Schmerz 2016 · 30:47–61
DOI 10.1007/s00482-015-0084-3
Published online: 14 January 2016

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Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis)

A systematic review of randomized controlled trials

Introduction

Prevalent pain is associated with rheumatic diseases, of which rheumatoid arthritis (RA), osteoarthritis (OA), chronic spinal (neck and back) pain, and fibromyalgia syndrome (FMS) are common [46]. Chronic pain associated with rheumatic diseases presents treatment challenges, with only a minority of individuals experiencing a clinically relevant benefit from any drug intervention. The proportion of patients who achieve clinically meaningful pain relief (typically at least 50 % pain intensity reduction) with nonsteroidal agents, antidepressants, and opioids is generally in the order of 10 to 25 % but more than with placebo, with numbers needed to treat (NNT) to benefit usually between 4 and 10 % [1, 15, 16, 29, 33, 37, 43]. A need therefore exists to explore new drug treatment options with different mechanisms of action.

The endocannabinoid system is increasingly known to play a role in pain modulation and attenuation of inflammation. Cannabinoid receptors are widely distributed throughout the central and peripheral nervous system with relatively low densities in the lower brain stem (areas controlling cardiovascular and respiratory functions). Receptors may also be found in peripheral nonnervous tissue [18]. The endogenous cannabinoid molecules that act as ligands for the receptors are derived from fatty acid metabolism which occurs throughout the organism. Therefore, engaging this system may provide therapeutic effects for conditions of pain and inflammation. It is hypothesized that cannabinoids function to reduce sensitization of nociceptive sensory pathways and induce alterations in cognitive and autonomic processing in chronic pain states [5, 14].

Neurophysiologic study suggests that cannabinoids may be of particular interest in FMS and inflammatory arthritis. One suggestion is that an endocannabinoid deficiency may underlie the pathophysiology of FMS [36], whereas another postulate is that cannabinoids may attenuate low-grade inflammation in fibromyalgia patients [42]. Finally, in view of the hypothesis that fibromyalgia is a stress-related disorder [44], cannabinoids might function as a buffer to stress and enable modulation of emotional and cognitive function [20, 23].

Evidence for effect on inflammation is from preclinical studies that have shown the ability for cannabidinol to block progression of joint inflammation in a murine model of RA [26]. With both cannabinoid receptors and endogenous ligands present in inflamed human joints, targeting this system may hold therapeutic

promise for both inflammatory as well as degenerative arthritis [35].

Other than the endogenous cannabinoid molecules, cannabinoids currently exist as pharmaceutical preparations or as a herbal product derived from the leaves and flowers of the plant *Cannabis sativa*. The first report of the use of cannabis to relieve "rheumatic" pain dates back to the time of the Chinese emperor Huang Ti, 2600 BC [5]. In current times, pharmaceutical cannabinoid preparations have been recommended by some pain specialists for treatment of chronic musculoskeletal pain [49], whereas there is growing public and legislative support for legalization of herbal cannabis for medicinal use, especially in North America, with increasing interest worldwide. Physicians can therefore expect to be caring for patients who may be self-medicating with herbal cannabis or may request medical advice about cannabinoids in general [9, 11]. Musculoskeletal complaints are a common reason for patients to seek authorization for medicinal herbal cannabis use with 82 and 27 % patients, respectively, reporting use for myofascial pain and OA pain in a Washington pain clinic, and 65 % of authorized users in Canada identified with "severe arthritis" [3]. However, physicians in North America have expressed concerns about the role of cannabinoids in general, and phytocannabinoids in particular, in patient care [11]. In response to increased public advocacy for access to medicinal herbal cannabis, the Canadian courts ruled that prohibition of cannabis for medicinal reasons is unconstitutional and invalid, leading the Canadian government to table regulations whereby herbal cannabis may be obtained by prescription [3]. Similarly, with a move of the German government to consider revision of current medical herbal cannabis policy, an updated systematic review should assist the health-care community in clinical care and function to inform policymakers.

In the absence of any consistent guideline recommendation for cannabinoid use in patients with chronic musculoskeletal pain, we have examined the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, FMS, OA, and RA pain.

Methods

This systematic review is an update and expansion of a systematic review mandated by the Canadian Rheumatology Association (CRA) and conducted in 2013 [22]. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27] and the recommendations of the Cochrane Collaboration [19].

Types of studies

We included studies if they were randomized double blind controlled trials (RCTs) of at least 2-week duration. We included studies with a parallel, cross-over, and enriched enrolment randomized withdrawal (EERW) design. Trials should have at least ten participants per treatment arm. We required full journal publication, with the exception of online clinical trial result summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis. We excluded short abstracts (usually meeting reports). We excluded studies that were nonrandomized, studies of experimental pain, case reports, and clinical observations.

Types of participants

Studies should include participants of any age, diagnosed with chronic musculoskeletal pain (duration at least 3 months) associated with the following:

a. Chronic spinal pain (myofascial and/or OA; neck and/or thoracic spine and/or low back) diagnosed by recognized diagnostic criteria (e.g., American College of Physicians)
b. RA diagnosed by recognized diagnostic criteria (e.g., American College of Rheumatology, European League Against Rheumatism)
c. Any OA diagnosed by recognized diagnostic criteria (e.g., American College of Rheumatology)
d. Fibromyalgia using the 1990 or 2010 criteria [51, 52] or the research criteria [53].

Types of interventions

Cannabinoids (either phytocannabinoids such as herbal cannabis [hashish, marijuana], plant-based cannabinoids [Nabiximol] or syntheto-cannabinoids [e.g., cannabidiol, dronabinol, nabilone]) at any dose, by any route, administered for the relief of chronic musculoskeletal pain, compared to placebo or any active comparators that were included. We did not include studies with drugs under development which manipulate the endocannabinoid system by inhibiting enzymes that hydrolyze endocannabinoids and thereby boost the levels of the endogenous molecules, for example, blockade of the catabolic enzyme fatty acid amide hydrolase (FAAH) [24].

Types of outcome measures

Outcomes were selected based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies [6]. These are defined as at least 30 % pain relief over baseline (moderate), at least 50 % pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC; moderate), and very much improved on PGIC (substantial).

Primary outcomes

1. Participant-reported pain relief of 50 % or greater
2. PGIC much or very much improved
3. Withdrawal due to adverse events (tolerability)
4. Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an "important medical event" that may jeopardize the patient, or may require an intervention to prevent one of the above characteristics/consequences

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Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis). A systematic review of randomized controlled trials

Abstract

Background. In the absence of an ideal treatment for chronic pain associated with rheumatic diseases, there is interest in the potential effects of cannabinoid molecules, particularly in the context of global interest in the legalization of herbal cannabis for medicinal use.

Methods. A systematic search until April 2015 was conducted in Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, www.cannabis-med.org and clinicaltrials.gov for randomized controlled trials with a study duration of at least 2 weeks and at least ten patients per treatment arm with herbal cannabis or pharmaceutical cannabinoid products in fibromyalgia syndrome (FMS), osteoarthritis (OA), chronic spinal pain, and rheumatoid arthritis (RA) pain. Outcomes were reduction of pain, sleep problems, fatigue and limitations of quality of life for efficacy, dropout rates due to adverse events for tolerability, and serious adverse events for safety. The methodology quality of the randomized controlled trials (RCTs) was evaluated by the Cochrane Risk of Bias Tool.

Results. Two RCTs of 2 and 4 weeks duration respectively with nabilone, including 71 FMS patients, one 4-week trial with nabilone, including 30 spinal pain patients, and one 5-week study with tetrahydrocannbinol/cannabidiol, including 58 RA patients were included. One inclusion criterion was pain refractory to conventional treatment in three studies. No RCT with OA patients was found. The risk of bias was high for three studies. The findings of a superiority of cannabinoids over controls (placebo, amitriptyline) were not consistent. Cannabinoids were generally well tolerated despite some troublesome side effects and safe during the study duration.

Conclusions. Currently, there is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases.

Keywords

Cannabinoids · Fibromyalgia syndrome · Osteoarthritis · Chronic spinal pain · Rheumatoid arthritis · Systematic review

Wirksamkeit, Verträglichkeit und Sicherheit von Cannabinoiden bei chronischen Schmerzen bei rheumatischen Erkrankungen (Fibromyalgiesyndrom, Rückenschmerz, Arthrose, rheumatoide Arthritis): Eine systematische Übersicht von randomisierten kontrollierten Studien

Zusammenfassung

Hintergrund. Bei Fehlen einer optimalen Behandlung von chronischen Schmerzen bei rheumatischen Erkrankungen besteht ein Interesse in dem Potential von Cannabinoiden, insbesondere auf dem Hintergrund eines weltweiten Interesses der Legalisierung von Cannabis für medizinische Zwecke.

Methoden. Systematische Literatursuche bis April 2015 in CENTRAL, Pubmed, www.cannabis-med.org und clinicaltrials.gov nach randomisierten kontrollierten Studien (RCT) mit einer Studiendauer von mindestens zwei Wochen und mindestens 10 Patienten pro Behandlungsarm mit pflanzlichem Cannabis oder pharmazeutisch hergestellten Cannabisprodukten beim Fibromyalgiasyndrom (FMS), bei Arthrose (OA), beim Rückenschmerz und bei rheumatoider Arthritis (RA). Zielvariablen waren Reduktion von Schmerz, Müdigkeit, Schlafstörungen und Einschränkungen der Lebensqualität als Indikatoren der Wirksamkeit, Abbruchraten wegen Nebenwirkungen für Verträglichkeit und schwerwiegende Nebenwirkungen für Sicherheit. Die methodische Qualität der RCTs wurde mit dem Cochrane Risk of Bias Tool bewertet.

Ergebnisse. Zwei RCTs mit Nabilon und einer Dauer von 2 bzw. 6 Wochen mit 71 FMS –Patienten, eine 4-wöchige Studie mit Nabilon und 30 Rückenschmerzpatienten und eine 5-wöchige mit Tetrahydrocannbinol/Cannabidiol mit 58 RA-Patienten wurden eingeschlossen. Ein Einschlusskriterium in drei Studien waren Schmerzen, die auf eine konventionelle Therapie nicht ansprachen. Keine RCT mit OA-Patienten wurde gefunden. Das Verzerrungsrisiko war hoch in drei Studien. Die Ergebnisse einer Überlegenheit von Cannabinoiden gegenüber Kontrollsubstanzen (Placebo, Amitriptylin) waren nicht konsistent. Cannabinoide wurden trotz einiger unangenehmer Nebenwirkungen gut toleriert und waren sicher während der Studiendauer.

Schlussfolgerungen. Aktuell besteht keine ausreichende Evidenz, eine symptomatische Behandlung von Patienten mit chronischen Schmerzen bei rheumatischen Erkrankungen mit Cannabispräparaten zu empfehlen.

Schlüsselwörter

Cannabinoide · Fibromyalgiesyndrom · Arthrose · Chronischer Rückenschmerz · Rheumatoide Arthritis · Systematische Übersicht

Secondary outcomes

1. Participant-reported pain relief of 30 % or greater
2. Sleep problems
3. Fatigue
4. Depression
5. Anxiety
6. Disability
7. Health-related quality of life
8. Other specific adverse events, particularly somnolence, dizziness and drug prescription abuse (addiction)
9. For inflammatory rheumatic diseases: Number of patients who achieved remission defined by established activity indices, for example, DAS 28 in RA

Search methods for identification of studies

Electronic searches

The following databases were searched without language restrictions till 30 April 2015:

Infobox 1

Search strategy for PubMed

1 ("cannabinoids"[MeSH Terms] OR "cannabinoids"[Tiab]) OR "cannabinoid"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab] OR "marinol"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab]) OR ("nabilone"[Supplementary Concept] OR "nabilone"[Tiab]) OR ("nabilone"[Supplementary Concept] OR "nabilone"[Tiab] OR "cesamet"[Tiab]) OR ("HU 211"[Supplementary Concept] OR "HU 211"[Tiab] OR "dexanabinol"[Tiab]) OR ("tetrahydrocannabinol-cannabidiol combination"[Supplementary Concept] OR "tetrahydrocannabinol-cannabidiol combination"[Tiab] OR "sativex"[Tiab]) OR ("dronabinol"[MeSH Terms] OR "dronabinol"[Tiab] OR "tetrahydrocannabinol"[Tiab])

#2. "fibromyalgia"[MeSH Term] OR "fibromyalgia"[All Fields] OR "fibrositis"[All Fields] OR FMS[all]

#3 "osteoarthritis "[MeSH Term] OR "osteoarthritis hip "[MeSH Term] OR "osteoarthritis spine "[MeSH Term] OR "osteoarthritis knee "[MeSH Term]

#4 "rheumatic diseases "[MeSH Term] OR "arthritis, rheumatoid" [MeSH Term]

5 "low back pain "[MeSH Term] OR " neck pain "[MeSH Term] OR "myofascial pain syndromes" [MeSH Term]

#6. randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]

#7. animals[mh] NOT humans[mh]

#8. #6 NOT #7

#9. #1 AND #2 AND 3# AND 4# AND #5 AND #6

- Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library
- MEDLINE (via Ovid)

Search strategy for MEDLINE is outlined in **Infobox 1**.

Searching other resources

We reviewed the bibliographies of any randomized trials identified and review articles, contacted the authors and known experts in the field, and searched for clinical trial databases ClinicalTrials.gov (ClinicalTrials.gov), International Association for Cannabinoid Medicines (IACM) databank (http://www.cannabis-med.org/studies/study.php) and WHO ICTTRP (http://apps.who.int/trialsearch/) to identify additional published or unpublished data and ongoing trials. We contacted investigators or study sponsors for missing data.

Data collection and analysis

Two review authors (M.-A. Fitzcharles and W. Häuser) independently extracted data using a standard form and checked for agreement before entry into RevMan 5.2 [41].

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly do not satisfy inclusion criteria, and we obtained full copies of the remaining studies; decisions were made by two review authors (M.-A. Fitzcharles and W. Häuser). Two review authors (M.-A. Fitzcharles and W. Häuser) read these studies independently and reached agreement by discussion. We did not anonymize the studies in any way before assessment. In case of disagreement, a third review author (J. Ablin) was involved.

Data extraction and management

Two review authors (M.-A. Fitzcharles and W. Häuser) independently extracted data using a standard form and checked for agreement before entry into RevMan [41]. Information about the pain condition, the study setting, the inclusion and exclusion criteria, the number and demographic and clinical characteristics of participants treated, drug and dosing regimen, co-therapies, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event or serious adverse event) were extracted.

Assessment of risk of bias in included studies

Two authors (W. Häuser and M.-A. Fitzcharles) independently assessed risk of bias for each study, using seven aspects of bias recommended by the Cochrane Collaboration [19]: selection bias, performance bias, detection bias, attrition bias, reporting bias, performance bias, and detection bias. The criteria of the assessment of the risks of bias are outlined in Appendix 1.

We defined a high-quality study (study with a low risk of bias) as a study that fulfilled six to seven of the seven validity criteria; a moderate-quality study (study with a moderate risk of bias) that fulfilled three to five, and a low-quality study (study with high risk of bias) that fulfilled zero to two of the seven validity criteria. Any disagreements were resolved by discussion.

Measures of treatment effect

The effect measures of choice were absolute risk difference (RD) for dichotomous data and standardized mean difference (SMD) for continuous data (pain intensity, physical functioning), calculated using a random effects model (method inverse variance). For subgroup analyses of dichotomous outcomes, we calculated risk ratios (RR). We expressed uncertainty using 95 % CIs. The threshold for "appreciable benefit" or "appreciable harm" was set for categorical variables by a relative risk reduction (RRR) or relative risk increase (RRI) ≥ 25 % [17]. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' g of 0.2 = small, 0.5 = medium, and 0.8 = large [4]. We labeled g < 0.2 to be a "not substantial" effect size. We assumed a minimally important difference if Hedges' g was ≥ 0.2 [7].

The numbers needed to treat for an additional beneficial outcome (NNTB) and the numbers needed to treat for an additional harm (NNTH) were calculated for dichotomous variables (50 % pain reduction, PGIC, dropout due to adverse events, serious adverse events, death) with an excel sheet provided by the Cochrane collaboration (personal communi-

cation with the Cochrane Musculoskeletal Group). We calculated NNTs as the reciprocal of the absolute risk reduction (ARR). The numbers needed to treat for an additional beneficial outcome (NNTBs) for continuous variables (fatigue, sleep problems, and HRQOL) were calculated by 1/absolute improvement.

Dealing with missing data

Where means or standard deviations (SDs) were missing, attempts were made to obtain these data through contacting trial authors. Where SDs were not available from trial authors, they were calculated from t-values, *p*-values, confidence intervals (CIs), or standard errors, where reported in articles [19]. Where 30 and 50 % pain reduction rates were not reported and not provided on request, they were calculated from means and SDs by a validated imputation method [13].

Unit of analysis issues

The control treatment arm was split between active treatment arms in a single study if the active treatment arms are not combined for analysis. Studies with a crossover design were included if (a) separated data from the two periods were reported, (b) data were presented which excluded a statistically significant carry-over effect, or (c) statistical adjustments were carried out in the case of a significant carry-over effect.

Assessment of heterogeneity

We assessed statistical heterogeneity with the use of the I^2 statistic. When I^2 was greater than 50 %, we considered possible reasons.

Assessment of reporting biases

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher) [28].

Data synthesis

We planned to use a fixed-effect model for meta-analysis. We used a random-effects model for meta-analysis if there was significant clinical heterogeneity, and it was considered appropriate to combine studies.

We analyzed data for each rheumatic disease in three tiers, according to outcome and freedom from known sources of bias [30]:

- The first tier used data meeting current best standards, where studies report the outcome of at least 50 % pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation methods for dropouts, report an intention-to-treat (ITT) analysis last 8 or more weeks, have a parallel group design, and have at least 200 participants (preferably at least 400) in the comparison. These top-tier results are reported first.
- The second tier used data from at least 200 participants but where one or more of the above conditions were not met (e.g., reporting at least 30 % pain intensity reduction, using LOCF or a completer analysis, or lasting 4–8 weeks).
- The third tier of evidence relates to data from fewer than 200 participants, or where there are expected to be significant problems because, for example, short duration studies of less than 4 weeks, where there is major heterogeneity between studies, or where there are shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses (studies with different cannabinoids, different routes of administration) if there were at least two studies available.

Sensitivity analysis

If individual peculiarities of the studies under investigation suitable for sensitivity analysis were identified during the review process, sensitivity analyses were performed accordingly.

Results

Results of the search

Searches found 245 reports, which we examined for possible inclusion (**Fig. 1**). We examined four studies in detail and included these studies in this systematic review, two studies in FMS, and one study each for chronic spinal pain (neck, thoracic, and low back) and RA. We found two completed studies with cannabinoids in FMS which were not yet published. We found no completed RCT in OA.

Included studies

For FMS, we included two studies with 71 participants [39, 48] using nabilone. Study recruitment was from a Musculoskeletal Rehabilitation clinic [39] and a chronic pain multidisciplinary clinic [48] [both single-center studies conducted in Canada). Studies enrolled adult participants of mean age ranging between 26 and 76 years, with upper limit of 75 years in one study [39] and no upper age limit in the other study [48]. In both studies there was a preponderance of women (ca 90 %). Inclusion criterion was continued pain despite the use of other oral medications [39] or self-reported chronic insomnia [48]. Diagnosis of FMS was established by the ACR 1990 classification criteria [51] by both studies. A history of substance abuse, current psychotic disorders, and unstable cardiac disease were exclusion criteria in both studies. The extent of other exclusion criteria varied between studies. Nabilone was compared with placebo [39] and with amitriptyline [48]. One study used a parallel group design [39], and the other was a crossover study [48]. This latter study reported data from the first phase separately only for the main outcome measure of sleep problems. To assess potential carryover effects, examination of treatment by period inter-

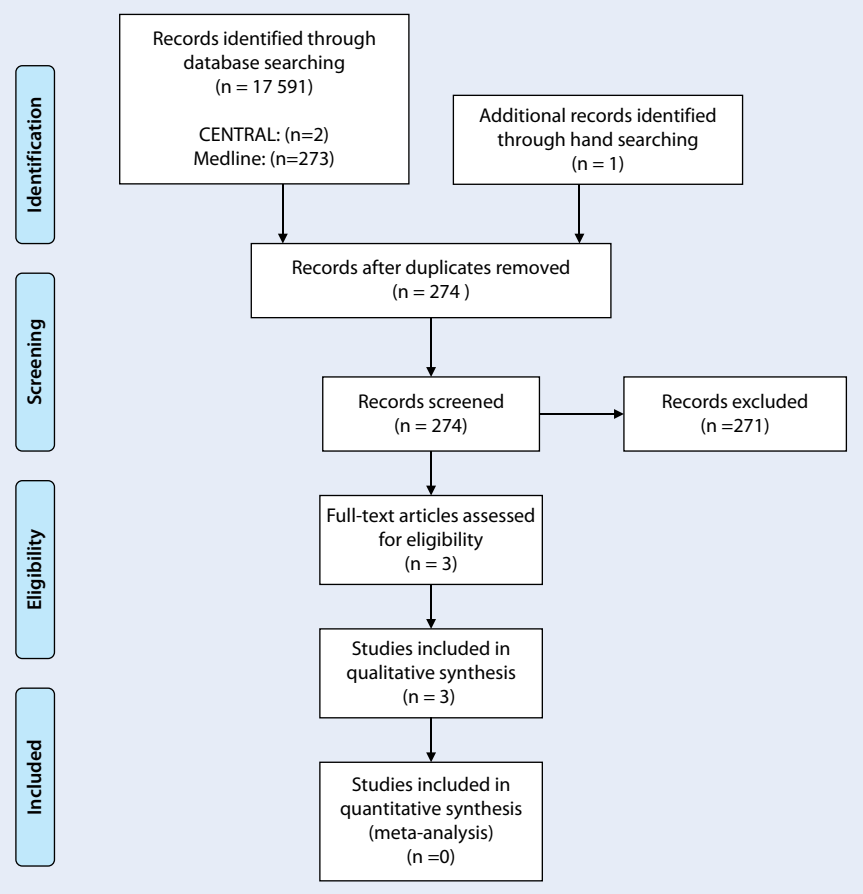

Fig. 1 ▲ PRISMA flow diagram

actions was conducted. Other stable medication (including pain medication) was continued unchanged. Study duration was 4 [39] and 2 weeks [48]. There was a 2-week washout between phases in the crossover study [48]. The dosage of nabilone was progressively increased from 0.5 to 1 mg/day at bedtime [48] and from 0.5 to I mg twice a day [39] (Appendix 2).

For chronic spinal pain, we included a single-center study conducted in Austria that enrolled 30 patients with back (neck, low back, and thoracicspine) pain due to various noncancer-related pathologies. Inclusion criterion was chronic refractory pain (pain intensity VAS > 5) despite conventional treatment with NSAIDS (nonsteroidal agents) and/or opioids. Patients with cancer pain and with a change of analgesic medication during the last 4 weeks were excluded. The mean age of patients was 55 years, 71 % were women. Nabilone flexible (0.25–1 mg/d) was compared to placebo, and the previous analgesic medication was continued unchanged. The study used a crossover design with 4 weeks for each period plus a 5-week washout [34] (Appendix 2).

For RA, we included one multicenter study conducted in the UK. The study enrolled 58 patients, mainly middle-aged women. Inclusion criteria were diagnosis of RA meeting ACR criteria, active arthritis not adequately controlled by standard medication, with NSAID and prednisolone regimes stabilized for 1 month, and disease-modifying anti-rheumatic drugs (DMARDs) stabilized for 3 months prior to enrolment. Exclusion criteria were a history of psychiatric disorders or substance misuse, severe cardiovascular, renal, or hepatic disorder, and a history of epilepsy. An oromucosal spray, each activation delivering 2.7 mg THC (Tetrahydrocannabinol) and 2.5 mg CBD (Cannabidiol), was compared to placebo. Starting dose was one activation within 0.5 h of retiring, and this was increased by one activation every 2 days to a maximum of six activations according to individual response. Stable dosing was then maintained for a further 3 weeks [2] (Appendix 2).

Excluded studies

We excluded no studies after reading the full reports.

Studies awaiting analyses

A German study investigated the combination of operant behavioral treatment and THC in patients with FMS and patients with back pain. The patients were randomly assigned to one of four groups: behavioral therapy and dronabinol, behavioral therapy and placebo, behavioral therapy only, and standard medical therapy (NCT00176163). Nabilone was not superior to placebo if combined with operant therapy (Flor, personal communication). An Israeli study with oral tetrahydrocannabinol (NCT01149018) in FMS patients was not completed due to logistical issues (Haroutiunian, personal communication).

Risk of bias in included studies

Table 1 and Fig. 2 illustrate the 'Risk of bias' assessments by category for each included study. In summary, three studies met the criteria of a low study quality (as reported) [2, 34, 39] and one study of a high study quality [48].

Effects of interventions

Efficacy

All included studies reported at least one pain-related outcome indicating some improvement with cannabinoids, although the comparator study of nabilone with amitriptyline showed no difference between the two treatments for pain [48]. Details of data from individual studies are shown in **Table 2**. There was no first- or second-tier evidence of efficacy.

Third-tier evidence: Skrabek [39] reported that statistically significant improvements were seen in pain, anxiety, and health-related quality of life. However, calculating SMDs by the means and SDs extracted from figures, we did not find a significant difference between nab-

Table 1 Risk of bias table

Bias	Authors' judgment	Support for judgment
Blake 2006		
Random sequence generation (selection bias)	Low	Permuted blocks of four
Allocation concealment (selection bias)	Unclear	No details reported
Blinding of participants and personnel (performance bias)	High	No blinding of oromucosal preparation
Blinding of outcome assessment (detection bias)	Unclear	No details reported
Incomplete outcome data (attrition bias)	High	Completer analysis
Selective reporting (reporting bias)	Unclear	No protocol available
Systematic selection bias	Low	No significant differences in clinical and demographic variables between the two study groups
Pinsger 2006		
Random sequence generation (selection bias)	Unclear	No details provided
Allocation concealment (selection bias)	Unclear	No details provided
Blinding of participants and personnel (performance bias)	Unclear	No details provided
Blinding of outcome assessment (detection bias)	Unclear	No details provided
Incomplete outcome data (attrition bias)	Unclear	ITT analysis by LOCF
Selective reporting (reporting bias)	Unclear	Study protocol available
Systematic selection bias	Low	No differences in clinical and demographic variables due to study design
Skrabek 2008		
Random sequence generation (selection bias)	Unclear	No details reported
Allocation concealment (selection bias)	Low	Pharmacy controlled
Blinding of participants and personnel (performance bias)	Low	Study medication was identical to placebo
Blinding of outcome assessment (detection bias)	Unclear	No details reported
Incomplete outcome data (attrition bias)	High	No ITT analysis
Selective reporting (reporting bias)	Unclear	No protocol available
Systematic selection bias	Low	No significant differences in clinical and demographic variables between the two study groups
Ware 2010		
Random sequence generation (selection bias)	Low	Randomly assigned block sizes by a computer program
Allocation concealment (selection bias)	Low	The schedule was retained by the study pharmacists only
Blinding of participants and personnel (performance bias)	Low	The sealed opaque capsules containing the study drugs were identical for both arms (personal communication)
Blinding of outcome assessment (detection bias)	Unclear	Assessor was not identified
Incomplete outcome data (attrition bias)	High	No ITT analysis
Selective reporting (reporting bias)	Unclear	No study protocol available
Systematic selection bias	Low	No differences in clinical and demographic variables between the two study groups due to crossover design

LOCF last observation carried forward, *ITT* intention-to-treat.

ilone and placebo. No significant differences from placebo were noted for fatigue and depression.

Ware [48] reported that nabilone had statistically significant better effects on sleep than amitriptyline for one of the two primary outcome measures. No significant differences between the two drugs were noted for pain and health-related quality of life. No data for the FIQ (Fibromyalgia Impact Questionnaire) subscales were provided. No significant differences between the two drugs in the Profile of Mood States were reported.

Pinsger [34] reported that the current spine pain intensity was significantly lower with nabilone than with placebo. There was no significant difference between the two study groups in the 4 weeks average pain intensity reduction and in improvement of health-related quality of life.

Blake [2] reported that THC/CBD was statistically significantly superior to placebo in reducing morning pain on movement and at rest (NRS) and pain at present (a subcomponent of the Short Form MCGill Pain Questionnaire), but not for total intensity of pain and intensity of pain at present. THC/CBD was statistically significantly superior to placebo in reducing sleep problems and DAS 28 score but not in reducing morning stiffness.

Tolerability

Details of adverse events reported in individual studies are in **Table 3**.

Ware [48] reported a total of 187 AEs (adverse events). Fifty-three AEs were deemed possibly or probably related to amitriptyline therapy and 91 AEs to nabilone therapy. Blake [2] and Skrabek [39] did not report the total number of AEs.

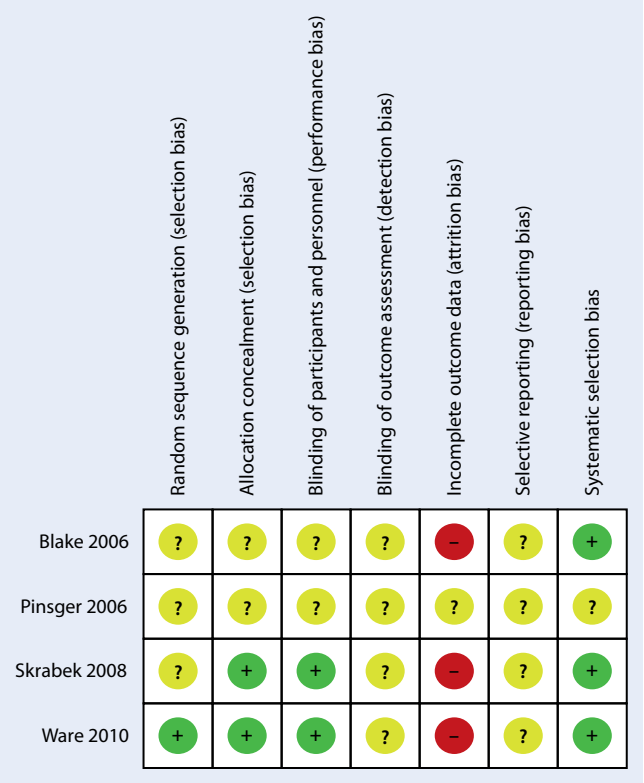

Fig. 2 ◀ Risk of bias graph

There were a total of 7 dropouts in the Skrabek study [39]. Three of 20 patients (15 %) in the nabilone and 1/20 patients in the placebo group dropped out due to side effects. The most frequent side effects noted by Skrabek et al. [39] were drowsiness (seven patients with nabilone, one patient with placebo), dry mouth (five patients with nabilone, one patient with placebo), and vertigo (four patients with nabilone, zero patients with placebo).

Ware reported that one patient dropped out because of side effects after a single dose of nabilone, and a further two withdrew after randomization for noncompliance and lack of effect. The most frequent side effects were dizziness (ten patients with nabilone compared to four patients with amitriptyline), nausea (nine patients with nabilone compared to one patient with amitriptyline), dry mouth (seven patients with nabilone compared to three patients with amitriptyline), and drowsiness (six patients with nabilone compared to one patient with amitriptyline) [47].

Pinsger reported the following adverse effects for nabilone and placebo respectively: fatigue 30 versus 13 %, dry mouth 20 versus 3 %, and vertigo 33 versus 10 %. Seven patients dropped out of the study. The reasons for dropping out of the study were not detailed [34].

Blake reported that 3/27 (11 %) patients dropped out due to side effects in the placebo group but without any dropouts in the cannabinoid group. The most frequent side effects for the TCH/CBD versus placebo group were dizziness (26 versus 4 %), light-headedness (10 versus 4 %), and dry mouth (13 versus 0 %), respectively and were mild or of moderate intensity. Two (6 %) of the patients in the cannabinoid group reported a severe side effect (constipation, malaise), whereas six (22 %) in the placebo group reported severe side effects without further description [2].

Safety

Skrabek [39] and Ware [47] reported no serious adverse events during the study period. Pinsger reported one serious adverse event (fall with fracture due to dizziness) associated with nabilone [34]. Blake noted two serious adverse events possibly, probably, or definitely related to placebo [2].

Discussion

Summary of main findings

A total of 159 patients with rheumatic disease-related pain or sleep disturbance have been studied for the effect of cannabinoids on rheumatic disease-associated symptoms refractory to conventional treatment. Conditions studied were FMS, RA, and spine pain due to noncancer pathologies. In three studies the cannabinoid was administered as a synthetic pharmaceutical product, nabilone, and in one was via an oromucosal spray of THC/CBD. There were no studies examining the use of herbal product. In these four short-term studies, cannabinoids provided some relief from pain in three and was equivalent to amitriptyline for effect on sleep in one study but without differing from amitriptyline for effect on pain. There was one serious adverse event related to cannabinoid treatment reported, but troublesome side effects were common.

In one short-term (2 weeks) trial, nabilone was superior to amitriptyline in reducing some parameters of sleep problems but did not differ from amitriptyline for effect on pain, limitation of health-related quality of life, or mood problems in FMS patients. In the second short-term (4 weeks) trial of nabilone in FMS, the authors reported superiority of nabilone over placebo in reducing pain and limitation of HRQOL but not for fatigue and depression. It is, however, notable that we were unable to confirm these positive results when the SMDs were recalculated by the means and SDs extracted from the figures. In the short-term (4 weeks) trial in patients with spinal pain, nabilone was superior to placebo in reducing current spine pain, but not average pain over a 4-week period, and with no change in limitation of health-related quality of life. In the single study in RA of 5-week duration, THC/CBD was superior to placebo in reducing selected parameters of pain, including morning pain on movement and at rest, and present pain, and in improving quality of sleep and the DAS 28. Cannabinoids were generally well tolerated across all studies but with frequent reports of troublesome side effects that included dizziness, drowsiness, nausea,

Table 2 Summary of efficacy in single studies

Study	Treatment	Efficacy outcomes at the end of treatment
Blake 2006	One to six activations of an oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per activitation versus placebo spray	50 % pain reduction: Not reported
		PGIC: Not assessed
		Pain (morning at rest): THC/CBD mean 3.1 (SD NR), placebo mean 4.1 (SD NR)[a] ($p = 0.02$)[c]
		Sleep: THC/CBD mean 3.4 (SD NR), placebo mean 4.6 (SD NR)[a] ($p = 0.03$)[c]
		Fatigue: not assessed
		Depression: not assessed
		Anxiety: not assessed
		Health-related quality of life: not assessed
		DAS 28: THC/CBD mean 5.0 (SD NR), placebo mean 5.9 (SD NR)[a] ($p = 0.002$)[c]
Pinsger 2006	Nabilone 0.25–1 mg/d orally, flexible	50 % pain reduction: not reported
		PGIC: not assessed
		Pain reduction (current in spine): nabilone median 0.9 (SD NR), placebo median 0.5 (SD NR)[a] ($p = 0.20$)[c]
		Sleep: not assessed
		Fatigue: not assessed
		Depression: not assessed
		Anxiety: not assessed
		Health-related quality of life (improvement): nabilone median 5.0 (SD not reported); placebo median 2.0 (SD not reported) ($p = 0.90$)[c]
Skrabek 2008	Nabilone 1 mg bid orally versus placebo Titration from 0.5 to 1 mg bid from week 1 to 4	50 % pain reduction: not reported and not provided on request
		PGIC: not assessed
		Pain: nabilone mean 4.8 (SD 2.2), placebo mean 5.7 (SD 1.8)[a] ($p = 0.02$)[c]
		Sleep: not assessed
		Fatigue: no significant difference[b]
		Depression: no significant difference[b]
		Anxiety: nabilone mean 4.3 (1.8), placebo mean 4.9 (2.2)[a] ($p < 0.01$)[c]
		Health-related quality of life: mean 54 (22.3), placebo mean 64 (13.4)[a]; ($p < 0.01$)[c]
Ware 2010	Nabilone 0.5 or 1 mg versus amitriptyline 10 or 20 mg at bedtime each Titration in each of 2 periods of 2 weeks, with 2 weeks washout	50 % pain reduction: not reported and not provided on request
		PGIC: not assessed
		Average pain intensity: no significant difference[b]
		Sleep: nabilone: mean 9 (SD 10.8); amitriptyline mean 13 (10.8)[a]
		Fatigue: not reported
		Depression: not reported
		Anxiety: not reported
		Health-related quality of life: no significant difference[b]

[a]Data extracted from figures.
[b]No means and SDs reported.
[c]*p* values as reported by authors.

and dry mouth. Only one serious adverse event attributable to cannabinoid treatment, a fracture following a fall due to dizziness, was reported for all of the studies.

Comparison with other reviews and studies

A recent systematic review with meta-analysis for cannabinoids for medical use concluded that cannabinoids were superior to placebo in reducing chronic pain [50]. However, this review included mainly studies with nabiximole in neuropathic pain. None of the studies of this review were included into the meta-analyses of Witting and coauthors [50]. Therefore, the conclusion that cannabinoids are superior to placebo in reducing chronic pain is only valid for neuropathic pain [8] but not for pain associated with rheumatic diseases.

The evidence for efficacy of cannabinoids for FMS symptoms in uncontrolled trials is inconsistent. In an experimental study designed to examine the effect of orally administered Δ^9-THC on electrically induced pain, nine German FMS patients received a daily dose of 2.5–15 mg of Δ^9-THC, with a weekly increase of 2.5 mg, as long as no side effects were reported. Five patients withdrew due to side effects. Daily-recorded pain was significantly reduced over a 3-month period [38]. A case series of 172 patients reported from Germany included 32 patients with

Table 3 Summary of adverse events in individual studies (cannabinoid versus control)

Study	Adverse events (cannabinoid versus control) (%)	Withdrawal due to adverse events (cannabinoid versus control) (%)	Serious adverse events (cannabinoid versus control) (%)
Blake 2006	Dizziness 26 versus 4	0 versus 11	0 versus 2
	Light-headedness 10 versus 4		
	Dry mouth 13 versus 0		
	Nausea 6 versus 4		
	Constipation 3 versus 4		
	Drowsiness 3 versus 4		
	Fall 6 versus 0		
	Headache 3 versus 4		
	Palpitations 0 versus 7		
	Vomiting 0 versus 7		
Pinsger 2006	Fatigue 30 versus 13	7 patients dropped out due to various reasons; no details reported	3.3 versus 0
	Dry mouth 20 versus 3		
	Vertigo 33 versus 10		
	Sleep problems 1´7 versus 3		
Skrabek 2008	Drowsiness 47 versus 6	15 versus 0	Not reported
	Dry mouth 33 versus 6		
	Vertigo 27 versus 0		
	Ataxia 20 versus 6		
	Confusion 13 versus 6		
	Decreased concentration 13 versus 6		
Ware 2010	Dizziness 32 versus 13	3 versus 0	0 versus 0
	Headache 13 versus 19		
	Nausea 29 versus 3		
	Dry mouth 23 versus 10		
	Drowsiness 23 versus 3		
	Constipation 19 versus 3		
	Insomnia 10 versus 0		

FMS. On average patients received 7.5 mg delta 9-THC over 7 months. Patients were assessed retrospectively in a telephone survey. On average, maximum pain intensity (according to a numeric rating scale (NRS) was recorded as 9.3 ± 1.1 prior to Δ^9-THC and 6.1 ± 2.1 thereafter, but without identification of the time period for assessment for change in pain. Data on HRQOL, disability and depression, and dropout rates due to side effects were not reported separately for FMS patients. About 25 % of the total sample did not tolerate the treatment [49]. In another study, 28 Spanish FMS patients who were herbal cannabis users and 28 nonusers, without differences in demographics and clinical variables, were compared. After 2 h of cannabis use for the herbal cannabis users, VAS scores showed a statistically significant ($p < 0.001$) reduction of pain and stiffness, enhancement of relaxation, and an increase in somnolence and feeling of well-being. The mental health component summary score of the SF-36 was significantly higher in cannabis users than in nonusers. No significant differences were found in the other SF-36 domains or in the FIQ [12]. In a Canadian case series of a tertiary care pain center, cannabinoids were being used by 13 % of FMS patients, of whom 80 % used herbal cannabis. Current unstable mental illness, opioid drug-seeking behavior, and male sex were all associated with herbal cannabis use. There was a trend for cannabinoid users to be unemployed and receiving disability payments [40].

The weak evidence of a limited efficacy of cannabinoids for some FMS symptoms and RA symptoms by controlled and uncontrolled trials is in contrast to the findings of patient surveys. In a UK survey of 2969 people who agreed to complete a questionnaire about medicinal cannabis, 947 (32 %) had obtained the drug illegally for symptom relief. Of these, 155 (16 %) reported use of cannabis for symptom relief for arthritis (type not specified). This was the fifth commonest indication after multiple sclerosis, neuropathy, chronic pain (which may have included musculoskeletal pain), and depression [47]. There is no record of amount used, dosing schedules, or concomitant medication use, and over a third reported recreational use of cannabis. In a study of the US National Pain Foundation, over 1300 FMS patients rated marijuana more effective than FDA-approved duloxetine, milnacipran, and pregabalin. The survey showed that only 8, 10, and 10 % of duloxetine, pregabalin, and milnacipran users, respectively, found the prescribed medication to be "very effective," while 60, 61, and 68 % replied that the medications, "do not help at all." In contrast, 62 % of marijuana users rated it very effective. Only 5 % said it does not help at

all [31]. In Canada, almost two third of the 32,000 persons with authorization by Health Canada to possess herbal cannabis for medicinal reasons in 2013 were identified as suffering from "severe arthritis," without further description [32].

The findings of this review regarding the most frequent adverse events associated with cannabinoids (drowsiness, dizziness, and dry mouth) and the safety of cannabinoids in the few controlled studies in rheumatic diseases available are in line with the findings of a systematic review of cannabinoids in chronic noncancer pain, which included 18 RCTs with 766 patients [22]. The two case series outlined above point to low tolerability and poorer mental health and functionality for cannabinoid users with FMS. Increasing and serious concerns for potential negative neuropsychiatric effects have been raised based on the data of long-term recreational use of cannabis [21, 45]. Notably, however, long-term recreational use may often be confounded by additional illicit drug use, alcohol consummation, and smoking, and hence it is not self-evident that this observation can be extrapolated to the regulated use of cannabis for medicinal purposes.

Conclusion for clinical practice

The low quantity and quality of data available on the efficacy, tolerability, and safety of cannabinoids in chronic pain refractory to conventional treatment associated with rheumatic diseases do not allow for any current recommendation for routine clinical use. Other than a weak recommendation for a trial of a pharmacologic cannabinoid preparation in patients with FMS in the setting of important sleep disturbance in the Canadian FMS guidelines [10], there is no other current guideline recommendation for use of any cannabinoid preparation in the management of chronic pain associated with rheumatic diseases. This paucity of evidence persists despite the millennial use of cannabis in various forms for the management of pain and other symptoms. Anecdotal medical experience and personal advocacy cannot supercede evidence-based rational clinical practice, emphasizing an urgent call for additional high-quality research, on both a clinical and physiological level.

More randomized controlled trials comparing herbal cannabis and pharmaceutical cannabinoids with established therapies are necessary to define their role in the management of chronic pain associated with rheumatic diseases. At the same time, additional basic science research focusing on the physiology of the cannabinoid system in pain and inflammation may act to broaden our understanding of this field and better inform the clinician of the expected effects when manipulating this intricate system.

In the clinical setting, a short-term trial of off-label use of nabilone may be considered for those patients with FMS who are refractory to established (guideline recommended) physical, psychological, and drug treatments, within a multicomponent treatment approach. Any continued treatment with nabilone should be guided and balanced by predefined treatment goals (e.g., substantial improvement of pain and/or sleep problems and/or disability) and with attention to emergent side effects. Rheumatic disease patients requesting treatment with herbal cannabis should be informed of the current absence of evidence for effect, and herbal cannabis should be reserved (on a compassionate grounds) for those few patients who have truly exhausted evidence-based, guideline-recommended modes of drug, psychological and physical treatments and remain severely symptomatic and disabled.

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Compliance with ethical guidelines

Conflict of interest. M.-A. Fitzcharles has received consulting fees, speaking fees and/or honoraria from ABBVIE, Abbott, Amgen, Bristol-Myers Squibb Canada, Janssen, Johnson & Johnson, Lilly, Pfizer, Purdue and Valeant. C. Baerwald has received speeking and consulting fees from Mundipharma, Grünenthal, Pfizer, MSD Sharp & Dohme and Merck. J. Ablin has no conflcits of interest to declare. W. Häuser has received speaking fees from Grünenthal, MSD Sharp & Dohme and Pfizer.

Appendix 1

Risk of bias assessment (Cochrane Collaboration, Häuser 2015)

1. *Randomization (systematic selection bias)*: There is a low risk of selection bias if the investigators describe the method of random allocation of patients in the therapy and control groups by the one of the following methods: referral to a random number table, use of computer-generated random numbers, coin tossing, shuffling cards or envelopes, dice throwing, or drawing lots. There is a high risk of selection bias if the allocation is generated in terms of odd or even numbers in the date of birth, date of hospital admission, or hospital record number, as well as in the case of allocation by judgment of the physician, the patient's wishes, results of a laboratory test, or availability of the intervention.

2. *Allocation concealment (selection bias)*: There is a low risk of systematic selection bias if the participants and investigators could not foresee allocations because one of the following methods, or an equivalent method, was used to conceal the allocation: central allocation (e.g., telephone, Internet, or pharmacy-controlled random allocation; sequentially numbered drug containers of identical appearance or sequentially numbered sealed opaque envelopes).There is a high risk of systematic selection bias if participants and investigators could possibly foresee allocations, for example due to the use of an openly available treatment plan (e.g., a list with randomly generated numbers); assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed, nonopaque, or not sequentially numbered); alternating or rotating treatment group allocation; date of birth; case record number; or other explicitly unconcealed allocation procedures.

3. *Blinding of participants and personnel/treatment providers (systematic performance bias)*: There is a low risk of performance bias if blinding of participants was ensured, and it was unlikely that the blinding could have been lacking or incomplete; or if blinding was lacking or incomplete, the review authors judge that the outcome was not influenced by the lack

of blinding. There is a high risk of performance bias if blinding of participants was not ensured.

4. *Blinding of outcome assessor (systematic detection bias)*: There is low risk of systematic detection bias if the outcome assessor assessing patient-reported outcomes is not the clinical investigator but rather a statistician not involved in the treatment of the patient. There is an unclear risk of systematic detection bias if no details on the identity of the outcome assessor are reported. There is a high risk of systematic detection bias if the outcome assessor was involved in treatment of the patients.

5. *Incomplete outcome data (systematic attrition bias due to loss of participants)*: There is low risk of systematic bias if all randomized patients were reported or analyzed in the group to which they were allocated by randomization, and dropouts were analyzed by the baseline observation carried forward (BOCF) method (baseline measurements used for data analysis). There is an unclear risk of systematic bias if all randomized patients were reported or analyzed in the group to which they were allocated by randomization, and dropouts were analyzed by the LOCF method (last measurements used for data analysis). There is a high risk of systematic bias if no intention-to-treat (ITT) analysis was carried out (analysis technique in which patients are analyzed according to their original group assignment, regardless of whether they received the intended therapy completely, in part, or not at all) or only study completers were evaluated.

6. *Selective reporting (systematic reporting bias)*: There is low risk of reporting bias if the study protocol is available and all of the study's prespecified primary and secondary endpoints that are of interest to the review have been reported in the prespecified way; or if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (a convincing text of this nature is probably uncommon). There is a high risk of systematic reporting bias if not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes are reported using measurements or analysis methods that were not prespecified; one or more of the reported primary outcomes were not prespecified (independently of whether justification for use of an unexpected result is provided); one or more outcomes that are of interest to the review are reported incompletely, such that they cannot be entered into meta-analysis; the study report fails to include results for a key outcome, which would be expected in a study of this nature.

7. *Group similarity at baseline (systematic selection bias)*: There is low risk of bias if groups are similar at baseline for demographic factors, values of main outcome measures, and important prognostic factors. There is high risk of bias if groups are not similar at baseline for demographic factors, values of main outcome measures, and important prognostic factors.

Appendix 2

Characteristics of included studies (Blake 2006)

Methods

Study setting: Multi center study, no further details provided, UK

Study design: Parallel

Duration therapy: 5 weeks

Follow-up: 7–10 days

Participants: 58 (79 % women, race not reported, mean age 49 years)

Inclusion criteria

- Diagnosis of RA meeting ACR criteria
- Active arthritis not adequately controlled by standard medication
- NSAID and prednisolone regimes had to have been stabilized for 1 month and DMARDs for 3 months prior to enrolment

Exclusion criteria

- A history of psychiatric disorders or substance misuse
- Severe cardiovascular, renal, or hepatic disorder
- A history of epilepsy

Interventions

Active drug: Oromucosal spray, each activation delivering 2.7 mg THC and 2.5 mg CBD; starting dose was one actuation within 0.5 h of retiring, and this was increased by one actuation every 2 days to a maximum of six actuations according to individual response. Stable dosing was then maintained for a further 3 weeks; 31 participants

Placebo: 31 participants

Rescue or allowed medication: No details reported. NSAID, prednisolone, and DMARDs regimen maintained during the study

Outcomes

Pain: Daily morning pain intensity at rest and on movement (NRS 0–10); Short Form McGill Questionnaire total pain intensity

Fatigue: not assessed

Sleep: not assessed

Depression: not assessed

Anxiety: not assessed

Disability: not assessed

Health-related quality of life: not assessed

Patient-perceived improvement: not assessed

Activity scores: DAS 28

AEs: No details reported

Notes

Safety: Three serious adverse events occurred during the study in the placebo group.

Funding sources and any declaration of interest of primary investigators: supported by GW Pharmaceuticals.

Pinsger 2006

Methods

Study setting: single-center study, private clinic, Austria

Study design: crossover

Duration therapy: 4 weeks for each period, washout period 5 weeks

Follow-up: 16 weeks with free choice of study drugs

Participants: 30 (71 % women, race not reported, mean age 55 years)

Inclusion criteria

- Chronic therapy-resistant pain in causal relationship with a pathological status of the skeletal and locomotor system

- Pain intensity VAS > 5 despite conventional treatment with NSAIDs and/or opioids

Exclusion criteria

- Cancer
- Change of analgesic medication in the past 4 weeks

Interventions

Active drug: nabilone oral flexible between 0.25 and 1 mg/d, 30 participants

Placebo: 30 participants

Rescue or allowed medication: no details on rescue medication reported. NSAID and opioid regimen maintained during the study

Outcomes

Pain: change of current spine pain intensity and spine pain intensity during the past 4 weeks (Visual Analogue Scale 0–10)

Fatigue: not assessed

Sleep: not assessed

Depression: not assessed

Anxiety: not assessed

Disability: not assessed

Health-related quality of life: score of Mezzich and Cohen

Patient-perceived improvement: not assessed

AEs: no details reported

Notes

Safety: One serious adverse event occured during the study in the nabilone group.

Funding sources and any declaration of interest of primary investigators: No details reported

Skrabek 2008

Methods

Study setting: single-center study, Outpatient Musculoskeletal Rehabilitation Clinic, Canada

Study design: parallel

Duration of therapy: 4 weeks

Follow-up: 4 weeks

Participants: 40 (93 % women, race not reported, mean age 49 years)

Inclusion criteria

- The patient meets The American College of Rheumatology (1990) criteria for the classification of fibromyalgia. [5]
- 18–70 years old.
- Any gender.
- The patient has not received benefit from a tricyclic antidepressant (TCA), muscle relaxant, acetaminophen, or nonsteroidal anti-inflammatories for management of their pain.
- No previous use of oral cannabinoids for pain management.

Exclusion criteria

- The patient's pain is better explained by a diagnosis other than fibromyalgia.
- Abnormalities on routine baseline blood work, including electrolytes, urea and creatinine, a complete blood count, and liver function tests (AST ALT GGT, Alk Phos, and LDH). Normal tests taken 3 months prior to the study will be accepted if there is no history of acute illness since the time the blood was drawn.
- Heart disease (cannabinoids can reduce heart rate and blood pressure). Patients with heart disease will be excluded based on a history of angina, MI, or CHF as well as a clinical exam.
- Schizophrenia or other psychotic disorder.
- Severe liver dysfunction (patients will be excluded if there is an elevation of any of the baseline liver enzymes).
- History of untreated nonpsychotic emotional disorders.
- Cognitive impairment.
- Major illness in another body area.
- Pregnancy.
- Nursing mothers.
- Patients less than 18 years old.
- History of drug dependency.
- A known sensitivity to marijuana or other cannabinoid agents.

Interventions

Active drug: nabilone 0.5 mg to 1 mg/twice a day: 20 participants

Placebo: 20 participants

Rescue or allowed medication: No details reported. Subjects were asked to continue any current medication including breakthrough medications but not to begin any new therapy

Outcomes

Pain: daily diary mean pain (VAS 0–10)

Fatigue: FIQ subscale VAS 0–100

Sleep: not assessed

Depression: FIQ subscale VAS 0–100

Anxiety: FIQ subscale VAS 0–100

Disability: FIQ subscale VAS 0–100

Health-related quality of life: FIQ total score (0–100)

Patient-perceived improvement: not assessed

AEs: AEs were recorded at each visit. No details reported

Notes

Safety: no serious adverse events occurred during the study

Funding sources and any declaration of interest of primary investigators: supported by Valeant Canada and an HSC Medical Stuff Council Fellowship Fund

No declaration of interest of primary investigators included

Ware 2010

Methods

Study setting: single-center study, pain clinic, Canada

Study design: crossover

Duration therapy: 2 weeks each with 2-week washout between the two periods

Follow-up: none

Participants: 32 (81 % women, race not reported, mean age 50 years)

Inclusion criteria

Patients aged ≥ 18 years

- A diagnosis of fibromyalgia according to the American College of Rheumatology classification criteria [51]
- Suffering from self-reported disturbed sleep
- Negative urine screen for cannabinoids
- Women of childbearing potential must agree to use adequate contraception during study and for 3 months after study
- Ability to attend research center every second week for approximately 7–9 weeks and be able to be contacted by telephone during the study period
- Stable drug regimen for 1 month prior to randomization

- Normal liver (AST < 3x normal) and renal function (serum creatinine < 133 µmol/L)
- Hematocrit > 38 %
- Negative serum bHCG
- Proficient in English or French
- Willing and able to give written informed consent
- Ability to follow study protocol (cognitive and situational)

Exclusion criteria:

- Patients currently using cannabis or cannabinoid or TCA and who are unable to undergo a 2-week washout period before entering the study
- Pain due to cancer
- Unstable cardiac disease such as cardiac arrhythmias, cardiac failure, ischemic heart disease, and/or hypertension on clinical history and examination
- History of psychotic disorder or schizophrenia
- Known hypersensitivity to cannabinoids, amitriptyline, or related TCAs
- Currently taking or unable to stop taking monoamine oxidase inhibitors (a two-week washout period is necessary for subjects taking MAOIs)
- History of seizures/epilepsy
- Diagnosis of glaucoma
- Urinary retention
- Pregnancy and/or breast-feeding
- Participation in other clinical trial in the 30 days prior to randomization
- A recent manic episode (within the past year)
- Current suicidal ideation or history of suicide attempts

Interventions

Active drug: nabilone 0.5 or 1 mg/d orally, flexible: 29 participants

Active comparator: amitriptyline oral, flexible, 10 or 20 mg/d: 29 participants

Rescue or allowed medication: no details reported

Outcomes

Pain: Mc Gill Pain Questionnaire total score

Fatigue: FIQ subscale VAS 0–100 (no details reported)

Sleep: Insomnia Severity Index (0–25) and Leeds Sleep Evaluation Questionnaire

Depression: FIQ subscale VAS 0–100

Anxiety: FIQ subscale VAS 0–100

Disability: FIQ subscale VAS 0–100

Health-related quality of life: FIQ total score (0–100)

Patient-perceived improvement: not assessed

AEs: AE were recorded at each visit by open questions to the patient (personal communication)

Notes

Safety: No serious adverse events occured during the study.

Funding sources and any declaration of interest of primary investigators: McGill Supported by the a grant of Valeant (Canada) and MC Gill University Health Center. Declaration of interest of primary investigators included

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