Comprehensive Review

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Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews

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Abstract

Cannabinoids, cannabis, and cannabis-based medicines (CBM) are increasingly used to manage pain, with limited understanding of their efficacy and safety. We assessed methodological quality, scope, and results of systematic reviews of randomised controlled trials of these treatments. Several search strategies sought self-declared systematic reviews. Methodological quality was assessed using both AMSTAR-2 and techniques important for bias reduction in pain studies. Of the 106 articles read, 57 were self-declared systematic reviews, most published since 2010. They included any type of cannabinoid, cannabis, or CBM, at any dose, however administered, in a broad range of pain conditions. No review examined the effects of a particular cannabinoid, at a particular dose, using a particular route of administration, for a particular pain condition, reporting a particular analgesic outcome. Confidence in the results in the systematic reviews using AMSTAR-2 definitions was critically low (41), low (8), moderate (6), or high (2). Few used criteria important for bias reduction in pain. Cochrane reviews typically provided higher confidence; all industry-conflicted reviews provided critically low confidence. Meta-analyses typically pooled widely disparate studies, and, where assessable, were subject to potential publication bias. Systematic reviews with positive or negative recommendation for use of cannabinoids, cannabis, or CBM in pain typically rated critically low or low (24/25 [96%] positive; 10/12 [83%] negative). Current reviews are mostly lacking in quality and cannot provide a basis for decision-making. A new high-quality systematic review of randomised controlled trials is needed to critically assess the clinical evidence for cannabinoids, cannabis, or CBM in pain.

1. Introduction

In 2018, the International Association for Study of Pain established a Task Force on the use of cannabinoids, cannabis, and cannabis-based medicines (CBM) for pain management. It has 4 Work Packages (WP) focused on (1) basic science and evidence for efficacy in preclinical models,[72] (2) evidence for clinical analgesic efficacy,[28] (3) risk and evidence of harm to the individual,[31,50] and (4) the societal impact and policy.

This overview review is part of the second Work Packages and is focused on summarizing the evidence of efficacy presented in systematic reviews of randomised controlled trials (RCTs) of any broadly defined cannabinoid product in any type of pain condition.

There have long been concerns about the quality of most of the medical literature.[37,68] A 1996 survey indicated that 90% of meta-analyses had methodological flaws that could limit their validity, and that meta-analyses of low quality produced significantly more positive conclusions.[39] There has subsequently been an epidemic of systematic reviews, with huge growth rates in their numbers without any necessary improvement in their quality,[68] leading to the conclusion that the large majority of systematic reviews and meta-analyses are unnecessary, misleading, and/or conflicted. Industry-

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supported meta-analyses have been found to be less transparent, with few reservations about methodological limitations of the included trials, and with more favourable conclusions than corresponding Cochrane reviews.[41]

Even in good-quality Cochrane reviews, the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) to summarise the quality of evidence indicates that fewer than 20% of reviews actually have any high-quality evidence.[30] Only confusion results from the product of low-quality evidence and low-quality systematic review of that evidence. High standards in clinical trials and systematic reviews of those trials are absolutely essential to improve knowledge, make policy, or make individual clinical decisions; anything else is guesswork.

The aim of this overview review of WP2 was therefore to assess the methodological quality, scope, and reported results of systematic reviews and meta-analyses of RCTs of cannabinoids, cannabis, and CBM for pain relief, and to determine whether any new systematic review was required.

2. Methods

A protocol for this overview is registered on Prospero (Prospero ID CRD42019124710) and published.[28] We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[49] A truncated report of methods is therefore given here.

2.1. Systematic reviews for inclusion

We chose to include any review whose authors defined as a systematic review of RCTs, although definitions of what comprises a systematic review are considerably more restrictive.[34] The intention in the protocol was to analyse only high-quality evidence found in Cochrane Effective Practice and Organisation of Care[25] GRADEs of evidence as high or moderate quality, although in the event this was not possible.

2.2. Participants

We included systematic reviews of RCTs involving people of any age with any form of acute and chronic pain, including pain secondary to another condition, such as pain with spasm, multiple sclerosis (MS), or leg cramps. Experimental pain was not included.

2.3. Interventions and comparators

We included any type of cannabinoid product (natural or synthetic), cannabis, or CBM, by any route of administration, at any dose, and with any comparison intervention. This included endocannabinoid system modulators such as fatty acid amide hydrolase inhibitors and *N*-palmitoylethanolamide. For inclusion, systematic reviews were required to examine interventions to reduce pain intensity.

2.4. Outcomes

A range of primary and secondary outcomes were proposed in the protocol. The limited nature of systematic reviews included meant that this overview was restricted to measures of analgesic efficacy only.

2.5. Search and selection of systematic reviews

We searched PubMed, EMBASE, DARE, and the Cochrane Controlled Register of Trials (CENTRAL) for systematic reviews of cannabinoids, cannabis, and CBM and for people with pain. The main search was completed in August 2019. Bibliographies of included and excluded reviews were examined for possible reviews, and electronic citations of PubMed and Google Scholar also examined. We conducted targeted searches for further systematic reviews through additional electronic searches, through reference lists of retrieved articles and reviews, or through other sources up to January 2020. Two authors independently sifted the titles and abstracts identified, with a third author resolving disagreement.

2.6. Data extraction

Data extraction was conducted by 2 authors (R.A.M. & E.F.) and checked by others; disagreement was resolved by consensus (initially discussion with C.E., but wider if needed). The following information was extracted from each review:

(1) Review characteristics, eg, design, participants, age and sex, pain condition, inclusion/exclusion criteria, and risk of bias method. In addition, we sought information related to Assessment of Multiple Systematic Reviews (AMSTAR)-2,[67] methodological issues related to known sources of bias in pain studies, use of GRADE, and GRADE assessment if used. We extracted the number of trials and patients used in assessment of pain, the number in randomised trials, and the number in randomised trials used to calculate any summary estimate of analgesic efficacy.
(2) Intervention and comparator characteristics, eg, type of cannabinoid, dose, route of administration, and comparator.
(3) Outcomes listed in the primary outcomes.

In addition, we made a judgement on the strength of any recommendation made by authors in the review abstract. This was done by R.A.M. and E.F., discussed initially with C.E., and then wider if needed. Judgements were based on being positive (recommended use), equipoise (a balance of evidence), or negative (recommended nonuse), or no statement. Strength was judged as strong (eg, provide reasonable therapeutic option, should not be used), moderate (eg, moderately effective, no unbiased evidence), or weak (eg, small analgesic benefit, more trials needed to support).

2.7. Assessment of review quality and validity

We assessed each included review using AMSTAR-2.[67] Two authors assessed each review using the criteria with disagreement resolved by consensus.

We also conducted additional validity checks of potential critical importance in the evaluation of analgesic efficacy. These included:

(1) Did the review use a defined diagnostic criterion for pain conditions?
(2) Did the reviews include only studies in which patients made their own assessment of pain? (professional and patient assessment often disagrees, with professionals significantly underestimating pain[66]).
(3) Did the reviews use studies with defined minimum pain intensity of moderate or severe pain? (mild pain can reduce the sensitivity of trials to demonstrate an analgesic effect).
(4) Did the reviews examine study size as a confounding factor in any analysis of efficacy? (systematic reviews have been criticised for being overconfident of results with inadequate data[2,65,79]; there is increasing evidence of the importance of small trial size, both because of random chance,[16,52,76] and as an important source of bias.[22,23,26,36,57]

(5) Did the review examine susceptibility to publication bias? (if possible, for each review with dichotomous numerical data, we will assess the likelihood of publication bias[51]).

2.8. Data synthesis and/or descriptive evaluation of reviews

We planned to evaluate strengths and weaknesses of systematic reviews of cannabinoids in treating pain by a descriptive analysis, and meta-analysis if appropriate. Because there was little high-quality evidence found, and none useable for meta-analysis, the descriptive analysis of all systematic reviews became the only mechanism of evaluation.

The absence of combinable data did not preclude unplanned evaluations, including links between AMSTAR-2 score-matched critical methodological criteria for evaluation of analgesic efficacy, the potential impact of reviews using Google Scholar citation numbers, judgement on the strength of recommendations by review authors based on language in the abstracts, numerical assessment of analgesic efficacy, and how these factors interacted.

The nature of the reviews precluded any useful independent assessment of GRADE for individual reviews.

3. Results

3.1. Results of search

Initial electronic searching found 685 possible systematic reviews, reduced to 559 after removal of duplicates. After reading the abstracts, 106 articles were obtained in full, and read for possible inclusion as a systematic review. Forty-nine were excluded (Appendix 1 lists the reasons and references, available as supplemental digital content at http://links.lww.com/PAIN/B61). Reasons for exclusions were:

(1) 12 were narrative or scoping reviews;
(2) 11 were practice guidelines, position papers, or therapeutic recommendations;
(3) 8 were overview reviews;
(4) 2 each were not systematic reviews, had no pain outcomes; did not investigate cannabinoids, were duplicates, were older versions of updated systematic reviews, or were thesis chapters not relevant to this overview;
(5) 1 each was a clinical trial, a review of consensus statements, investigated placebo only, investigated experimental pain, investigated adverse events, or investigated combination therapies without cannabinoids alone.

Fifty-seven[3,5–15,17,19–21,24,27,29,32,33,35,38,40,42–48,54–56,58–64,69–71,73–75,77,78,80–87] were included in this overview review as systematic reviews investigating cannabinoids, cannabis, or CBM in RCTS with pain as an outcome (Appendix 2 gives information on date of publication, pain or other condition examined, type of CBM investigated, route of administration, and abstract conclusion; available as supplemental digital content at http://links.lww.com/PAIN/B61). Seven were Cochrane reviews,[5,10,15,54,59,64,82] and 6 reported either financial sponsorship from a pharmaceutical company or were conflicted because authors were employees of a company with interests in cannabinoids.[8,38,46,69–71]

Forty-seven reviews specifically examined pain (10 neuropathic pain, 10 any type of pain, 8 chronic noncancer pain, 7 cancer pain, 4 rheumatic pain, 2 fibromyalgia, 2 spinal cord injury, 1 acute pain, 1 pain in children, 1 HIV neuropathy, and 1 phantom limb pain). Ten reviews considered conditions in which pain was one of several symptoms (5 muscular dystrophy, 3 neurological conditions, 1 leg cramps, and 1 gastrointestinal conditions).

3.2. General description of included studies

Included studies were mostly published recently. The earliest was published in 2001[17] and the most recent in 2019.[13,33,56,63,86] Only 5 were published before 2010; most (90%) were published since 2010 (**Fig. 1**), and two-thirds of the included reviews had been published in the past 5 years.

Summary information on these 57 systematic reviews is shown in **Table 1**, organised by pain condition. Because several of these systematic reviews examined a wide range of medical conditions, only the information involving pain and cannabinoids is shown.

Neuropathic pain, chronic noncancer pain, all pain, and cancer pain predominated, but 15 distinct areas were recognised. Some were not classic pain conditions, for example, pain associated with spasm in MS or leg cramps.

The number of studies and patients involved, the number of randomised trials included, and the number available for any statistical analysis varied widely between reviews and pain conditions. For 6 pain conditions, there were no available data for

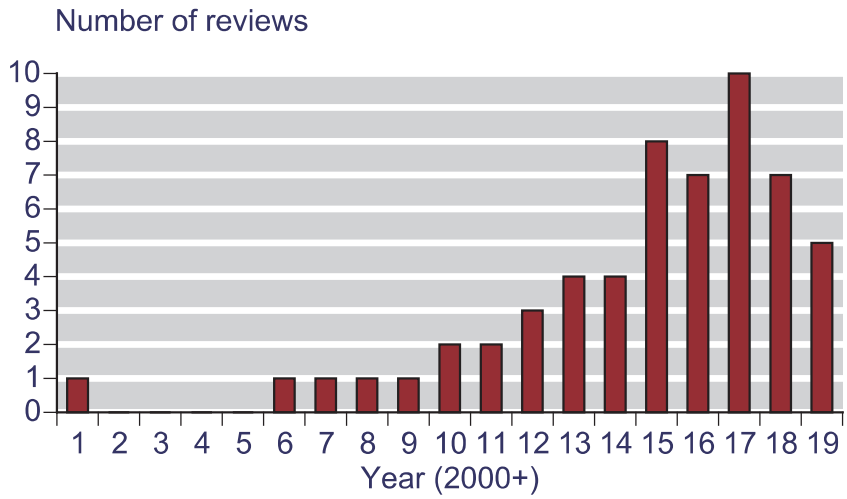

Figure 1. Rate of publication of 54 included systematic reviews. Number of systematic reviews on cannabinoids, cannabis, or CBM published each year between 2001 and 2019. No systematic review was published before 2001. CBM, cannabis-based medicines.

Table 1

Summary information on included reviews, with data for pain and cannabinoid only.

Type of pain	Number of reviews	Total for pain		RCT		Analysis	
		Studies	Patients	Studies	Patients	Studies	Patients
Acute pain	1	7	611	7	611	None	None
Chronic noncancer	8	6–91	226–N/A	6–47	226–N/A	0–9	0–1734
Fibromyalgia	2	2	69–72	2	69–72	None	None
GI	1	1	21	1	21	None	None
HIV	1	2	89	2	89	2	89
Leg cramps	1	1	22	1	22	1	22
MS	5	3–11	N/A–2692	3–11	N/A–2692	0–11	0–2692
Neurology (other)	3	0–7	0–17	0–7	0–17	None	None
Neuropathic	10	0–16	0–1750	0–16	0–1750	0–10	0–1001
Phantom	1	0	0	0	0	None	None
Rheumatic	4	0–4	0–203	0–4	0–203	1	58
SCI only	2	0–2	0–20	0–2	0–20	None	None
Cancer only	7	0–8	0–1539	0–8	0–1539	2–5	537–1333
All pain	10	4–43	N/A–2454	4–43	N/A–2437	0–25	0–2248
Children (all pain)	1	4	19	0	0	None	None

MS, multiple sclerosis; N/A, not available in the review; RCT, randomised controlled study.

analysis. Some reviews in some conditions analysed data from several thousand patients. For example, Yanes et al.[86] analysed data from 25 trials and 2248 patients in a meta-regression for all pain conditions, and Torres-Moreno et al.[77] pooled data from 2692 patients in 11 MS trials. The variation in numbers between reviews in apparently the same condition reflected different approaches in analysing drug and formulation, route of administration, and whether a broad or narrow approach to type of condition was used (eg, painful diabetic neuropathy rather than all neuropathic pain).

Risk of bias was assessed in 45 of the 57 reviews, predominantly using Cochrane risk of bias tools (27), the Oxford quality scale (13) or a modification of it (3), an American Academy of Neurology tool (1), or a Physiotherapy Evidence Database tool (1). Twelve systematic reviews made no apparent mention of formal risk of bias assessment.[8,11,12,20,42,60,62,78,80,85–87]

3.3. Cannabinoid used and route of administration

Reviews examined the effects of a wide range of cannabinoid drugs or preparations, although these were seldom clearly defined. The most common definition was "cannabinoid" in 36 reviews, "any cannabis preparation" in 8, "plant-based cannabis preparation" in 6, 2 each examined nabilone, dronabinol, or nabiximols, 2 palmitoylethanolamide derivatives, and one each Δ^9-tetrahydrocannabinol (THC), cannabidiol, and *Cannabis sativa*. Appendix 3 shows their use by pain condition (available as supplemental digital content at http://links.lww.com/PAIN/B61).

Route of administration was generally not defined (36 reviews), or "any route" (15 reviews), oral or topical (4 reviews), or smoked or inhaled (2 reviews) (Appendix 4, available as supplemental digital content at http://links.lww.com/PAIN/B61).

3.4. Pain outcome used in systematic reviews

Few reviews clearly defined an outcome of at least 30% or 50% pain intensity reduction considered by patients to be a good outcome[53](see Appendix 5 for results according to pain condition, available as supplemental digital content at http://links.lww.com/PAIN/B61); only 14 reviews (25%) sought these outcomes. Most, 28 reviews, did not define an outcome. The remaining reviews used some calculation based on continuous variables, mostly standardised mean difference or mean difference (10 reviews), effect size (3 reviews), or other (2 reviews). Three-quarters of the reviews therefore made no prior adjudication of what a successful outcome might be or justified the choice of outcome.

3.5. Use of GRADE

GRADE evaluation of overall evidence certainty was used in 17 systematic reviews, and not used in 40. Of the 17 that used GRADE, 13/17 (76%) included very low certainty; the ratings were:

(1) 0 high certainty
(2) 4 moderate certainty
(3) 1 moderate or very low certainty
(4) 3 low certainty
(5) 2 low or very low certainty
(6) 7 very low certainty.

3.6. Assessment of multiple systematic reviews rating

Each review was judged according to the 16-criterion AMSTAR 2 list; Appendix 6 shows scoring for individual reviews (available as supplemental digital content at http://links.lww.com/PAIN/B61). The results (**Table 2**) showed that only 4 of the criteria were met by more than half of the reviews (showing some detail of included studies [85%], conflict of interest reporting [81%], study selection in duplicate [65%], and data extraction in duplicate [56%]).

Meeting some criteria was not applicable. For example, because many reviews had few studies, with those studies often small and clinically heterogeneous, no meta-analysis was

Table 2

The extent to which reviews met individual AMSTAR 2 criteria (critical criteria in italic and noncritical criteria in bold).

Number	Criterion	Met	Not met	Partially met	Not applicable
1	**PICO**	13	44		
2	*Protocol established before review*	17	40		
3	**Study design explanation**	0	57		
4	*Comprehensive literature search*	1	3	53	
5	**Study selection in duplicate**	36	21		
6	**Data extraction in duplicate**	33	24		
7	*List of exclusions + justification*	26	31		
8	**Included studies in detail**	48	9		
9	*RoB assessment satisfactory*	27	13		17
10	**Sources of funding for studies**	10	47		
11	*Appropriate meta/analysis*	20	8		29
12	**Impact of RoB on result**	17	25		15
13	*Impact of RoB in discussion/interpretation*	22	31		4
14	**Heterogeneity investigated discussed**	22	28		7
15	*Publication bias (small study bias)*	14	36		7
16	**CoI of review authors reported**	45	12		

Bars indicate critical AMSTAR-2 criteria.
CoI, conflict of interest; PICO, patient, intervention, comparator, outcome; RoB, risk of bias.

appropriate. That situation made it difficult to discuss risk of bias or heterogeneity on the result. It was also difficult to judge whether risk of bias was satisfactory. In addition, the AMSTAR criterion for a comprehensive literature search demanded searches of gray literature, consulting experts in the field, and searching of trial registries. One review met all those criteria,[13] and 53 reviews partially met the criteria for a literature search, typically not searching gray literature.

Other criteria met uncommonly were a study design explanation (no reviews), reporting on sources of funding of studies (19 reviews), production of a complete PICO (Patient, Intervention, Comparison, Outcome; 13 reviews), assessment of small study bias (14 reviews), and prior publication of a protocol (17 reviews).

The failure to meet critical and noncritical AMSTAR criteria resulted in generally low assessments of overall confidence in the results of the review. Using the AMSTAR definitions, confidence in the results of 86% of the reviews was critically low (41 reviews) or low (8 reviews). For 6 reviews, confidence in the results was moderate, and for only 2 was it high; only 1 in 7 systematic reviews had moderate or high AMSTAR confidence.

For the 7 Cochrane reviews, overall confidence was high or moderate in 4, and low in 3; none was critically low. All 6 conflicted reviews were assessed as having critically low confidence (**Fig. 2**). Of the 12 reviews not specific for pain, 9 were evaluated as critically low, and 3 of low confidence.

Appendix 7 shows AMSTAR confidence assessments in the results of the reviews according to the pain condition investigated (available as supplemental digital content at http://links.lww.com/PAIN/B61).

3.7. Use of critical criteria for assessment of analgesic efficacy

Because AMSTAR is a generic instrument not specifically designed for use with analgesic studies, we also assessed the systematic reviews for the use of methodologies designed to avoid significant biases in pain trials (Appendix 6 for individual result scoring and Appendix 8 for summary results by pain condition; available as supplemental digital content at http://links.lww.com/PAIN/B61). The results for this assessment demonstrated that methods used to minimise bias in analgesic studies were typically not used (**Fig. 3**).

Only half of the reviews specified using trials that were both properly randomised and properly double blind. About 10% or fewer required patient-reported pain only, performed any sensitivity analysis for small trials, evaluated sensitivity of a result to publication bias, used studies where entrants were required to have pain with a minimum pain intensity, or evaluated the potential impact of imputation method for missing data.

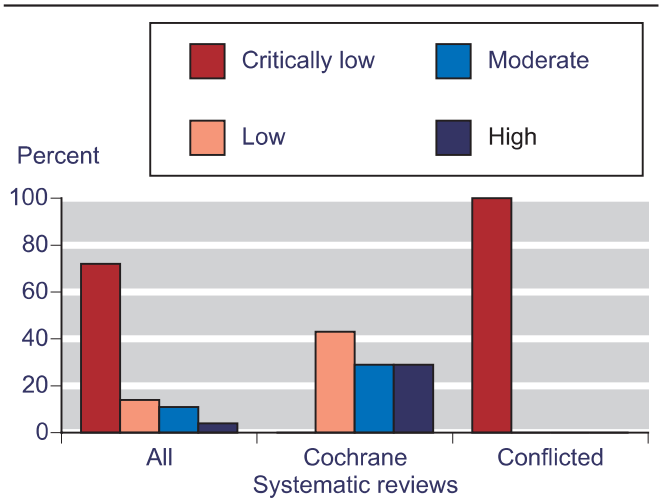

Figure 2. AMSTAR evaluation of confidence in results of systematic reviews. AMSTAR-2 evaluations as percentages of 57 systematic reviews, 7 Cochrane reviews, and 6 conflicted reviews with industry sponsorship.

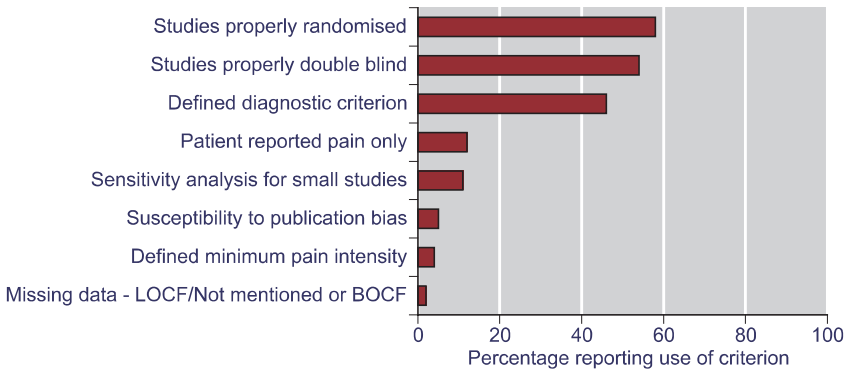

Figure 3. Percentage use of criteria designed to minimise bias in analgesic trials. Percentage of reviews using criteria designed to minimise bias in analgesic trials. BOCF, baseline observation carried forward; LOCF, last observation carried forward.

Results for the 7 Cochrane reviews overall confidence were mixed. Three from a pain-specific group used only randomised and double-blind studies and met 50% or more of the criteria. The other 4 accepted studies were not necessarily randomised or double blind and met 25% of criteria or fewer. Four of the 6 conflicted reviews used only randomised and double-blind studies and met 38% or fewer of the criteria. Of the 12 reviews not specific for pain, only 4 used randomised and double-blind studies and 11 met 25% or fewer of the criteria.

3.8. Concordance between assessment of multiple systematic reviews and critical pain criteria

Thirty-seven of the 39 (95%) reviews with AMSTAR ratings of critically low met 2 or fewer of the 8 critical pain criteria compared with 5/8 (63%) rated low, and 2/7 (29%) of those rated moderate or high. There was a tendency for higher scores in reviews with AMSTAR rating of moderate or high (**Table 3**).

A few individual reviews stood out against the trend. For example, Finnerup et al.[27] had a critically low AMSTAR rating, but met 6 of 8 critical pain criteria, whereas Brettshneider et al.[15] had a high AMSTAR rating but scored only 1 of 8 criteria. Results of the 3 Cochrane reviews from a pain-specific group scored reasonably well on both.

3.9. Impact of systematic reviews

We examined the impact of the 54 of the 57 systematic reviews by looking at the number of citations for each as reported by Google Scholar on Sept 20 2019; three 2019 publications were identified after that date, and would have had few if any citations. The 54 reviews had been cited a total of 6760 times (mean 125 citations, median 47 citations), with about 1100 citations a year (mean 22 citations a year, median 9 citations a year).

The majority of citations came for a small number of systematic reviews (**Fig. 4**). Two reviews were cited on average over 200 times a year,[27,84] and 3 other reviews were cited between 50 and 100 times a year.[5,42,54] Because most reviews had been published within a limited period, no effect of recency in citation rate was discernible.

There was no consistency as why these 5 were particularly heavily cited. **Table 4** summarises information on these reviews, with possible reasons for their high citation rate.

3.10. Judgement on abstract strength of recommendation

Abstracts of systematic reviews typically provide some comment on the strength of evidence or the direction of any effect, and frequently both. These can be interpreted as recommendations or are frequently framed as recommendations. We made a judgement as to whether the implied recommendation in an abstract was positive or negative (strong, moderate, or weak), or showed equipoise, or whether there was no recommendation relating to the use of cannabinoid-based medicines for treatment of pain. **Table 5** shows examples of how we made these judgements, with details of each in Appendix 7 (available as supplemental digital content at http://links.lww.com/PAIN/B61).

Of the 44 systematic reviews making a recommendation, 27 were moderate or strong, 10 weak, and 7 indicated equipoise. Of the 7 Cochrane reviews, 3 had no opinion, 2 were strong negative, one at equipoise, and one was weak positive. Of the 6 conflicted reviews, 3 had no opinion, one was weak positive, and 2 were strong positive. Eight of the 19 reviews with moderate or strong positive recommendation had no formal risk of bias assessment.[8,11,12,20,42,60,61,86] All reviews making weak recommendations had a risk of bias assessment.

3.11. Relationship between abstract strength of recommendation, assessment of multiple systematic reviews rating, and critical pain criteria

Table 6 shows the AMSTAR rating and critical pain criteria score. Systematic reviews with any positive recommendation of use of cannabinoids, cannabis, or CBM in pain typically rated critically low on AMSTAR (20/25; 80%) or critically low or low (24/25; 96%). They typically used 2 or fewer of the 8 critical pain criteria to avoid bias. Reviews with negative recommendations were somewhat less likely to have a critically low (6/12; 50%) or critically low or low rating (10/12; 83%), and used 3 or more critical pain criteria.

Reviews making weak positive or negative recommendations were more likely to use more critical pain criteria than those making moderate or strong recommendations.

Table 3

Concordance between AMSTAR rating and critical pain criteria score (of 8).

AMSTAR rating	Range	Mean	Median
Critically low	0–6	1.5	2.0
Low	1–3	2.1	2.0
Moderate or high	1–6	4.0	4.0

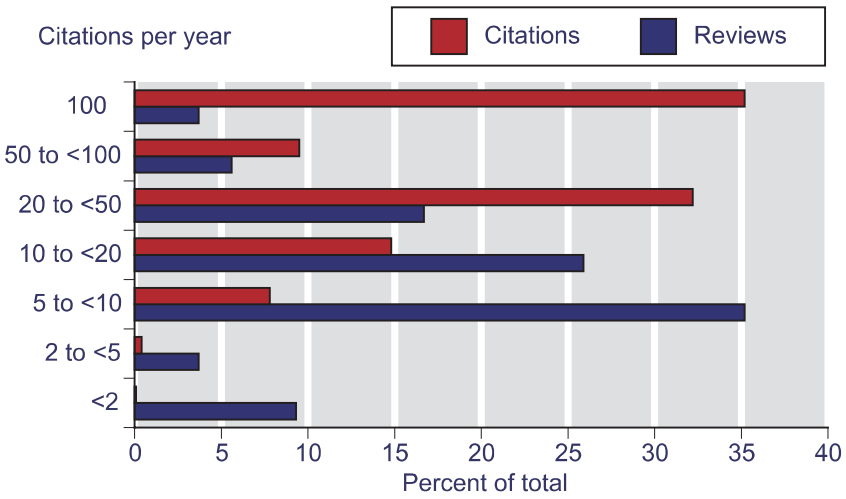

Figure 4. Distribution of total citations and total publications according to annual rate of citation. Distribution of the percentage of total citations and total reviews according to the average number of citations per year for each review calculated from the number of Google Scholar citations divided by the number of years since publication. A small percentage of reviews accounted for the largest percentage of citations.

3.12. Calculation of magnitude of analgesic effect

Seventeen systematic reviews used numeric data to calculate the magnitude of any analgesic effect, for a variety of interventions, routes of administration, and painful condition, using a range of different pain outcomes and statistical outputs (**Table 7**). Analyses were conducted on data sets that varied between 1 and 25 trials, and 22 and 2692 patients. No analysis was conducted on a defined intervention, defined dose or intensity, or defined route of administration in a defined pain condition.

Ten of 18 reported results showed statistical difference from placebo, whereas 8 showed no difference. Statistical significance was associated with positive abstract recommendation, whereas no significance was associated with negative abstract recommendations.

Table 7 also shows AMSTAR-2 confidence level and the number of points scored for critical pain elements. Statistical significance was generally associated with critically low AMSTAR assessment and 3/8 or fewer pain criteria. The exception was a review of short-term (6 hours to 5 days) effects of inhaled or smoked cannabis in small number of patients with chronic pain conditions in trials with significant risk of bias.[7]

Reviews without statistical significance generally made no recommendation or a negative recommendation, with a tendency to higher AMSTAR grades and higher scores for critical pain elements. Exceptions were the study by Stockings et al.[74] with bare significance for one outcome, and the study by Phillips et al.,[61] which included only 89 patients.

A calculation of the susceptibility to publication bias from studies with null results was based on a number-needed-to-treat of 10 or greater being clinically not relevant.[51] No calculation was possible where there was no statistical significance (number-needed-to-treat is then essentially infinity), or for reviews reporting continuous outcomes. For only 3 of these reviews were data available that allowed for the calculation. The number of people in trials with null results required to overturn the statistically significant results for cannabinoids was 213 in Nugent et al.,[58] 237 in Phillips et al.,[61] and 145 in Andreae et al.[7]

4. Discussion

To the extent that any conclusions can be drawn from existing systematic reviews, they can only be made with respect to the types of cannabinoid, cannabis, and CBM investigated to date, in the specific patient groups and pain types studied. No

Table 4

Information on 5 systematic reviews with high average annual citation rates.

Review and journal	Average annual citations	AMSTAR rating	Pain criteria met	Probable reason for high citation rate
Finnerup,[27] Lancet Neurology	320	Critically low	6/8	Broad systematic review of interventions for neuropathic pain from a Special Interest Group of International Association for the Study of Pain published in Lancet Neurology.
Whiting et al.,[84] JAMA	209	Critically low	2/8	Systematic review of cannabinoids for medical use published in JAMA—pain was only one component, and highlighted in the section on chronic pain of the 2017 national Academies report in the United States.
Koppel et al.,[42] Neurology	70	Critically low	1/8	Report of a guideline development committee of the American Academy of Neurology and published in Neurology.
Mücke et al.,[55] Cochrane	56	High	6/8	Broad review of pharmacologic interventions for treating phantom limb pain published in Cochrane.
Alviar et al.,[5] Cochrane	50	Moderate	4/8	Systematic review of cannabis-based medicines for neuropathic pain published in Cochrane.

Table 5

Examples of judgements on abstract strength of recommendation.

Judgement on abstract strength of recommendation	Number	Examples
No opinion	13	No recommendation relating to CBM and pain
Strong positive	6	"Currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic noncancer pain" (Lynch 2015) "Cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in MS" (Iskedihan 2007) "…Cannabinoid-based pharmacotherapies may serve as effective replacement/adjunctive options regarding pain" (Yanes 2019)
Moderate positive	12	"There is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis" (Lynch 2011) "Cannabis and cannabinoids provide an interesting treatment choice for PDN" (Alessa 2018)
Weak positive	10	"Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients" (Nugent 2017) "Selective cannabinoids provide a small analgesic benefit in patients with chronic neuropathic pain" (Meng 2017)
Equipoise	3	"The quality of currently available evidence on the effectiveness of adjuvant analgesics in the treatment of cancer pain is low" (van den Beuken 2017)
Weak negative	6	"More trials with rigorous design and reporting are needed" (Jawahar 2013) "Very low-quality evidence suggests that oromucosal nabiximols and THC have no effect on pain" (Häuser 2019)
Moderate negative	3	"No convincing, unbiased, high-quality evidence suggesting that nabilone is of value in treating people with fibromyalgia" (Walitt 2016) "Smoked cannabis cannot be recommended as routine therapy" (Phillips 2010)
Strong negative	4	"Cannabinoids have no role in the management of acute pain" (Stevens 2017) "The available evidence does not support current use in the management of rheumatoid arthritis" (Macfarlane 2011) "Do not offer [nabilone, dronabinol, THC, a combination of cannabidiol (CBD) with THC] to manage chronic pain in adults" (NICE 2019) "…For adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain." (Boland 2019)

CBM, cannabis-based medicines.

conclusions with respect to other interventions yet to be tested are possible.

Of the many reviews of the effects on pain of studies concerning cannabinoids, cannabis, and CBM published to the end of 2019, 57 claimed to be systematic reviews. The Cochrane Handbook lists 5 key characteristics of a systematic review[34]: a clearly stated set of objectives, explicit and reproducible methods, systematic and comprehensive searches, assessment of validity of results including risk of bias, and a systematic presentation of those results. Although relatively few of the 57 systematic reviews examined here would meet these criteria, the cachet of a review claiming to be systematic is such that all required examination.

Included reviews examined 15 distinct pain areas. Most accepted any type of cannabinoid, at any dose, by any route of administration, although some had a more defined scope. No review examined the effects of a particular cannabinoid, at a particular dose or dose range, given by a particular route of administration, for a particular pain condition, and reporting a particular analgesic outcome.

The degree of pooling for any effect calculations could be extreme; for example, one review of cannabinoids in chronic pain pooled data from trials as short as 6 hours, and as long as 15 weeks.[57] Almost 80% of the reviews failed to define what a successful outcome might be; rather than defining a measure that is important to patients,[54] the approach was to make important that which had been measured.

Judging systematic review quality is difficult. The most often used methodology is AMSTAR, and we used the most recent version, AMSTAR-2.[67] This is a generic tool examining what is

Table 6

Relationship between abstract strength of recommendation and AMSTAR rating and critical pain criteria.

	No opinion	Positive			Equipoise	Negative		
		Any	Strong or moderate	Weak		Weak	Strong or moderate	Any
Number	13	25	19	6	7	4	8	12
AMSTAR rating								
Critically low	10	20	17	3	5	2	4	6
Low	1	4	1	3	0	1	2	3
Moderate	1	1	1	0	1	1	2	3
High	1	0	0	0	1	0	0	0
Critical pain criteria score (of 8)								
Mean	1.6	1.5	1.4	1.7	2	4.0	2.8	3.2
Median	1	2	2	1.5	2	4	2	3
Range	0–4	0–5	0–5	1–3	1–3	2–6	1–4	1–6

Table 7

Magnitude of analgesic effect calculations in 15 systematic reviews reporting it.

Review	Intervention	Route of administration	Condition	Trials/patients in analysis	Outcome	Statistical result	Strength of abstract recommendation	AMSTAR-2 confidence rating	Pain criteria (of 8 points)
Andreae et al.[7]	*Cannabis sativa*	Inhaled	Neuropathic	5/185	≥30 pain reduction NNT	**5.6 (3.4 to 13)**	Strong +	Moderate	5
Yanes et al.[86]	Cannabinoids	Any	All pain	25/2248	Effect size, mean	**Cohen's d = −0.58, 95% CI (−0.74 to −0.43)**	Strong +	Critically low	0
Artukoglu et al.[8]	Palmitoylethanolamide	Not defined	All pain	8/1244	Unclear WMD	**2.03 (1.19 to 2.87)**	Moderate +	Critically low	0
Martin-Sanchez et al.[46]	Any cannabis preparation	Not defined	Chronic noncancer	7/288	Effect size, mean	**−0.61 (−0.84 to −0.37)**	Moderate +	Critically low	2
Nugent et al.[58]	Plant-based cannabis preparations	Not defined	Chronic noncancer	9/1042 neuropathic only	≥30 pain reduction RR	**1.4 (1.2 to 1.9)**	Moderate +	Critically low	2
Whiting et al.[84]	Cannabinoids	Not defined	All pain	8/1370	≥30% pain reduction OR	1.41 (0.99 to 2.00)	Moderate +	Critically low	2
Aviram et al.[9]	Any cannabis-based medicines	Any	All pain	24/1334	Mean change 0-10 scale	**−0.61 (−0.78 to -0.43)**	Weak +	Critically low	2
Meng et al.[48]	Dronabinol, nabilone, naboximols	Any	Neuropathic	10/973	Mean difference 0-10 scale	**−0.65 (−1.06 to −0.23)**	Weak +	Critically low	3
Torres-Moreno et al.[77]	Cannabinoids	Oral or oromucosal	MS pain	11/2692	SMD	**−0.17 (−0.31 to −0.03)**	Weak +	Critically low	2
da Rovere et al.[19]	Cannabinoids	Not defined	MS pain	3/not stated	SMD	0.55 (−3.3 to 4.4)	None	Critically low	1
Jawahar et al.[40]	Cannabinoids	Not defined	MS pain	3/565	Effect size, mean	0.08 (−0.74 to 0.89)	None	Critically low	3
Stocking et al.[74]	Cannabis and cannabinoids	Any	Chronic noncancer	5/753	≥50% pain reduction OR	1.4 (0.97 to 2.1)	None	Moderate	3
				8/1734	≥30% pain reduction OR	**1.4 (1.2 to 1.8)**	None	Moderate	3
Finnerup et al.[27]	Cannabinoids	Any	Neuropathic	5/815	≥50% reduction RD	0.027 (−0.034 to 0.088)	Weak −	Critically low	6
Mucke 2018[54]	Any cannabis-based medicines	Any	Neuropathic	8/1001	≥50% reduction RD	0.05 (0.00 to 0.09)	Weak −	High	6
Boland 2019[13]	Cannabinoids	Any	Cancer	5/1442	Mean difference 0-10 scale	Mean difference −0.21 (−0.48 to 0.07, $P = 0.14$)	Strong −	Moderate	3
Baldinger et al.[10]	THC	Not defined	Muscle cramps	1/22	VAS, mean	0.24 (−0.31 to 0.79)	Strong −	Low	2
Phillips et al.[61]	Any	Not defined	HIV neuropathy	2/89	≥30 pain reduction RR	**2.4 (1.4 to 4.1)**	Strong −	Critically low	3

Bold entries were significantly different from placebo. NNT, number-needed-to-treat.

regarded as best practice in systematic review methodology. The 16 items are themselves not controversial, although judging whether a review meets a particular criterion is often subjective, open to disagreement between assessors because details of methods may be omitted from publications for reason of space. An AMSTAR-2 score probably represents a "worst case." No single criterion was met by more than 50% of the reviews, and confidence in the results of 86% of the reviews was critically low (41 reviews) or low (8 reviews). This is similar to an assessment of systematic reviews in back pain where 74% rated critically low and 16% low.[4]

A generic approach to quality is of limited value in assessing analgesic effects because it does not examine criteria known to be associated with considerable bias in pain trials. We examined 8 of those with established association with risk of bias, and again few reviews used them. Randomisation and blinding were defined criteria in just over half of the reviews, but 5 of the 8 criteria were used by 10% or fewer of the reviews. Reviews with low AMSTAR-2 rating typically used few pain-associated risks of bias, whereas those providing moderate or high confidence used more.

The implication is that significant sources of potential bias were likely to have affected results from most of the 57 systematic reviews. Cochrane reviews tended to be better, especially more recent reviews, whereas conflicted systematic reviews with pharmaceutical company backing were poor.

Quality was not associated with the impact of reviews as judged by annual citation rates on Google Scholar. Three of the top 5 cited reviews met many pain criteria (although not necessarily AMSTAR); the strength of recommendation in the abstracts of these reviews was weak negative or none. Two were rated critically low confidence by AMSTAR and used very few important criteria for avoiding bias in pain studies and reviews (**Table 4**); their strength of recommendation was moderately or strongly positive.

Of the 17 reviews attempting a numerical calculation of the magnitude of the analgesic effect, 9 had a positive and 5 a negative recommendation. Reviews with positive recommendations were associated with a statistically significant analgesic effect, but not reviews with negative or no recommendation. Susceptibility to publication bias for 3 reviews with statistical significance showed that the result would have been overturned by a null result from a clinical trial of 100 to 250 patients. Moreover, 8 of 19 reviews with moderate or strong positive assessment, whether or not they found a significant benefit, did not evaluate risk of bias, whereas all making a negative recommendation assessed risk of bias.

To summarise, what we have is a body of work that tells us little about whether any particular cannabinoid or cannabis-based treatment tested to date, at a particular dose and route of administration, given to someone with a particular form of pain could lead to a particular degree of pain reduction (at least 50% pain intensity reduction or reduction of pain to just mild[54]). Low-quality reviews do no more than suggest there may be, whereas the highest quality say probably not.

It is telling that a U.S. National Academies of Sciences, Engineering and Medicine report on therapeutic effects of cannabis and cannabinoids, and a later update,[1,18] concluded that there is "substantial" evidence that cannabis is an effective treatment for chronic pain in adults. The committee included experts in substance abuse, cardiovascular health, epidemiology, immunology, pharmacology, pulmonary health, neurodevelopment, oncology, pediatrics, public health, and systematic review methodology, but not pain. It based much of its findings on pain on the systematic review of Whiting et al.[84] That review was given an AMSTAR rating of critically low confidence and used only 2/8 pain methodologies. Moreover, for the patient-orientated outcome of at least 30% pain intensity reduction, it reported a result not significantly different from placebo, including, as it did, no significant difference in the 95% confidence interval (odds ratio 1.41 [0.99-2.00]). That conclusion should be revisited, revised, or retracted, because it is significantly misleading.

There are several lessons:

(1) The label of systematic review does not itself confer value for pain. Generic scoring systems for systematic reviews provide limited confidence, and the best mechanism to ensure that a systematic review provides a robust and reliable answer is to combine generic Cochrane approaches with pain-specific criteria, as several Cochrane review groups do. Systematic reviews of cannabinoids, cannabis, and CBM in pain require authors skilled not only in systematic review methodology but also those knowledgeable about pain and cannabinoids.

(2) Clinical trials to measure analgesic effect have a long-established basic methodology, but recent decades have demonstrated additional situation-specific factors needing consideration. Trials need to be conducted to the highest standards (especially those for registration or marketing purposes) and provide outcomes of clinical as well as statistical relevance to both efficacy and harms.

(3) RCTs investigating cannabis, cannabinoids, and CBM and pain should be designed to include well-defined populations with specific pain diagnoses, evaluate particular interventions (specific cannabinoid, doses, and route of administration) and comparators, and report on meaningful patient-reported pain outcomes (including functional outcomes and not just analgesic efficacy). Good RCTs can be complemented by patient registries to gather data on long-term patient outcomes to explore effectiveness of cannabinoids, cannabis, and CBMs for the treatment of pain and function in real life.

(4) More details of the clinical trials should be provided in reviews, particularly relating to concomitant analgesic medication, previous use of cannabinoids and other analgesics, and whether testing has been conducted to exclude nontrial use of drugs in test or placebo arms.

(5) The fact that on AMSTAR-2 alone, 41 systematic reviews providing critically low confidence in their results were published in medical journals (including some prestigious journals) indicates a potential problem with research quality. It is debatable whether this is a failure of journals and the peer review system, or whether scoring systems are unrealistic and penalise reviews unnecessary. Does a literature search of gray literature actually improve systematic reviews of RCTS, for example?

(6) Low quality and overclaiming positive benefits have long been associated.[37,39] There is no obvious sign of improvement, and that is a matter of considerable concern.

(7) The link between the low quality of reviews and the positive or negative assessment of analgesic efficacy in review abstracts (often the only part that is read in any detail, or at all) is of concern. It begs the question not of challenge to these reviews, but to whether the implications are such as to consider calls for retraction. A Cochrane review compromised by methodological faults would likely be retracted, perhaps the only situation in which that would happen.

5. Conclusion

The primary reasons for this overview review were to examine the quality of the extant review literature and question whether a new systematic review would be needed. The results of the overview demonstrate that most reviews are lacking in quality and cannot provide a basis for decision-making. In the circumstances, a new systematic review adhering strictly to methodological requirements of AMSTAR and pain studies is required.

Conflict of interest statement

C. Eccleston reports grants from vs Arthritis, MayDay Foundation, Cochrane, and NIHR outside the submitted work. D.P. Finn reports grants from Alkermes Inc and Shionogi Ltd, outside the submitted work. N.B. Finnerup reports personal fees from Novartis Pharma, personal fees from Mitshubishi Tanabe Pharma, personal fees from Merck, personal fees from Almirall, personal fees from NeuroPN, and grants from EU PainCare, outside the submitted work. I. Gilron reports he is a Council Member of the International Association for the Study of Pain, as is part of the Presidential Task Force on Cannabis and Cannabinoid Analgesia, personal fees from Adynxx, personal fees from Biogen, personal fees from Eupraxia, personal fees from Novaremed, nonfinancial support from Canopy Health, nonfinancial support from Toronto Poly Clinic, and nonfinancial support from CannTrust, outside the submitted work. S. Haroutounian reports grants from Pfizer Inc and Disarm Therapeutics, and personal fees from Medoc Ltd and Rafa laboratories, outside the submitted work. A. Rice is a Council Member of IASP and Chair of the Presidential Task Force of the IASP. He undertook consultancy and advisory board work for Imperial College Consultants in the last 24 months; this has included personally remunerated work outside of the submitted work for: Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Toray, Abide, Asahi Kasei, and Theranexis. He was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued between 2015 and 2019 upon the acquisition of Spinifex by Novartis. Prof Rice is a named inventor on the patents—A.S.C. Rice, Vandevoorde S. and Lambert D. M Methods using N-(2propenyl)hexadecanamide and related amides to relive pain. WO2005/079771 pending, and Okuse et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/WO2013110945 pending. During the conduct of the study, Imperial College received grants funding to support Prof Rice's programme of research from Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC), Wellcome Trust, Alana and Sheila Diamond Charitable Trust, British Pain Society, Royal British Legion, and the European Commission (IMI2 (EQIPD); FP7 (Neuropain) and H2020 (Dolorisk)). M. Rowbotham reports personal fees from Adynxx, personal fees and other from CODA Biotherapeutics, and personal fees and other from SiteOne Therapeutics, outside the submitted work; and none of the entities listed are developing cannabinoid or cannabis-based medicines. M. Wallace Wallace reports personal fees from Insys, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

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