in multiple sclerosis patients with chronic pain precludes specific recommendations for treatment strategies
Petzke et al. (2016)	MEDLINE, the Cochrane central register of controlled trials (CENTRAL) and clinicaltrials.gov up until November 2015	SMD − 0.10 (−0.20 to −0.00); 13/1565 RD 30% pain relief and more 0.10 [0.03 to 0.16]; NNTB 10 (6 to 33); 9/1346	RD drop-out due to adverse events 0.04 (0.01 to 0.07); NNTH 25 (16 to 100); 11/1572 RD central nervous system 0.38 (0.18 to 0.58); NNTH 3 (2 to 6); 9/1304 RD psychiatric side effects 0.11 (0.06 to 0.16); NNTH 9 (6 to 16); 9/1304 There were no statistically significant differences between cannabinoids and placebo in the frequency of serious adverse events	Short-term and intermediate-term therapy with cannabinoids can be considered in selected patients with chronic neuropathic pain after failure of first-line and second-line therapies

CI, confidence interval; NNTB, number needed to treat for additional benefit; NNTH, number needed to treat for additional harm; OR, odds ratio; RD, risk difference; SMD, standardized mean difference.

One systematic review (Whiting et al., 2015) presented a subgroup analyses for six studies mit THC/CBD spray in chronic neuropathic pain with OR for pain relief of 30% and greater 1.38 (95% CI: 0.93 to 2.03). The subgroup analysis for chronic pain did not include other cannabinoids. Therefore, this systematic review was not included into this table.

Table 5 Results of the systematic reviews of randomized controlled trials of cannabis-based medicines for rheumatic diseases included in the systematic reviews

Reference	Databases and period covered by search of literature	Results for efficacy (95% CI) Number of studies/patients in case of quantitative synthesis	Results for tolerability and safety (95% CI) Number of studies/patients in case of quantitative synthesis	Conclusions of the authors
Fitzcharles et al. (2016a)	Cochrane Central Register of Controlled Trials (CENTRAL),PubMed, www.cannabis-med.org and clinicaltrials.gov to April 2016	No statistically significant differences between nabilone and placebo in pain reduction (as calculated by the review authors based on study data) in 40 fibromyalgia patients No statistically difference between nabilone and amitriptyline in pain reduction in one study with 32 fibromyalgia patients THC/CBD was statistically significantly superior to placebo in reducing morning pain on movement and at rest (NRS) and pain at present but not for total intensity of pain and intensity of pain at present in 58 rheumatoid arthritis patients. No statistically significant difference between nabilone and in average pain intensity reduction in 30 patients with musculoskeletal pain	Three of 20 FM-patients in the nabilone and 1/20 patients in the placebo group dropped-out due to side effects. 1/32 of FM patients dropped-out because of side effects after a single dose of nabilone. The two FM-studies reported no serious adverse events during the study period. The study with musculo-skeletal pain reported one serious adverse event (fall with fracture due to dizziness) associated with nabilone. The study in rheumatoid arthritis noted two serious adverse events possibly, probably or definitely related to placebo	There is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases.
Fitzcharles et al. (2016b)	MEDLINE, Embase, BIOSIS Previews, Web of Science, Scopus, CENTRAL, DARE, CINAHL, PsycINFO, AMED, ClinicalTrials.gov, International Clinical Trials Registry Platform Current Controlled Trial, Natural Standard as various drug and device regulatory approval sites until January 2015	THC/CBD was superior to placebo in pain relief in 58 patients with rheumatoid arthritis Nabilone was superior to placebo in reducing pain in 40 fibromyalgia patients. Nabilone and amitriptyline did not differ in reducing pain in 32 patients with fibromyalgia. FAAH1 inhibitor did not demonstrate difference from placebo in pain relief in 75 patients with osteoarthritis	Dizziness, cognitive problems and drowsiness, as well as nausea were reported for almost half of the patients. No serious adverse events were reported for cannabinoids during study duration.	Pain relief and effect on sleep may have some potential therapeutic benefit, but with considerable mild to moderate adverse events. There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases pending further study.
Walitt et al. (2016)	Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE and EMBASE to April 2016, three clinical trial registries, and contact with trial authors	Greater reduction of pain compared to placebo in one study with 40 fibromyalgia patients reported by the authors. No statistically difference between nabilone and amitriptyline in pain reduction in one study with 32 fibromyalgia patients	More participants dropped-out due to adverse events in the nabilone groups (4/52 participants) than in the control groups (1/20 in placebo and 0/32 in amitriptyline group). Neither study reported serious adverse events during the period of both studies	We found no convincing, unbiased, high-quality evidence suggesting that nabilone is of value in treating people with fibromyalgia

The THC content of medical cannabis ranged from 2.5% to 9% in the RCTs included into the review.

Study quality was rated by the Cochrane ROB tool (Andreae et al., 2015; Petzke et al., 2016), by the Jadad score (Finnerup et al., 2015) and the American Academy of Neurology classification scheme (Jawahar et al., 2013). The majority of studies had a moderate risk of bias.

The number needed to treat for an additional benefit (NNTB) for a 30% and more pain relief compared to placebo was 5.6 (95% CI: 3.4 to 13.7) in Andreae et al. (2015) and 10 (95% CI: 6 to 33) in Petzke et al. (2016). Finnerup et al. (2015) did not calculate NNT for a 30% and more pain relief because the risk difference (RD) was not statistically significant. SMD for mean pain intensity reduction was 0.08 (95% CI: −0.74 to 0.89) in the SR of Jawahar et al. (2013). One SR stressed that the benefits of cannabinoids over placebo were marginally (Petzke et al., 2016).

Two SRs did not provide a quantitative analysis of adverse events (Jawahr et al., 2013; Andreae et al., 2015). Finnerup et al. (2015) calculated a NNNT for drop-out due to side effects to be 12 (95% CI: 8 to 20). Petzke et al. (2016) reported that the RD of drop-out due to adverse events was 0.04 (95% CI: 0.01 to 0.07) with a number needed to treat for additional harm (NNTH) of 25 (95% CI: 16 to 100). The reported central nervous system side effects occurred more frequently with cannabis-based medicines with a RD of 0.38 (95% CI: 0.18 to 0.58]) or a NNTH of 3 (95% CI: 2 to 6), and psychiatric side effects with an RD of 0.11 (95% CI: 0.06 to 0.16] and with a NNTH of 9 (95% CI: 6 to 16). There were no statistically significant differences between cannabis-based medicines and placebo in the frequency of serious adverse events (Petzke et al., 2016).

Only the review on medical cannabis analysed dose-dependent efficacy and safety. Estimated daily THC dosages ranged between 1.6 and 96 mg. The breakdown of responder data by dose suggested an increased effect with increased THC content. Declines in declines in attention, psychomotor performance and learning and memory as well as feeling 'high' increased in frequency with increasing dose (Andreae et al., 2015). Only one SR (Petzke et al., 2016) performed subgroup analysis of the cannabis-based medicines: There was no significant reduction of mean pain intensity by any of the cannabis-based medicines dronabinol, medical cannabis and nabilone. Dronabinol and nabilone, but not medical cannabis, had statistically significant higher drop-out rates due to side effects than placebo.

Andreae et al. (2015) stated that inhaled cannabis appeared to provide short-term relief from chronic neuropathic pain. Finnerup et al. (2015) gave a weak recommendation against the use of cannabinoids in neuropathic pain. Jawahar et al. (2013) stated that the relatively small number of trials in MS patients with chronic pain precludes specific recommendations for treatment strategies. Petzke et al. (2016) recommended that cannabinoids should not be used as first-line therapy in chronic neuropathic pain, but may be a suitable third-line agent in carefully selected patients.

3.2.3 Rheumatic diseases

Three reviews covered five studies with 234 patients (Fitzcharles et al., 2016a,b; Walitt et al., 2016; see Table 2 and Supporting Information Table S3).

Two studies were conducted with patients with fibromyalgia and one study each with patients with musculoskeletal pain, osteoarthritis and rheumatoid arthritis. Two studies tested nabilone and one study each THC/CBD and a FAAH1 inhibitor. Study duration ranged between 4 and 8 weeks.

The dosages of nabilone ranged from 0.25 to 2 mg/day. The maximum allowed dosage of THC/CBD oromucosal spray was 16/15 mg/day.

Study quality was rated by the Cochrane ROB tool by all SRs to range between low and high risk of bias. The Cochrane review only covered the two studies with fibromyalgia patients. Two reviews included three identical studies and one different study each (Fitzcharles et al., 2016a,b).

Due to the small number of patients, none of the reviews did perform a quantitative analysis. One SR (Fitzcharles et al., 2016a) concluded that THC/CBD and nabilone, respectively, were superior to placebo in rheumatoid arthritis and fibromyalgia, respectively. The review did not analyse all study results. Another review (Fitzcharles et al., 2016b) analysed the same studies and concluded from a more detailed analysis of all outcomes that there are no consistent results of superiority of the two drugs over placebo.

The SRs did not comment on potential differences of cannabinoids in efficacy and safety and on dosages.

Walitt et al. (2016) concluded that there is no high-quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. All three reviews agreed that nabilone was not superior to amitriptyline in pain relief in one study with fibromyalgia patients. All three reviews did not find significant differences in tolerability and safety between cannabinoids and controls and concluded that there is insufficient evidence to recommend any cannabis-based medicine for symptom management in patients with chronic pain associated with rheumatic diseases or fibromyalgia.

3.2.4 Cancer pain

Two SRs (Whiting et al., 2015; Mücke et al., 2016) covered the same two RCTs with 307 patients and a study duration of 2 and 3 weeks (see Tables 2 and 6). One study each tested dronabinol (range: 5 to 20 mg/day) and THC/CBD oromucosal spray (range: 30/32 to 43/40 mg/day) versus placebo.

One study each had a moderate and high risk of bias according to the Cochrane risk of bias tool.

Both reviews concluded from quantitative analysis that cannabinoids were not statistically superior to placebo in 30% and more pain relief.

Whiting et al. (2015) did not analyse adverse events separately for the cancer pain studies. Mücke et al. (2016) did not find statistically significant differences in tolerabilty and safety between cannabinoids and placebo.

The SR did not perform subgroup analyses of cannabinoids and dosages.

Mücke et al. (2016) concluded that due to the sparse amount of data, it is not possible to recommend a favoured use of cannabis products for cancer pain. Whiting et al. (2015) did not give a separate recommendation for cannabis-based medicines for cancer pain.

2.3.5 Multiple sclerosis and paraplegia-associated spasticity

One SR (Whiting et al., 2015) covered 14 studies with 2280 participants (see Table 2; Supporting Information Table S1) as a subgroup analysis, of which 11 included patients with MS, while three included patients with paraplegia. Cannabis-based medicines tested were dronabinol (up to 10 mg/day), nabilone (1 mg/day), plant-based THC (800 mg cigarette) and THC/CBD oromucosal spray (maximum dosages ranged from 27/25 to 130/120 mg/day). Study duration ranged between 2 and 52 weeks.

Study quality was assessed by the Cochrane ROB tool (Whiting et al., 2015). Study quality ranged between low and high (2, low; 5, unclear and 7, high risk).

Only MS trials reported data suitable for meta-analysis. Whiting et al. (2015) found by quantitative analysis that if the Asworth Scale for spasticity (assessment by physician) was used with a WMD −0.12 (95% CI: −0.24 to 0.01], cannabis-based medicines were not statistically superior to placebo, but if self-reported spasticity was assessed using numerical rating scales (mean difference, −0.76 (95% CI: −1.38 to −0.14) this was the case. Other measures of change suggested a greater benefit of cannabis-based medicines without reaching significance, with the exception a greater global impression of change score for nabiximols compared to placebo (OR 1.44 (95% CI: 1.07 to 1.94; 3 of 14 trials). The SR did not present data on tolerability and safety separately for patients with MS. The SR did not perform subgroup analyses of cannabis-based medicines and dosages.

Whiting et al. (2015) concluded that there was moderate-quality evidence to support the use of cannabis-based medicines for the treatment of spasticity.

4. Discussion

4.1 Summary of main findings

There were inconsistent findings of four SRs on the efficacy of cannabis-based medicines compared to placebo in chronic neuropathic pain. There were

Table 6 Results of the systematic reviews of randomized controlled trials of cannabis-based medicines for cancer pain included in the systematic reviews

Reference	Databases and period covered by search of literature	Results for efficacy (95% CI) Number of studies/patients in case of quantitative synthesis	Results for tolerability and safety (95% CI) Number of studies/patients in case of quantitative synthesis	Conclusions of the authors
Mücke et al. (2016)	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, PubMed, Scopus and Clinicaltrials.gov up to April 2015	RD 30% and more pain relief 0.07 (95% CI: 0.0 to 0.16) 2/387	RD Drop-out due to adverse events 1.15; 95% CI: 0.80 to 1.6)[a]; 4/825 RD Serious adverse events 1.12 (95% CI: 0.86 to 1.46) 4/825	Due to the sparse amount of data, it is not possible to recommend a favoured use of cannabis or cannabinoids at this time
Whiting et al. (2015)	Twenty-eight databases and grey literature sources were searched from inception to April 2015	OR 30% and more pain relief 1.41 [95% CI: 0.99 to 2.00]; 2/387	No separate analysis for cancer pain	No separate statement for cannabis-based medicines in cancer pain

CO, confidence interval; OR, odds ratio; RD, risk difference.

[a]Two additional studies with cancer patients included which did not measure pain but other outcomes.

consistent results of three SRs that there was insufficient evidence that cannabis-based medicines were superior to placebo for pain management in patients with rheumatic diseases. There were consistent results of two SRs that cannabis-based medicines were not superior to placebo in reducing cancer pain. In contrast to the authors of one SR, we conclude that there were inconsistent results of the efficacy of cannabis-based medicines for painful spasms in MS.

The results of the SR do not allow conclusions if a one specific cannabis-based medicine should be preferred based on the results of efficacy and safety and which is its optimal dosage balancing efficacy, tolerability and safety.

4.2 Discussion of differences between the systematic reviews

We found inconsistencies in one SR with a bias towards a positive evaluation of cannabis products. The results of the quantitative analyses of Whiting et al. (2015) for any chronic pain and for MS-related spasticity were inconsistent with one statistically significant and one statistically non-significant finding each. Nevertheless, the authors stated a moderate-quality evidence of the efficacy of cannabis-based medicines for these indications.

Although the majority of studies assessed the study quality by different tools, only the minority of the SR critically discussed the quality of evidence. The quality of evidence for the use of cannabis-based medicines for chronic pain is limited by the short duration and the small sample sizes of most studies reviewed. Andreae et al. (2015) did not discuss critically the very short duration of the majority of studies with medical cannabis included (two studies each with 5 days and 5–6 h study duration) which do not allow to make a statement on effectiveness in any clinical setting. Only four reviews (Finnerup et al., 2015; Fitzcharles et al., 2016b; Mücke et al., 2016; Petzke et al., 2016) required a minimum study duration. Only 12 RCTs included in the selected SR met the requirement of a study duration of at least 12 weeks for approval by the European Medicines Agency (2007).

Small sample sizes overestimate treatment effects (Dechartres et al., 2013). Only four studies met the criterion of a low risk of bias of sample size which requires >200 participants per treatment arm (Moore et al., 2010).

In addition, the evidence for the efficacy and safety of cannabis-based medicines for chronic pain is threatened by selective publishing. The SR which included grey literature found three industry-sponsored studies of THC/CBD spray with negative results which have not been fully published yet (Whiting et al., 2015; Petzke et al., 2016). In addition, we found three public-funded studies with nabilone and unknown results in clinicaltrials.gov (Mücke et al., 2017).

The slightly more positive findings with regard to neuropathic pain as well as the inclusion of single dose and short-term studies may have also influenced the conclusions in two SRs jointly analysing data on any type of chronic pain (Martin Martín-Sánchez et al., 2009; Whiting et al., 2015). Their overall supporting conclusion for the effectiveness of cannabis-based medicines is contrasted by the negative results of SR focusing on more defined clinical entities such as cancer and rheumatic pain.

The SRs which performed a quantitative analysis of adverse events (Martín-Sánchez et al., 2009; Petzke et al., 2016) came to cautious conclusions on the role of cannabis-based medicines in chronic pain management, namely that the benefits of cannabis-based medicines might be outweighted by their harms.

One SR concluded – based on the inclusion criteria of the studies reviewed – that cannabis-based medicines should only be considered as third-line therapy in carefully selected patients with neuropathic pain conditions (Petzke et al., 2016).

To sum up, some divergent conclusions of SRs on the efficacy of cannabis-based medicines in chronic pain might be due to the analyses of different studies based on different inclusion criteria for study duration and in the way of balancing benefits and risks. In addition, only some SRs (Finnerup et al., 2015; Fitzcharles et al., 2016b; Mücke et al., 2016; Petzke et al., 2016; Walitt et al., 2016; Whiting et al., 2015) predefined criteria for the quality of evidence. Only one SR (Petzke et al., 2016) commented on clinically relevant benefits and harms.

4.3 Recommendations for cannabinoids in guidelines for chronic pain

The divergent conclusions of SRs on the efficacy and safety of cannabis-based medicines for some chronic pain conditions are reflected by different guideline recommendations.

A pathway for care of chronic neuropathic pain developed by the British Pain Society does not mention cannabis-based medicines (Smith et al., 2013). The Special Interest Group on Neuropathic Pain

(NeuPSIG) of the International Association for the Study of Pain concluded that cannabinoids are not effective in chronic neuropathic pain and gave a weak recommendation against their use (Finnerup et al., 2015). In contrast, the Canadian Pain Society recommended cannabis-based medicines as a potential third-line treatment (Moulin et al., 2014).

The German guideline on fibromyalgia (Sommer et al., 2017) and the European League Against Rheumatism (Macfarlane et al., 2017) gave a negative recommendation for the use of cannabinoids in fibromyalgia syndrome. In contrast, the Canadian guideline recommended to consider a trial of a prescribed pharmacological cannabinoid in patients with fibromyalgia, particularly in the setting of significant sleep disturbance (Fitzcharles et al., 2013). The Israeli guideline mentioned cannabis under 'Investigational treatments' and stated that at the current time the evidence supporting the efficacy and safety of cannabis treatment in fibromyalgia are not sufficient, and additional research is necessary regarding this topic (Ablin et al., 2013).

The American Academy of Neurology stated that clinicians might offer THC/CBD oromucosal spray or oral THC to reduce symptoms of spasticity and pain in MS. Evidence was inadequate to support or refute use of smoked cannabis for spasticity and pain (American Academy of Neurology, 2014). The British NICE guideline recommended that THC/CBD oromucosal spray should not be offered because it was not a cost-effective treatment (NICE, 2014).

5. Conclusion

Our conclusions concur with the ones of a review of the Canadian Agency for Drugs and Technologies in Health (2016) of RCTs with cannabinoid buccal spray for chronic non-cancer or neuropathic pain: The available evidence comparing patient outcomes following cannabis-based medicines treatment versus placebo appears insufficient to make well-founded conclusions about the clinical advantage and use of cannabis-based medicines for the management of cancer and non-cancer pain.

The US Food and Drug Administration (FDA) requires evidence from at least two adequately powered randomized clinical trials before approving a drug for any specific indication (D'Souza and Ranganathan, 2015). These standards have only been met by THC/CBD oromucosal spray for spasticity in MS. The key question if there are any people with another defined chronic pain condition who maintain a substantial reduction in pain with tolerable adverse events on any cannabis-based medicines in the long term (>3 months) has not been answered yet by RCTs or rigorous longitudinal observational studies.

Cannabis is becoming approved for medical use in an increasing number of countries. Since medical marijuana is not a life-saving intervention, it may be prudent to wait until high-quality evidence is available before widely adopting or considering its use (D'Souza and Ranganathan, 2015). In addition, considerable controversy exists regarding the public health impact of such as dependence/addiction, mental health disorders including psychosis, and pulmonary disorders (Wilkinson et al., 2016).

Jurisdictions considering legalization of medical cannabis must also be cognizant of the potential for far-reaching societal effects. The two immediate concerns relate to cannabis effects on driving ability and risk of motor vehicle accidents and unintentional ingestion of cannabis products by children, issues that are emerging as important and previously less recognized (Wilkinson et al., 2016).

Irrespective of the findings of the current overview, medicinal cannabis has already entered mainstream medicine in many countries. Cannabis-based medicines undoubtedly enrich the possibilities of drug treatment of chronic pain conditions. It remains the responsibility of the health care community to continue to pursue rigorous study of cannabis-based medicines to provide evidence that meets the standard of 21st century clinical care and not to simply follow an individuals' 'right' to test an assumed pain relief. The necessary studies need public funding. Unrealistic expectations of patients with chronic pain and their families on the efficacy and safety of cannabis products must be tempered by pain physicians.

Author contributions

WH performed the search of literature. WH and FP selected the studies. All authors extracted data and performed quality ratings. WH wrote the manuscript. All authors discussed the results, commented on the manuscript and approved its final version.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Results of the systematic reviews of randomized controlled trials of cannabis-based medicines for multiple sclerosis associated spasticity included in the systematic reviews.

Table S2. Randomised controlled trials which were included into systematic reviews of cannabis-based medicines in any chronic pain (in alphabetical order).

Table S3. Randomised controlled trials which were included into systematic reviews of cannabis-based medicines in chronic neuropathic pain (in alphabetical order).